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Variations in the Surgical Management of Older Women Presenting with Breast Cancer

Mr Tom Bates

A thesis submitted in fulfilment of the requirement for a PhD by Published Works, Warwick Medical School, University of Warwick

1st April 2015

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APPENDICIES

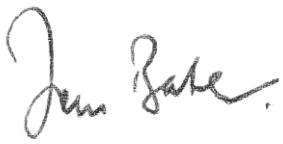
Declaration

I, Tom Bates, declare that

(a) the submitted material as a whole is not substantially the same as published or unpublished material that I have previously submitted, or am currently submitting, for a degree, diploma, or similar qualification at any university or similar institution;

(b) that I have stated clearly which parts of the work or works submitted have previously been submitted for any such qualification; and

(c) where the work submitted includes work conducted in collaboration with others, I have provided a written statement on the extent of my individual contribution to the material and the conditions and circumstances under which the work was carried out. This statement has been signed by all collaborating parties with whom I have been able to make contact.



Index of Published Works for consideration

	Reference
Study 1 (Appendix 1)	Bates T, Riley DL, Houghton J, Fallowfield L, Baum M. Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. Br J Surg 1991; 78: 591-4.
Study 2 (Appendix 2)	Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M. Late follow-up of a randomised trial of surgery plus tamoxifen versus tamoxifen alone in women over 70 with operable breast cancer. Br J Surg 2004; 91: 699-704.
Study 3 (Appendix 3)	Moritz S, Bates T, Henderson S, Humphreys S, Michell MJ. Variations in management of small invasive breast cancers detected on screening in the former South Thames East Region: observational study. BMJ 1997; 315: 1266-72
Study 4 (Appendix 4)	Bates T, Kearins O, Monypenny I, Lagord C, Lawrence G. Clinical outcome data for symptomatic breast cancer: the breast cancer clinical outcome measures (BCCOM) Project. Br J Cancer 2009; 101(4): 395-402.
Study 5 (Appendix 5)	Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: Failure to operate for early breast Cancer in older women. Eur J Surg Oncol. 2014; 40: 1230-1236.

Statement of candidate's contribution to published work

Contributions of the candidate	Co-authors in agreement	
Paper 1. Breast cancer in elderly women: CRC trial comparing tamoxifen and surgery with tamoxifen alone. TB took a lead role as principal investigator in the design, conduct and evaluation of this RCT in collaboration with Professor Baum and the CRC Unit at Kings. He wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.	D Riley	√
	J Houghton	√
	L Fallowfield	√
	M Baum	√
Paper 2. Late follow-up of CRC trial: tamoxifen v surgery + tamoxifen. Tom Bates in collaboration with Professor Baum decided that a long-term follow-up of this trial was important and Michael Fennessy accessed and analysed the archival data. TB wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.	M Fennessy	*U
	D Riley	√
	J Houghton	√
	M Baum	√
Paper 3. Variations in management of screen-detected breast cancer As the Surgical Coordinator for the Region Tom Bates was responsible for the surgical aspects of the BSP and audited the process. Sabine Moritz collected and collated the data. TB wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.	S Mortiz	√
	S Henderson	√
	S Humphreys	*U
	M Michell	√
Paper 4. The BCCOM Project for symptomatic breast cancer. The need for this audit was identified by Ian Monypenny, Tom Bates and Gill Lawrence and they drew up the surrogate KPI's. The data were collected and analysed by Olive Kearins, Catherine Lagord and Gill Lawrence. TB checked the data and wrote the manuscript in liaison with the co-authors.	O Kearins	√
	I Monypenny	√
	C Lagord	√
	G Lawrence	√
Paper 5. Variation in operation rates: comorbidity and older women. The data were collected by Olive Kearins, Catherine Lagord and Gill Lawrence. The data were analysed by Tim Evans who calculated the CCI values. TB checked the data and wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.	T Evans	√
	C Lagord	√
	I Monypenny	√
	O Kearins	√
	G Lawrence	√

*Unable to contact

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I am grateful to Professor Michael Baum who encouraged me at an early stage to collaborate with the Cancer Research Campaign Clinical Trials Centre at King's and who supported me in setting up the Elderly Breast Cancer randomised controlled trial.

I am grateful to Joan Houghton, Tim Evans and the Late Ken MacRae for statistical support and much more.

I am grateful to Mike Michell for leading the breast screening programme in the Region and to Gill Lawrence for support and careful oversight of the BCCOM Project and its subsequent iteration.

I must thank my co-authors, my surgical colleagues, the Breast Unit staff at the William Harvey Hospital for their untiring support and not least the patients who participated in the clinical trials and observational studies.

Abbreviations

ABS	Association of Breast Surgery
ASCO	The American Society of Clinical Oncologists
ALND	Axillary Lymph Node Dissection
BASO	British Association of Surgical Oncology
BCCOM	Breast Cancer Clinical Outcomes Measures
BMI	Body mass Index
CI	Confidence Interval
CCI	Charlson Comorbidity Index
CRC	Cancer Research Campaign
DCIS	Ductal carcinoma in situ
DCO	Death certificate only
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ER	Oestrogen receptor
EPG	Excellent Prognostic Group
GHQ-28	General Health Questionnaire- 28 question
GPG	Good Prognostic Group
HR	Hazard Ratio
HER2	Human Epidermal Growth Factor Receptor-2
HES	Hospital Episode Statistics
MDT	Multi-Disciplinary Team
NATO	Nolvadex Adjuvant Trial Organisation
NHSBSP	NHS Breast Screening Programme
NICE	National Institute for Health and Clinical Excellence
NPI	Nottingham Prognostic Index
OR	Odds Ratio
PPG	Poor Prognosis Group
PREM	Patient Recorded Experience Measure
PR	Progesterone receptor
RCT	Randomised Controlled Trial
RT	Radiotherapy
SEER	Surveillance, Epidemiology and End Results
QARC	Quality Assurance Reference Centre
WMCIU	West Midlands Cancer Intelligence Unit

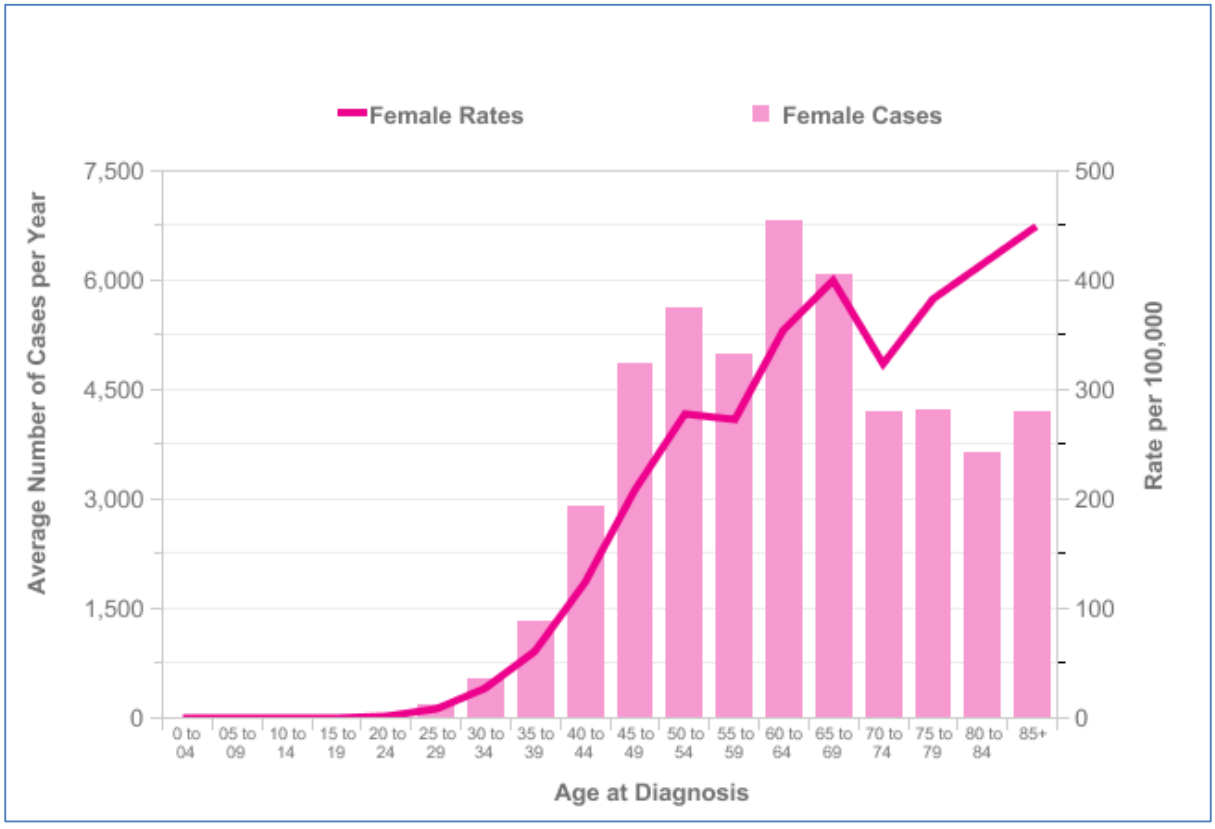
Chapter 1 – Epidemiology, risk factors

1.1 Epidemiology of Breast Cancer

Breast cancer is the most common form of malignancy in women and since the incidence of the disease rises steeply with age, the number of breast cancer registrations worldwide continues to rise with the increasing age of the population. In the UK nearly 50,000 new breast cancers in women are diagnosed each year and 12,000 will die of the disease, which is the second most common cause of death from cancer in women. However almost 80% of women diagnosed with breast cancer will be alive 10 years later. The incidence of breast cancer rises sharply with age and the age-specific rate continues to rise indefinitely (Figure 1). Furthermore the age-specific incidence rates continue to rise over time. This trend is probably related to demographic changes in the female population with an increase in many of the risk factors considered below.

Average number of new cases of breast cancer per year and age-specific incidence rates per 100,000 population. Source: Cancer Research UK (2014)[1]

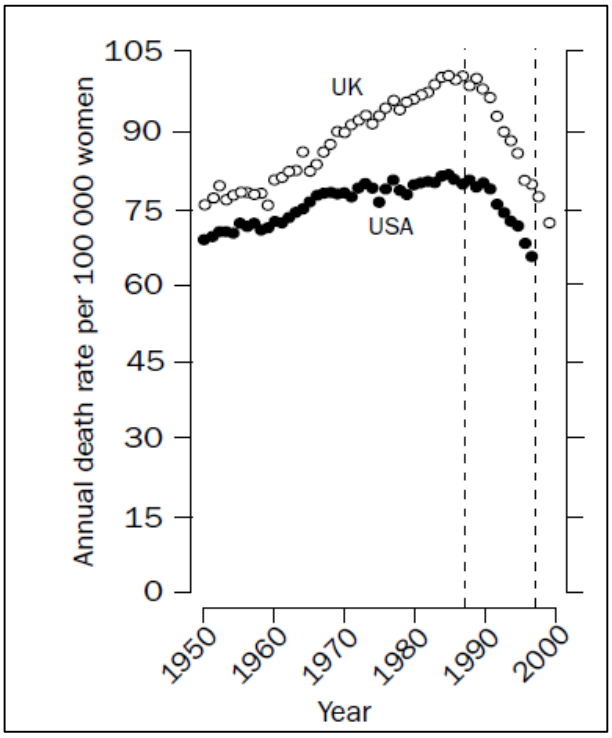
Figure 1 - Breast Cancer incidence UK 2009-2011



In the UK 20% of breast cancers in the UK were diagnosed in the NHS Breast Screening Programme which was opened in 1988 but this proportion has now risen to over 30%.

Breast screening is further considered in Chapter 3 but in common with most countries the introduction of breast cancer screening has led to an additional increase in incidence[2]. However although the number of deaths from breast cancer has risen commensurately with the incidence, Peto and colleagues[3] were perhaps the first to point out that from the late 1980's breast cancer mortality in the UK and USA had fallen 25% by the year 2000. They argued that the reason for this precipitous fall in mortality in both countries was likely to be multi-factorial but largely centred on the changes in the diagnosis and treatment of breast cancer.

Figure 2 - Breast cancer mortality per 100,000 population 1950-2000 UK and USA



from Peto et al (2000)[3]

1.2 Risk factors for breast cancer

The main risk factors for the development of breast cancer, apart from age and family history, concern the length of time that women are exposed to the effects of oestrogens. Five of the eight factors considered by the Million Women Study Collaborators[4] are oestrogen related: age at menarche; parity; age at first birth; age at menopause and hormone replacement therapy. The three other contributing factors are family history, alcohol consumption and Body Mass Index (BMI). Excess weight is only a significant risk factor in postmenopausal women and paradoxically, height is a risk factor in young women[5].

Of the several other risk factors that have been considered, increased breast density on mammography[6] is likely to be related to oestrogen exposure and benign breast disease is related to cellular atypia as in atypical ductal hyperplasia[7]. Diet[8-10], physical exercise[11,12] and smoking[12-14] have been extensively investigated but any attributable risks remain controversial.

Ionising radiation is a known but now rare risk for the subsequent development of breast cancer, exemplified by radiological screening for pulmonary tuberculosis[15] and mantle radiotherapy for Hodgkin's disease[16,] especially in young women. Digoxin[17] has recently been associated with an increased risk of breast cancer and metformin[18] is known to have a protective effect.

1.3 Ethnicity

Breast Cancer is less common in Japan[19] and in much of the developing world although there is a rising trend due to changes in life-style and life expectancy. The incidence in Black and Asian women in the UK is lower than in the white population but this may be largely explained by differences in known risk factors rather than in true ethnic factors[20.] Nevertheless when women of non-white ethnicity develop breast cancer this tends to have a worse prognosis[21-23].

1.4 Clinical Management of Breast Cancer

For a newly presenting patient with possible breast cancer the clinician will wish to establish a histological diagnosis by carrying out a core biopsy at an early stage in order that the recommendations for treatment can be considered by the Multi-Disciplinary Team (MDT) in a timely manner. The clinician will then be in a better position to discuss the diagnosis, the outlook and the treatment options with the patient before any surgery is carried out. The MDT will normally be attended on a weekly or even twice weekly basis by an oncologist, a pathologist, a radiologist, a surgeon or breast physician, a breast specialist nurse and a data manager. These specialists will all have a dedicated practice in breast cancer and where appropriate will have access to reconstructive surgery and genetic, psychological, geriatric and palliative care advice. The clinician will wish to establish the extent of the disease in the breast and axilla and if there is any suspicion, to exclude metastatic disease. The histology will reveal the tumour type and grade, the oestrogen and progesterone receptor (ER/PR) and Human Epidermal Growth Factor Receptor 2 (Her2) receptor status. If the tumour is locally advanced or has particularly unfavourable features on histology such as a Triple Negative (ER/PR/Her2 -ve) tumour, this may lead the MDT to advise neoadjuvant therapy with chemotherapy.

1.5 Surgical options

The axilla will usually be assessed by ultrasound examination and, if the nodes are suspicious of secondary disease, a needle or core biopsy will be taken. The most appropriate management of the minimally node positive axilla is currently uncertain and this is further discussed in Section 4.15. Unless conservative surgery is contraindicated by a large or multifocal tumour, a wide local excision to clear margins will be advised with post-operative radiotherapy. There has been uncertainty as to what constitutes a 'clear margin' with some centres requiring 1cm between the tumour and the inked margin which many clinicians felt was excessive and which has resulted in re-excision rates of 20-25%. However there has recently been a definitive statement from The American Society of Clinical Oncologists (ASCO) which is a highly influential body worldwide, that no ink on the tumour (a minimal clearance) should be the new standard of care[24], which will hopefully lead to a change in clinical practice. If a mastectomy is indicated the patient should be offered a reconstruction, which can be immediate unless post-operative radiotherapy is likely. There is concern that when radiotherapy is given after a breast reconstruction that the long-term cosmetic outcome is disadvantaged, especially when an implant has been inserted.

Subsequent examination of the resected tumour will give further information such as the presence of lymphovascular invasion, the invasive tumour size and the resection margins. Increasingly genomic tests such as the 21 gene signature Oncotype DX[25] or more recently a 70 gene profile are being used to tailor adjuvant treatment by genomic profiling. Adjuvant hormone therapy would normally be advised for ER+ve tumours, usually with an aromatase inhibitor[26] or for Her 2 positive tumours with a monoclonal antibody, trastuzumab (Herceptin)[27]. The potential advantage of adjuvant chemotherapy will often be assessed with a prediction tool such as Adjuvant! Online, although this may not be accurate in older women[28], or sometimes with Predict[29] which is modelled on a population of patients in the UK.

The difficulties of communicating this information and the alternative of primary endocrine therapy to an elderly woman in a holistic setting are not inconsiderable and are further considered in the Discussion section (5.10).

Chapter 2 – Tamoxifen in the older woman

2.1 Introduction

This chapter presents a brief historical perspective of the main treatment strategies for breast cancer. This chapter also presents two completed studies, a clinical trial with subsequent long-term follow-up which investigates the role of tamoxifen in older women with breast cancer, on outcomes of survival and quality of life. The contribution of these studies to the broader evidence base is considered.

2.2 Hormone Therapy

The first indication that the outcome of advanced breast cancer could be improved by hormone manipulation came from Beatson in 1896 who achieved an objective remission of locally advanced disease in three women from bilateral oophorectomy without knowledge of the endocrine mechanism[30]. However it was many years later that the value of ovarian ablation in the management of breast cancer was recognised. The discovery of sex hormones led Haddow to give stilboestrol (an oestrogen) to women with advanced breast cancer[31] and subsequently for the UK Christie group[32] and the Scandinavian group[33] in the 1960's to trial adjuvant ovarian ablation with radiotherapy in early breast cancer with limited success. However the subsequent overview of all randomised trials of ovarian ablation[34] by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) left no doubt as to the value of the intervention.

2.3 Surgery

The effective surgical treatment of early breast cancer only became a real option with the advent of general anaesthesia but it was William Halsted of Baltimore who pioneered radical mastectomy for the cure of the disease[35]. However the disappointing late results of survival from his operations published in 1932 showed that few if any patients had actually been cured[36]. At the same time as this publication, Geoffrey Keynes reported that conservative surgery for breast cancer with adjuvant radium needles showed similar outcomes to radical mastectomy, albeit from historical controls[37,38]. Nevertheless radical mastectomy remained the accepted standard of care for many years until randomised trials of conservative surgery with adjuvant radiotherapy showed equivalent outcomes to radical surgery for early breast cancer[39,40]. Historically, the surgical management of early breast cancer in older women was essentially the same as in younger women within the constraints of increasing comorbidities and fitness for anaesthesia.

2.4 Clinical Management

Breast cancer is a multi-faceted disease and the outlook for patients depends on many factors so that the prognosis for survival, free of recurrent disease may vary between an essentially normal expectation of life seen with many screen-detected tumours, and an aggressive cancer which fails to respond to the best efforts of surgeons and oncologists. The management of breast cancer has changed over time with the advent and increasing use of adjuvant therapies and more conservative surgery[41,42], which has substantially improved the outcome for patients[43].

The prognosis for recurrence-free survival from breast cancer may be substantially improved with the use of hormones and radiotherapy [41] and with chemotherapy[42] but the extent of local[44] and axillary disease[45], the tumour size, grade, node status[46] and hormone receptor status[44] also affect the outcome as may the age of the patient and the presence of comorbid disease or obesity in older women[47,48]. However the optimal clinical management of the patient is crucial to achieving the best outcome in any given clinico-pathological situation.

2.5 Tamoxifen – early trials

Tamoxifen is an anti-oestrogen, which was first synthesised and developed by ICI (now AstraZeneca) in the 1960's. The first clinical trial investigating survival in patients with advanced breast cancer at the Christie Hospital in 1971 was equivocal[49] but a second trial in 1973 was more successful at a higher dose[50]. From this time onwards several studies of tamoxifen (Nolvadex) in various settings were carried out. On the premise that breast cancer is often a systemic rather than a localised disease, a randomised controlled trial (RCT) was set up in 1977 of adjuvant tamoxifen for two years versus no further treatment, all patients having a mastectomy and axillary surgery. This was a multicentre trial run by the Nolvadex Adjuvant Trial Organisation (NATO) and chaired by Michael Baum at King's College Hospital. My role in this trial was to enter all eligible patients from the Breast Clinic at Ashford Hospital Kent, from trial inception until closure in 1981[51]. By four years follow-up, this trial was already showing an overall survival benefit from adjuvant tamoxifen[52] and at six years of follow-up the improvements in disease–free and overall survival were highly significant[53]. This early trial was conducted without knowledge of ER status and the known benefits were likely to have been underestimated.

Subsequent trials have shown that five years of tamoxifen are superior to two years but that there is no benefit in patients who are ER negative. A meta-analysis of published RCTs conducted by the EBCTCG[54] found that five years of tamoxifen reduced breast cancer mortality by one third at up to 14 years follow-up. As was common practice the NATO trial had an upper age limit of 75 years (although 70 years was more common), with the result that evidence from most RCTs cannot be extrapolated to older women with any confidence.

Postscript. Tamoxifen is not a pure anti-oestrogen and does have an agonist effect on the endometrium, which leads to an excess of endometrial cancers although these are usually low-grade. To some extent the use of tamoxifen has been overtaken by pure antagonists such as fulvestrant (Faslodex) and by the aromatase inhibitors such as anastrozole (Arimidex). Nevertheless, its widespread use is generally considered to be responsible for much of the reduction in breast cancer mortality over the last 20 years.

2.6 Primary Tamoxifen Therapy

At about the same time that the NATO trial of adjuvant tamoxifen was set up several uncontrolled, non-randomised studies of tamoxifen as the sole primary treatment for operable breast cancer in older women were undertaken on the premise that frail elderly patients with significant morbidity might be spared an operation. The results from these relatively small pilot studies showed that approximately one third of patients had a complete remission and a further one third had static disease. All the reported studies gave a positive recommendation for use of primary tamoxifen therapy in elderly women[55-59] with one exception[60]. However, Bradbeer recommended that an accurate assessment of the role of tamoxifen in older women warranted investigation within a rigorous RCT[57].

2.7 Need for clinical trials

There have been many changes in the management of breast cancer over the last forty years but the RCT was introduced to surgical practice at a relatively early stage[51,61,62]. It gradually became accepted that for any change in current clinical practice, evidence from rigorously conducted clinical trials should take precedence over guidance based on the consensus of expert opinion[63].

2.8 Study 1 (Appendix 1)

Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. Bates T, Riley DL, Houghton J, Fallowfield L, Baum M. Br J Surg 1991; 78: 591-4.

It was in the above setting of uncertainty in the use of tamoxifen as a sole treatment strategy that three RCTs of primary tamoxifen therapy for operable breast cancer in older women were set up in the 1980's in the UK, at St George's, at Nottingham and the present multicentre Cancer Research Campaign (CRC)[61] study centred at King's College Hospital, London.

The Trials at Nottingham[64] and St George's[65] both compared surgery alone with tamoxifen alone but at about the same time, it was felt that there was an ethical difficulty in withholding tamoxifen from one group of patients in view of the mounting evidence of benefit from primary endocrine therapy. As principal investigator and in collaboration with

Michael Baum at the CRC Unit, I therefore set up a multicentre RCT to compare tamoxifen alone with tamoxifen together with optimal surgery in women over the age of 70 with operable breast cancer[61].

2.9 Interim Results

An interim analysis of this trial was reported on 354 women[61]. The extent of surgery was at the discretion of the individual surgeon and the majority of women (77%) had a wide local excision rather than mastectomy. Post-operative radiotherapy was not included in the protocol and although this led to a high local recurrence rate (17%) in those patients having breast conservation, in those randomised to tamoxifen-alone a change of management due to progressive disease was significantly more frequent. The results of this trial indicated that for the first change of management there was an excess of local treatment failure in the conservatively treated patients on tamoxifen alone compared with the surgically treated patients (n=64 vs. n=33). This led to further surgery in 35 vs 15 patients respectively ($p<0.001$). Figure 1 of the published document in Appendix 1 shows that most changes of management occurred in the first 12 months from randomisation.

2.10 Other key findings from Study 1

Quality of Life Evaluation: Postoperative quality of life was assessed by the General Health Questionnaire 28 (GHQ-28) at one year after treatment. There was no difference in the quality of life between the two arms in this trial.

Tumour Response: Of those patients receiving tamoxifen alone, the best ever tumour response was complete remission in one third and a partial remission or no change in almost two thirds. However 12% of patients in this group had tumour progression at six months and 6% at the best ever assessment. Ten patients in the surgically treated group did not undergo surgery, eight because they declined an operation post randomisation.

Interim Conclusion: Analysis was by intention to treat[61] and showed no difference in survival at three years. It was therefore concluded that there was no disadvantage to initial primary treatment with tamoxifen-alone although 20% of women eventually progressed to surgery.

2.11 Other UK tamoxifen trials

The other two UK tamoxifen trials found no differences in overall survival at a median follow-up of two[64] or three years[65]. However these trials came to different conclusions: that tamoxifen[65] or an untested combination of mastectomy plus tamoxifen[64] was the best option. The Nottingham group subsequently carried out a second trial confined to patients who were ER-positive[66]. Although this reduced tumour progression on tamoxifen-alone from 26% in the first trial to 3% there was no difference in overall survival compared with surgery alone at five years. It should be noted that ER status was not taken into account in

the early trials since the test was not widely available at that time but the proportion of ER positive cases rises with age as does the level of oestrogen receptor expression[67].

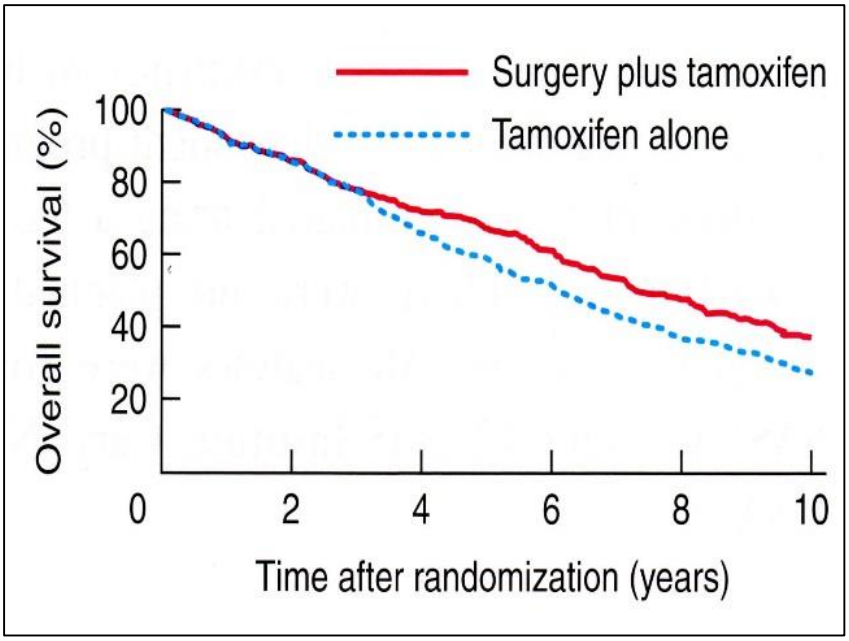
2.12 Study 2 (Appendix 2)

Late follow-up of a randomised trial of surgery plus tamoxifen versus tamoxifen alone in women over 70 with operable breast cancer. Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M. Late follow-up of a randomised trial of surgery plus tamoxifen versus tamoxifen alone in women over 70 with operable breast cancer. Br J Surg 2004; 91: 699-704

In view of the short three year follow-up of our CRC study it was decided to carry out a late review of overall survival at a median of 12.7 years[68]. A final analysis was undertaken on the complete trial dataset where 455 patients from 27 hospitals were randomised between 1984 and 1991. These patients were followed up for a median of 12.7 years. As in the earlier analysis there was an early and marked separation of the progression-free survival curves with the maximum event rate now extending to the first two years of follow-up (Figure 2, Appendix 2[68]). A total of 40% patients in the tamoxifen alone group had subsequent surgery for local disease progression. 14 patients randomised to surgery rejected the allocation and received tamoxifen alone. Three patients allocated to tamoxifen alone elected to have surgery. Statistical analysis was by intention to treat and not by treatment received.

Survival analysis. Both the overall and cancer specific survival rates were significantly prolonged in the surgical group shown in Figure 3 (Figure 3, Appendix 2[68]). The survival curves did not separate for the first three years, which has since led to conjecture as to the possible cause. The overall mortality was increased in the tamoxifen alone group, Hazard ratio (HR) 1.29 (95% CI 1.04, 1.59) and in the cancer specific mortality HR 1.68 (95% CI 1.15, 2.47). It is possible that there may be a bias in the latter analysis since the tamoxifen alone group are more likely to have a residual local tumour at the time of death and to be certified as having died of breast cancer. There was a clinically significant difference in 10 year survival rates between groups [surgery 37.7% (95% CI 31.2, 44.2) vs. tamoxifen alone 28.8% (95% CI 22.9, 34.8].

Figure 3 - Overall mortality in 455 women aged over 70 years with breast cancer



2.13 Other UK Tamoxifen trials: long-term follow-up

The long-term results of the St George's[69] and Nottingham[70] studies were subsequently published with a median follow-up of six and twelve years respectively. Two European RCT's with long term follow-up were published in 2003[71,72] and although both showed an increased tumour progression in the tamoxifen-alone group, neither found any difference in overall survival at seven and ten years respectively. The CRC study is the only RCT to show a significant overall survival advantage from surgery in addition to tamoxifen in this age group.

2.14 Strengths of the study

This was the first UK multicentre trial which compared tamoxifen only with tamoxifen and surgery. The trial was of high methodological quality whereby participants were randomised using a computer generated randomisation programme and allocation prior to informed consent and confirmation of eligibility was concealed by a central secretariat within the trial centre. Recruitment to the trial was good and met the required sample size. Long-term follow-up was conducted and provided evidence of outcome 12.7 years after randomisation. An additional strength was that the analysis was conducted by intention to treat.

2.15 Weaknesses

Participant ER status was not available even in retrospect, so that circa 10-15% of patients with ER negative tumours were unlikely to have benefitted from tamoxifen[54]. Protocol failure to prescribe post-operative radiotherapy for those patients who had conservative surgery led to a high level of local recurrence. Furthermore, there was increasing difficulty in achieving informed consent so that this trial did not include all eligible patients.

2.16 Contribution to wider evidence base

All the randomised tamoxifen trials were included within a Cochrane review and meta-analysis[73] which found that although the combination of surgery plus tamoxifen gave a highly significant advantage to progression-free survival, the overall survival advantage did not reach statistical significance [HR 0.86, 95% CI 0.73,1.00; p=0.06]. However our CRC Trial[68] is the only RCT to demonstrate a significant overall survival benefit from surgery plus tamoxifen in the long term and it made a significant contribution to the conclusion of the meta-analysis and Cochrane review.

The Cochrane review authors nevertheless concluded that primary endocrine therapy should only be offered to patients who are unfit or refuse surgery[73]. [Comment: Inevitably this begs the question as to how fitness and refusal should best be assessed. These issues are subsequently considered in the Discussion.]

Chapter 3 – Variations in management of screen-detected breast cancer

This chapter presents one paper on the variation in management of screen-detected breast cancers in women and its contribution as a fore-runner to the present national audit. Issues relating to screening and management of women by age are considered. Firstly, a brief introduction to breast screening is presented.

3.1 Breast Screening Programme

The NHS breast screening programme[74], introduced in 1988, was initially offered to women from the age of 50 to 64 and although this has been extended to age 70 and in some regions to age 74, older women have always been allowed to self-refer. There has been continuing controversy over the NHS Breast Screening Programme fuelled by the work of Peter Gotzsche[75] and supported by Michael Baum[76]. The main criticisms of the programme are that the benefits from breast screening have been exaggerated and the harms of over-diagnosis largely ignored. This situation has been compounded by the failure of the letter of invitation to screening and the accompanying information leaflet to give an honest account of the benefits and risks of harm. However, the public anxiety regarding the appropriateness of the screening programme led to the setting up of an Independent Review chaired by Sir Michael Marmot in 2013[2].

3.2 Independent Review: The Marmot Report

Having considered all the available evidence the Review panel found that the six evaluable estimates of the number of women that needed to be screened in order to save one life varied between 113[77] and 2,000[75]. The disparities depended largely on the age groups considered and the length of follow-up but the panel's final conclusion lay towards the smaller number at 180 women that needed to be screened. It was acknowledged that the risk of over-diagnosis, that a woman may be treated for an invasive or in-situ breast cancer that would not become apparent in her lifetime was very real and that although the estimate of that risk was very provisional, their best estimate was that 19% of the cancers diagnosed during the screening programme were over-diagnosed. The panel concluded that on the balance of benefit and harm any excess mortality from over-diagnosis would be small and considerably outweighed by the benefits of treatment. The screening programme delivers a 20% reduction in breast cancer mortality in the UK and prevents 1,300 breast cancer deaths a year[2].

The panel also concluded that the impact of screening outside the ages 50-69 was very uncertain and supported the ongoing randomised trials of inviting women aged under 50 and over 70, although the ethics of these trials have been challenged[78]. Inevitably criticism

has not been silenced and for older women in particular the risks of over-diagnosis would seem to increase with advancing years[77,79-82]. On the other hand, screening young women who are at high risk would seem to have a sound basis[83]. It is very likely that population screening for genetic defects will become more common but this has not so far yielded any major advance[84].

3.3 Study 3 (Appendix 3)

Variations in management of small invasive breast cancers detected on screening in the former South Thames East Region: observational study. Moritz S, Bates T, Henderson S, Humphreys S, Michell MJ. BMJ 1997; 315: 1266-72

Historically, patients presented to surgeons with a palpable lump in the breast but the screening programme diagnosed a high proportion of tumours which were impalpable. The practical problems which this presented only came to light with the introduction of breast screening. It soon became apparent that there were considerable variations in the treatment of breast cancer when for the first time there was a move to record the treatment that each patient received in the expectation that there should be a considerable degree of uniformity. One of the first hurdles to address was the ownership of the data which was often regarded as the personal property of individual consultant surgeons who were not accustomed to being audited and still less to having their judgment questioned. As the Surgical Coordinator for the former South East Thames Region it became apparent that to get the agreement of one's surgical colleagues to release their patient data required some tact but also a change of culture. This was only the start of the process to try and achieve some degree of uniformity in the treatment of similar patients.

This paper reports a surgical audit of the management of patients with screen-detected breast cancer in the South East Region. This was one of the first regional audits to investigate surgical management of screen-detected breast cancers.

3.4 Key Messages from this study:

- In the South East Thames Region, the mastectomy rate varied between surgeons. Surgeons with higher caseloads tended to be more conservative, but the wide variation in clinical practice was not related to caseload.
- The use of adjuvant tamoxifen in postmenopausal women with invasive breast cancer was high (94%) and the use of adjuvant chemotherapy low (2.5%).
- Adjuvant radiotherapy after conservative surgery was omitted in one in five cases, but the omission was not related to risk factors for local recurrence.

- A weekly multidisciplinary meeting is an important safeguard to ensure optimal treatment, and any MDT should include a radiotherapist or an oncologist. (Now designated clinical and medical oncologist respectively).
- When benefit has already been clearly established, treatment should be guided by evidence based protocols and audited by regular site visits.

This early study addressed the variation in operation rates and adjuvant therapy in women with screen-detected breast cancer. These variations subsequently became apparent with audits of the management of patients who presented symptomatically[85]. These audits revealed major variations in the management of older women with symptomatic breast cancer which soon became apparent in screen-detected patients. This is an on-going problem which is highlighted in the current audit for 2012/2013[86].

These age-related and other variations continue to a lesser extent despite the constant attention and active intervention of an intensive and ongoing national Quality Assurance Reference Centres (QARC) network which was introduced with the screening programme.

3.5 Strengths

With the advent of the NHS Breast Screening Programme (NHSBSP) consultant breast surgeons were for the first time required to produce their patient data for audit. They were expected to meet published Guidelines for the management of screen-detected breast cancer. The weaknesses of some aspects of the Guidelines then current were identified, in particular the absence of oncologists from the multi-disciplinary team and the failure to recommend radiotherapy after conservative surgery. This audit highlighted seemingly illogical variations in clinical practice between surgeons which did not match the severity of casemix with the adjuvant treatment.

3.6 Weaknesses

The data quality was not as robust as it would be now but care was taken to ensure that adjuvant treatment “not given” was correct and not in fact “given but not recorded”. This has been an on-going problem for the National Screening audit. Although these data had been presented at the annual regional breast audit meeting several surgeons complained that they had not given their permission or been consulted. Note the published Conflict of interest. Although there is now a more general acceptance that patient care should be monitored and guided by a multi-disciplinary team to agreed standards rather than by an individual clinician, significant variations in treatment with surgery, radiotherapy and adjuvant hormone and chemotherapy are still not unusual at both a local and regional level[86].

3.7 Overall Contribution

What did this study add?

This Regional audit was a forerunner of the national annual audit of the NHSBSP first published for 1996/1997 and presented to the Annual Meeting of the Breast Group of BASO (now the Association of Breast Surgery). This is now an annual event and publication; there are increasingly prescriptive Key Performance Indicators[86]. Regional Coordinators with responsibility for units with outlier data are publicly held to account. The publication of the Key Messages in the BMJ raised the profile of this study.

Chapter 4 - Variations in management of symptomatic breast cancer

4.1 Study 4 (Appendix 4)

Clinical outcome data for symptomatic breast cancer: the breast cancer clinical outcome measures (BCCOM) Project. Bates T, Kearins O, Monypenny I, Lagord C, Lawrence G. Br J Cancer 2009; 101(4): 395-402.

This study[85] documents the first national audit of the management of breast cancer which presented symptomatically (as opposed to screen-detected breast cancer). There were major variations in clinical management with age and in data capture and recording by Regional Cancer Registries. There were also professional problems in the validation and release of clinical audit data.

4.2 Background to national data collection

Despite the initial difficulties with data collection for screen-detected breast cancers referred to in Chapter 3, there was a dedicated computer programme which was funded at the outset by the NHSBSP in c1988 and data collection was supported by the QARCs. Although an annual national audit of the screening programme had become well established by 1998, it became increasingly apparent that it was not possible to audit the majority of breast cancers (80%) which were not screen-detected but mostly presented to general practitioners with symptoms. There was no database on which to collect the data since an early database initially funded by industry collapsed. In 2000 the Association of Breast Surgery (ABS) started a national data collection for symptomatic breast cancer, but this depended on the enthusiasm of units with good independent databases and was unfunded, with the result that only a third of the estimated cases were documented.

Involvement of the Cancer Registries. In 2003 there was a move to use the Regional Cancer Registries as the primary resource for symptomatic breast cancer data but it became apparent that written permission of individual clinicians was required for the release of identifiable patient data and that anonymised data might be difficult to process. There was also concern that data held by some Registries might be less than complete or accurate.

Surrogate Key Performance Indicators: The outcome of suboptimal breast cancer treatment may take several years to become apparent and for this reason a series of surrogate key performance indicators was set up to indicate what was considered best practice by what became known as the Breast Cancer Clinical Outcomes Measures (BCCOM) Group.

Table 1 Surrogate clinical outcome measures for breast cancer proposed by the BCCOM Project Team

Proposed surrogate clinical outcome measures
1. Number and proportion of breast cancers for which complete information is received
2. Number of symptomatic and screen-detected breast cancers treated in a hospital per annum
3. Number and proportion of breast cancers for which there is a pre-operative diagnosis
4. Number and proportion of breast cancers given medical treatment only
5. Number and proportion of breast cancers treated surgically
6. Mastectomy rate by size of breast: <15; >=15 and <=20; >20 and <=35; >35 and <=50; >50mm invasive diameter
7. Number and proportion of invasive breast cancers for which nodal status is known
8. Number and proportion of histologically node negative invasive breast cancers for which more than seven nodes were harvested
9. Number and proportion of invasive breast cancers treated by breast conserving surgery and receiving radiotherapy
10. Number and proportion of node positive patients with invasive breast cancers, aged 60 or under, receiving chemotherapy
11. Number and proportion of patients with ER positive invasive breast cancers, receiving hormone therapy

A breast cancer data set was designed after consultation with the ABS and the UK Association of Cancer Registries. The next section will discuss how the surrogate clinical outcome measures listed above, which were considered to represent best practice at the time of the study relate to the findings of the national audit of the management of breast cancer and its documentation.

Surrogate Clinical Outcome Measure Nos. 1 & 2

4.3 Separation of Screen-Detected from Symptomatic Cases

In order to separate the screened from the symptomatic cases the Registries were asked to flag the screen detected cases but compliance was variable and by year three of the study, only 70% of screen-detected cases were identified. The resulting contamination was only apparent from the higher than expected rate of non-invasive ductal carcinoma in situ (DCIS) - 3% for symptomatic cases and 21% for screened cases. This was not the only difficulty in retrieving complete and accurate data from the Registries.

In year 1 (2002): Registry data were sent to individual consultant surgeons for validation but surgical compliance to check or even to accept the data without checking was poor with the result that case ascertainment was far from complete.

In year 2 (2003): compliance with Section 60 of the Health & Social Care Act 2001 required writing to individual surgeons for permission to release the data to the lead breast surgeon in each hospital. Predictably this further reduced the flow of data.

In year 3 (2004): the requesting of permissions (with three exceptions) was transferred from the Cancer Registries to the BCCOM team at the West Midlands Cancer Intelligence Unit (WMCIU). It was then possible to liaise with the ABS secretariat in order to identify unknown surgeons and to encourage compliance as a professional duty. Numbers were reduced by the increasing exclusion of screen detected cases but the Registries gave BCCOM the anonymised total of all new breast cancers so that there was now a reliable denominator.

4.4 Variations of Prognostic Factors and Treatment with Age

4.4.1 Variation of Node status with Age

Node status in patients under 50 years was recorded in 89% but in those aged over 80 this fell to 72%. It was suggested that this difference was largely because the over 80's were less likely to have surgery and the data would not therefore be available. [Comment: However there may also be an element of surgical reluctance to explore the axilla when knowledge of the node status may be perceived to be less important to guide subsequent adjuvant therapy and to indicate prognosis[87].]

Table 2 (see Appendix 6) - Variation of the Nottingham Prognostic Index[88,89] (NPI) with Age (Extrapolated from Figure 3, Appendix 4[85])

Nottingham Prognostic Index Group compared with Age					
NPI Group	<50	50-59	60-69	70-79	80+
PPG (Poor)	25.5%	23.5%	22.4%	22.2%	22.4%
EPG + GPG (Good/Excellent)	22.1%	25.2%	28.2%	27.3%	28.0%

PPG: Poor Prognosis Group, EPG: Excellent Prognostic Group, GPG: Good Prognostic Group (Appendix 6)

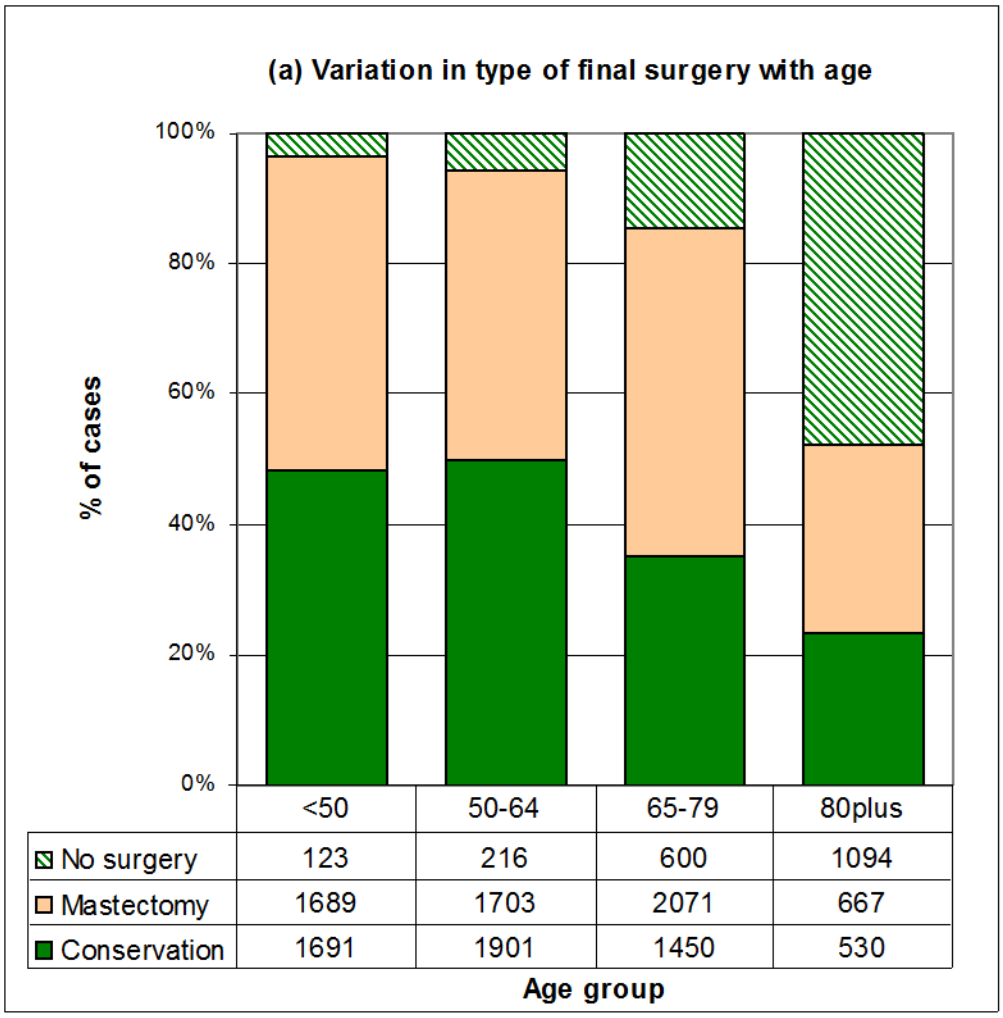
Interpretation: Women aged 60 and over have marginally better prognostic tumours than younger women. There is a possible bias in interpreting this analysis in that the higher proportion of unoperated cases which were excluded in women aged 8o and over may have excluded larger tumours. However size has only a small effect on the NPI (Appendix 6).

Comment: The apparent excess of Poor Prognosis Group tumours in women aged 70 or over with screen-detected tumours seen in Figure 3 of Appendix 4[85] may be explained by the presence of symptomatic women who are able to self-refer at this age.

4.4.2 Variation in Surgical Treatment with Age

The proportion of women with breast cancer who did not receive surgery increased with age from 3.5% in women aged less than 50 years, to 48% in women aged 80 or more.

Figure 4 - Variation in surgical treatment with age - year 3, 2004. (Revised from Figure 5 Bates et al 2009 Appendix 4))



The proportion of women having conservative surgery rather than a mastectomy for breast cancer fell from 51% in those younger than 65 years, to 42% in those aged 65 or more. This variation was most marked in Wales (54% vs 26%).

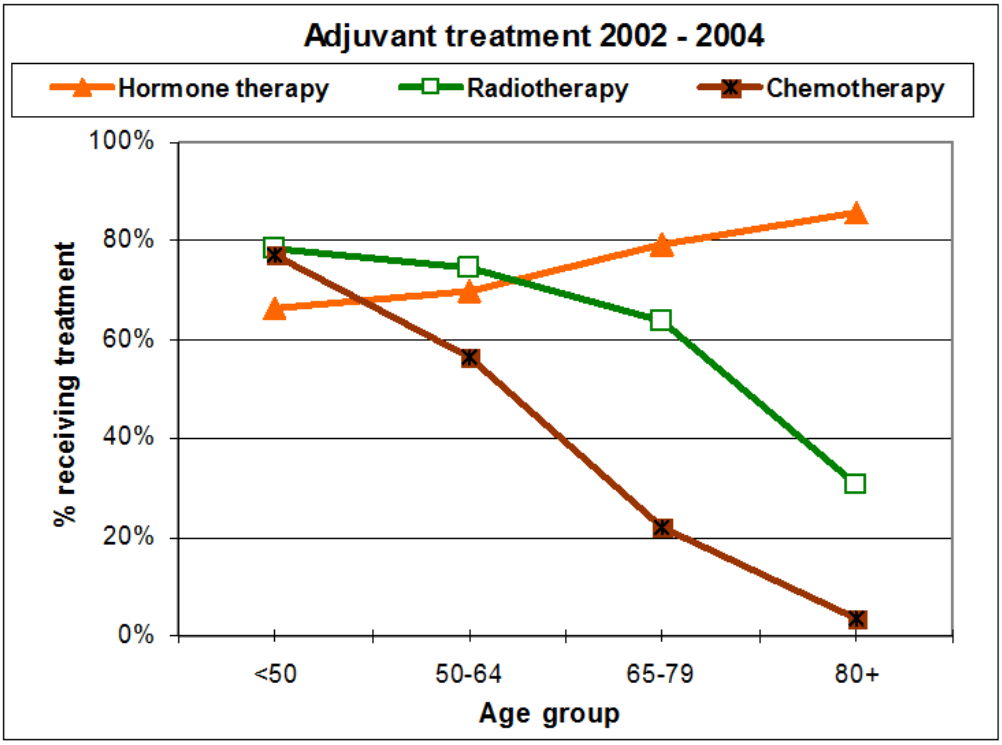
Comment: The high proportion of older women not having surgery for operable breast cancer has subsequently been the subject of much criticism[90-92]. The reduced rate of conservative surgery in older women may be related to the recommendation for post-operative radiotherapy. (See below).

4.4.3 Variation in Adjuvant Treatment with age

Surrogate Clinical Outcome Measure Nos. 9, 10 & 11.

Figure 5 - Variation in adjuvant Treatment with age at diagnosis, 2002-2004

(Figure 7 Extracted from Bates et al 2009, Appendix 4)



With increasing age, the use of adjuvant Hormone therapy gradually increased but adjuvant treatment with Radiotherapy and Chemotherapy rapidly declined (see below).

4.4.4 Variation in Hormone Therapy with Age

Surrogate Clinical Outcome Measure Nos. 4 & 11. (Figure 5)

Data on the proportion of women who received hormone therapy either as adjuvant therapy or as the sole primary treatment of operable breast cancer were seriously inadequate. Similarly knowledge of the oestrogen receptor (ER) status and the correlation with hormone therapy was sparse[54]. Of 5,112 women who did not undergo surgery, 61% were recorded as receiving hormone therapy but in only 43% was the ER status known.

Comment: The form of hormone therapy was not recorded but in 2002-2004 this is likely to have been tamoxifen in the majority of cases.

4.4.5 Variation in Radiotherapy with Age

The recorded use of radiotherapy decreased with age (Figure 5). Of those aged under 50 years, 78% received radiotherapy compared with only 31% of those aged over 80. For those women who had conservative surgery, in those aged under 50 years 70% received post-operative radiotherapy but this decreased to 43% in those aged 80 or above. In the three year period 2002-2004 radiotherapy post conservative surgery was recorded in 69% women but was not given in 7%. There was no record of such patients receiving post-operative radiotherapy in 24% cases.

Comment: It is now well recognised that failure to give radiotherapy after conservative surgery leads to an unacceptably high rate of local recurrence[93-95]. It is of concern that many older women were put at risk by this omission but also that in a quarter of cases the use of radiotherapy was unknown. The high mastectomy rate in older women in Wales may be related to the rural population and the longer travelling times/distances to radiotherapy facilities which may discourage some patients, especially the elderly from having conservative surgery. This rationale has been disputed but similar trends have been reported from rural populations in Australia[96] and the Netherlands[97].

4.4.6 Variation in Chemotherapy with Age

The proportion of women with node positive disease who had adjuvant chemotherapy, in those under the age of 70 was 68% but in those aged 70 or over this was only 12%. For those under 50 years of age c78% received chemotherapy and Figure 5 (Figure 7 of Appendix 4[85]) shows a progressive reduction in the use of chemotherapy for each age decile thereafter.

Comment: The EBCCTG's meta-analyses show a clear survival benefit from adjuvant chemotherapy in both node positive and negative women [98]. It is again of concern that in a quarter of cases this therapy is unknown or unrecorded.

4.4.7 Variation in Pre-operative diagnosis*

Surrogate Clinical Outcome Measure No. 3

*This is now described as non-operative diagnosis.

A pre-operative diagnosis of invasive breast carcinoma by Fine Needle Aspiration Cytology or preferably by core biopsy, greatly enhances the planning of any further investigations such as axillary ultrasound, with or without a biopsy. Confirmation of malignancy by open

excisional biopsy is therefore kept to a minimum which enables the treatment options to be discussed with the patient before any surgery is carried out. The guideline for a pre-operative diagnosis of invasive breast cancers in 1998 was >70% and by 2004 was 90%. The current guideline is for a minimum standard of 90% non-operative diagnosis with a Target Standard of 95%.

The stated pre-operative diagnosis rate in the West Midlands was 87% but in four regions it was 40% or less and in Scotland only 12%. However it seems that most Cancer Registries at that time only recorded the histology of resection specimens and not cytology or even core biopsies.

4.4.8 Variation in Recruitment of cases with Registry and Clinical Compliance

Wales submitted the highest proportion of eligible cases at 94% in year three (2004) but Thames which is the largest Registry gave only 29% cases (Table 2, Appendix 4). In 54% cases the surgeon was non-compliant in submitting data on request or was unknown.

4.4.9 Variation in Mastectomy rates by Region

Surrogate Clinical Outcome Measure Nos. 5 & 6

Where surgery was carried out and the details are known, the mastectomy rate for the whole cohort was 52.4% compared with 47.6% who had conservative surgery (Table 4, Appendix 4). The proportion of women with the smallest tumours, <15mm having known mastectomy varied by Region from 25% in Oxford to 42% in Trent (Figure 6, Appendix 4). The mastectomy rates for the larger size bands are not available. Comment: The stated mastectomy rates for Northern Ireland, 19% and North West Region, 23% include a large proportion of unoperated or unknown cases. Where the surgery was known the mastectomy rates were 31% and 33% respectively.

The Erratum for Figure 6 (Appendix 4) published in Br J Cancer 2009; 101(6): 1032 refers to the Title of the Figure which originally stated that the data were for year three (cancers diagnosed in 2004). The Corrigendum corrects the Title to state that the data apply to years one - three (cancers diagnosed in 2002-2004). The data in the Figure are unchanged.

4.4.10 Variation in Prognostic Factors and Pathology Reporting Nodal Status

Surrogate Clinical Outcome Measure No. 7

The overall rate of positive nodes was 32% where the denominator included unknown and unoperated cases. The stated node +ve rate for operated cases was 40.5%, but if the unknown cases (14%) are excluded the actual rate was 47% (Table 4 / Figure 2, Appendix 4).

The high rate of unknown data items where the patient had been operated on may be partly explained by the understandable reluctance of some pathologists to record the node status

where the patient had received preoperative neoadjuvant chemotherapy or radiotherapy. The concern that this might under-stage the patient is also reflected by a higher than expected rate of unknown values for tumour size and grade and of a calculated value for the NPI.

4.5 The number of Nodes removed in a negative axillary sample – 8 or more nodes

Surrogate Clinical Outcome Measure No. 8

The number of cases in which eight or more nodes were removed from a negative axilla is shown in Figure 4 (Appendix 4). In those patients who had conservative surgery this was found in the majority. Following the publication of the Z 11[99] and the more recent Amaros Trial[100] it seems inevitable that practice will change with the evidence from these two randomised trials of node positive disease that where the tumour burden is low there is no advantage from radical axillary lymph node clearance. ASCO has now published a Clinical Practice Guideline Update[101] which states that "Women with one or two metastatic SLNs planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo Axillary Lymph Node Dissection (ALND) (in most cases)".

Comment: There is increasing awareness that extensive axillary dissection leads to a high risk of lymphoedema[102] and following the subsequent introduction of sentinel node biopsy (SLNB) with a much reduced number of nodes sampled from a node negative axilla, the incidence of lymphoedema is likely to be reduced[103] although this finding has not been confirmed. The recently advice from ASCO is certain to accelerate change of practice and although the Guideline is not specific to older women it will benefit this age group as well.

Histological type: The data were as expected although it was noted that the incidence of DCIS at 5% indicated that there was still some contamination with screen detected cases.

Tumour size: For surgically treated cases the invasive tumour size was unrecorded in 7% which would be largely explained by neoadjuvant therapy. Any association between tumour size and age was not stated.

Tumour grade: The spread of tumour grades was as expected, G1: 13%, G2: 48%, G3: 40%. There was a clear association between tumour size, grade and node status shown in Table 3 (Table 4, Figure 2, Appendix 4 [85])

Table 3 - Correlation of tumour size, grade and node status

Grade	1	2	3
Nodes Positive	29%	47%	54%
Size >5cm	3%	8%	10%

Any association between tumour grade and age was not stated.

4.6 Completeness of Regional Records

Surrogate Clinical Outcome Measure Nos. 1 & 2

The shortfall in data collection, or those data which were retrievable, has been highlighted in each section of this audit. The main shortfall has been the amount and accuracy of data items held by individual Cancer Registries of which the Thames Region was the largest and most conspicuous outlier (Table 2, Appendix 4[85)]. The use of surrogate measures to reflect compliance with best practice produced valuable data on current practice with the exception of Measures 1 & 2 where the requirement for written permission for the release of individual patient data severely restricted access to data. However much of the shortfall of data stemmed from the reluctance of some surgeons to verify the data held on their patients.

The voluntary release of data "has been a prerequisite of the BCCOM audit to date, (and) it seems clear that the collection of cases will not approach completeness on this basis". Comment: The recent government requirement that the results of individual surgeons should be published and the need to document clinical practice for annual appraisal and subsequent revalidation has transformed the situation. However the management of an individual patient with breast cancer often involves care given by several professionals and sometimes by more than one surgeon.

4.7 Variation in the management of Breast cancer in the UK

There are still major variations in the management of breast cancer in the UK[104] which may also affect outcome; variations in mastectomy rates, in the use of adjuvant therapy and with the management of older patients. Such variations colloquially known as a "Postcode Lottery" may affect the management of breast cancer at every point in the patient's journey and have sometimes depended upon the decision of a clinician, which may be idiosyncratic rather than evidence based.

4.8 Strengths

This audit documented for the first time the extent and shortfall of retrievable data on the management of symptomatic breast cancer from Regional Cancer Registries in the UK in 2002-2004. It also documents the extent of the reluctance of surgeons to validate and release data for audit on patients under their care. The audit set up a series of surrogate measures to reflect best practice at the time. Having indicated the expected surrogate outcome measures the audit was able to document variations from best practice.

4.9 Weaknesses

The surrogate measures did not include important criteria for best practice for which data were not available at that time e.g. reconstruction post-mastectomy, quality of life measures and patient reported outcome measures (PROMS). The large proportion of unrecorded data items retrievable from most UK Cancer Registries. Finally, another weakness is the lack of any statistical analysis.

4.10 Overall Contribution

Key messages for Chapter 4:-

- First UK national audit of surgical practice for symptomatic breast cancer.
- Overall findings included identification of variation in surgical participation for the release of data by UK region from 29% to 94%.
- Poor quality data reporting includes the challenge of missing data.
- Variation by age:
    - Reduced surgical treatment.
    - Reduced use of adjuvant therapy.
    - Reduced identification of axillary node status.
    - National study identified major regional differences in treatment by age.

This was a wake-up call to the Cancer Registries and the breast surgical community to agree a common process and to improve overall reporting and data quality. It was acknowledged that patient data does not belong to an individual surgeon and that there is a professional responsibility that this should be validated and be made available for audit and research within appropriate safeguards. Finally, this was the forerunner to the regular National audit of symptomatic breast cancer.

Chapter 5 - Variation in Operation Rates for Breast Cancer with Age, Comorbidity, Ethnicity, Socio-economic status, Screening status and Prognostic Factors

5.1 Study 5 (Appendix 5)

A Population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: Failure to operate for early breast cancer in older women. Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. Eur J Surg Oncol. 2014; 40: 1230-1236.

This study[21] expanded on the 2007 data published in the Second All Breast Cancer Report[105], in particular it evaluated comorbidity data using Hospital Episode Statistics (HES) data for England. Cancer statistics for England are now reported separately since the other countries in the UK capture and report social deprivation status using different methods. At this time, comorbidity data were only available for England.

5.2 Comorbidity Assessment Scales

There are several assessment scales of comorbidity which have been reviewed by Stotter[106] who, having trialled the Satariano Index[107], settled on the validated Charlson Comorbidity Index (CCI)[108]. The CCI has been criticised as being potentially biased towards cancer comorbidity[109] and for this reason all cancer diagnoses were removed from the modified version[110] in the current study. There are several population studies of comorbidity with age and these suggest that even where it was possible to calculate the CCI in the very elderly, that the HES data under-record the true incidence of comorbidity [111-113]. The CCI was not available for 9% of those under the age of 80 but in those aged 80 or over there was no HES record in 22% which will largely include those who were not operated on and had not therefore had a hospital admission. It seems very probable that this group will have had a higher degree of comorbidity.

5.3 Variation in Operation Rates with Comorbidities

Variation in operation rates and in comorbidities with age are shown in Table 4 and Figure 6 (Figure 1, Appendix 5[21]) and in the Supplementary Data (Table 4[21]).

Table 4 - Supplementary Data: Correlation between Charlson Comorbidity Index (CCI) and No Surgical Treatment

Age	CCI=0	CCI=1	CCI=2	CCI ≥ 3	CCI 2+	Surgery	No Surgery	Not Surgically treated
17-24	17	3	0	0	0%	21	1	5%
25-29	111	8	1	0	1%	114	16	12%
30-34	353	22	2	0	1%	370	46	11%
35-39	999	54	9	2	1%	1044	112	10%
40-44	1901	153	14	3	1%	2079	223	10%
45-49	2609	229	42	8	2%	2907	285	9%
50-54	3263	327	51	22	2%	3720	282	7%
55-59	3320	412	87	21	3%	3917	320	8%
60-64	3845	598	125	41	4%	4629	402	8%
65-69	3388	639	155	72	5%	4125	429	9%
70-74	2236	492	163	72	8%	2698	531	16%
75-79	2108	554	188	106	10%	2410	905	27%
80-84	1559	376	170	103	12%	1471	1211	45%
85-89	960	237	131	91	16%	639	1225	66%
90+	443	110	72	40	17%	174	807	82%

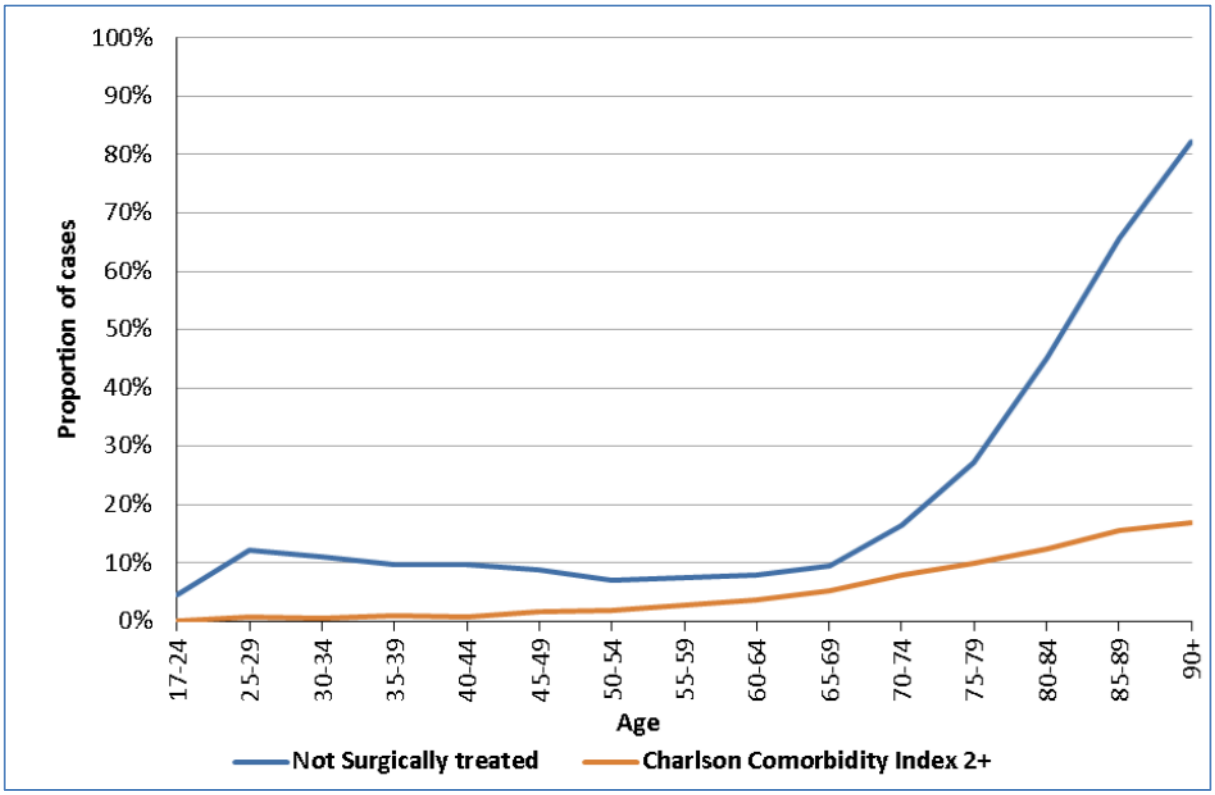
CCI = Charlson Comorbidity Index

Modified CCI comorbidity scores were scored 1,2,3 and 6 depending on risk from death[110]. The comorbidity values were obtained from HES data for each patient based upon the previous 18 months of hospital admissions prior to cancer diagnosis, up to and including the date of diagnosis. The score reflects a sum of each comorbidity score diagnosed.

5.4 Failure to operate

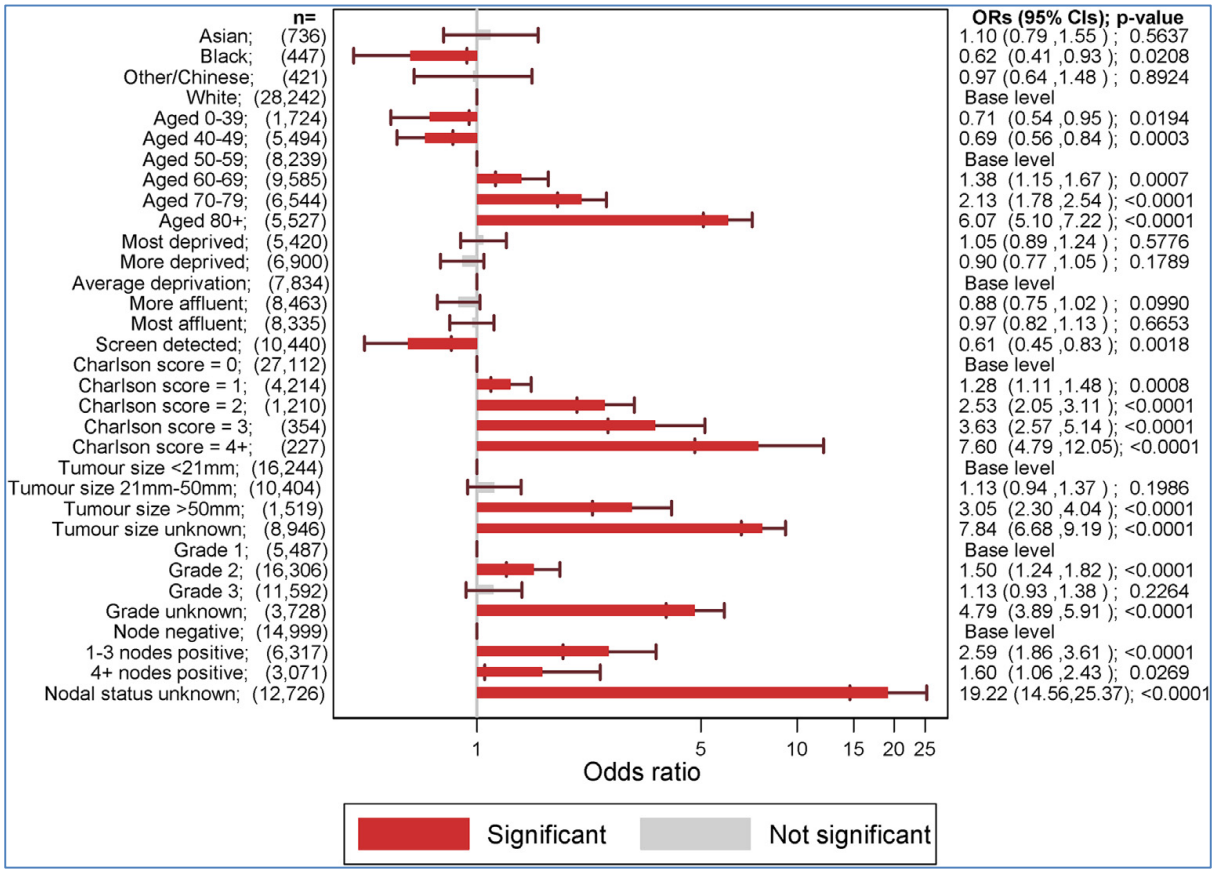
Variation with age: the proportion of women aged 35 or over not having surgery for breast cancer up to the age of 70 varied between 7% & 10% but thereafter rose steadily by 3.1% per year of age to reach 82% in those aged 90 or over: Figure 6 (Figure 2, Appendix 5[21]).

Figure 6 - Variation in operation rates for breast cancer with age and the proportion of women with a Charlson Comorbidity Index (CCI) of 2 or more



The factors which affect the likelihood of not having a surgical operation for breast cancer are shown in Figure 7 (Figure 2, Appendix 5[21])

Figure 7 - Factors associated with not having a breast cancer operation (odds ratio, 95% CI)



The likelihood of not having an operation rose progressively with an increasing CCI score. The odds ratios taken from Figure 7 are for a CCI score of 1: OR 1.28 (95% CI 1.11, 1.48), CCI 2: OR 2.53 (95% CI 2.05, 3.11), CCI 3: OR 3.63 (95% CI 2.57, 5.14) and for CCI 4+: OR 7.6 (95% CI 4.79, 12.05)

5.5 Variation with Ethnicity

Women of all non-white ethnic groups were more likely to present with poor prognosis PPG breast cancer (Table 3, Appendix 5[21]) and women of Asian or black ethnicity were less likely to present with tumours of good prognosis EXG/GPG or small tumours (Tables 1&2, Appendix 5[21]). This finding is not unexpected especially with respect to black women, OR 0.36 (95% CI 0.25, 0.53) p<0.001[22,114,115]. However black women were more likely to have had an operation in the present study: Figure 7 (Figure 2, Appendix 5[21]). Ethnic differences in survival are confounded but not wholly explained by socio-economic status[23,116].

5.6 Variation with Socio-economic status

As expected, women from the more and most deprived cohorts were less likely to present with a good prognosis breast cancer (Table 1, Appendix 5[21]) and the most deprived were less likely to have small tumours (Table 2, Appendix 5[21]). However there was no variation in operation rates by socio-economic status shown in Figure 7 (Figure 2, Appendix 5[21]). The American Surveillance, Epidemiology and End Results (SEER) data up to 2005 do not suggest failure to operate for breast cancer due to socio-economic/ethnic factors, but failure to give radiotherapy after conservative surgery is clear[94,95].

5.7 Variation with Screen Detected cases

As expected the screen detected cases were more likely to have presented with uniformly favourable features; good prognosis tumours: OR 4.78 (95% CI 4.43, 5.16), small tumours: OR 3.96 (95% CI 3.69, 4.24), and less likely to have poor prognosis tumour: OR 0.2 (95% CI 0.18, 0.22) and less likely to not have an operation: OR 0.61 (95% CI 0.45, 0.83).

5.8 Prognosis

Although we have used the extremes of the Nottingham Prognostic Index (NPI) as two of the four criteria to indicate a good or a poor prognosis it should be appreciated that the NPI has not been validated for women aged over 70 in either the UK cohort[117] or the extensive European Oncopool Study[118] since Blamey excluded this age group "because treatment was not always operative, axillary status was not established in all, adjuvant systemic therapies were frequently not applied and to avoid the confounding factor of high mortality from causes other than breast cancer".

In considering prognosis, Voogd et al[119] point out that international comparisons of cancer survival such as the EUROCARE studies may be confounded by variations in the proportion of death certificate only (DCO) registrations, where there has been a prior failure of case ascertainment. The Thames Region reported 24% of cancer cases as DCOs in 1987-1989 which were positively associated with increasing age[120]. Although this rate subsequently improved the high rate of DCO cases was initially responsible for a significant difference in unadjusted survival rates compared with the Finnish Cancer Registries data which were largely complete[121].

5.9 Variation with Prognostic Factors

Variation with tumour size: women with tumours greater than 5cm in diameter were less likely to have an operation, as were those where the tumour size was unknown – because the tumour was un-operated. Variation with tumour grade and node status: women with tumours of grade 2 versus grade 1 were less likely to have an operation as were those who were node positive versus node negative. As with tumour size, surgery was unlikely where the grade or node status was unknown.

5.10 Discussion

The current NICE Guidance (2009) recommends that clinicians treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy rather than endocrine therapy alone, unless significant morbidity precludes surgery[122]. However there are many reports which document the reduced rate of surgical treatment for breast cancer with advancing age but the extent to which this is related to increasing comorbidity is considered in the Discussion[21], pp 1132s-5 and in a review of 18 international studies[123]. There can be no doubt that increasing levels of comorbidity reduce non-cancer and overall survival[124-129] but where there is a reduction of cancer-specific survival this may be related to reduced treatment[130,131]. The question arises as to whether failure to operate is always a real failure or whether this sometimes reflects the patient's well-informed choice? There is a wealth of literature that documents reducing operation rates for operable breast cancer with advancing age with the presumption that patients are being denied optimal treatment on the basis of surgical prejudice[90-92,132,133] and with the recommendation that more appropriate preoperative assessment will lead to better treatment of the elderly[134-138]. On the other hand there are those who express doubts as to whether the elderly are significantly disadvantaged by perceived under-treatment[139-141]. The literature on patient choice as a cause for variation in operation rates in older women is relatively sparse and not conclusive. In a review of patients' records Lavelle et al. concluded that poor health or patient choice did not wholly account for the lack of surgery in patients aged over 85[142]. However others have found in the over 80's that patient choice accounted for a third of those who did not have surgery for operable breast cancer[92,143]. In a cohort of older patients with breast cancer, of those who did not have surgery Tang et al commented, "when offered a genuine choice....most patients chose non-operative treatment"[144]. In a study of an MDT for breast cancer patients, 4.5% did not receive the treatment recommended, of which patient choice was the most common factor and accounted for 42% of discordant treatments[145].

In an audit of a dedicated Multidisciplinary Elderly Breast Cancer Clinic, as to why under-treatment of the elderly with breast cancer was so common, Stotter[106] found that the patient's "frailty was overestimated …… (and their) life expectancy was underestimated". However she acknowledged that the discussion with the patient can be a very slow process and that support of the accompanying person can sometimes create a problem in failing to recognise the patient's wishes and priorities.

The report by the Royal College of Surgeons England, "Access all ages: Assessing the impact of age on access to surgical treatment"[146] spells out the constraints imposed by the Equality Act 2010, which bans age discrimination without strong clinical evidence to justify this. However as well as operation rates by age for breast cancer the examples from a raft of common operations show little difference. The rates for surgery by age for each of these operations show a peak between 70 and 80 and a precipitous decline thereafter. The

Report recommends a geriatric input to MDT's but this would not seem to be a realistic expectation in the near future. Schonberg et al[147] found that most women over 75 just followed the surgeon's recommendation which was the most influential factor affecting their treatment decision. The breast clinician therefore has a considerable responsibility for giving the older woman a balanced view[132], allowing time for her to make a decision and using a basic geriatric screening instrument[138] where appropriate.

5.11 Personal perspective

I feel that consent to treatment of breast cancer should be a process rather than a one-off event and the breast specialist nurse is often an important intermediary in enabling the patient to reach a decision having considered all the reasonable options. The opinion of the multidisciplinary meeting is very important but in the setting of this age group it should ideally be couched in terms of treatment options, albeit with prioritisation rather than as a directive. A Comprehensive Geriatric Assessment should be available when this is appropriate but this will not always be the case in many smaller units. I would agree with the position of the Cochrane Review[73,148] and the current NICE Guidance[122] which conclude that that surgery for the elderly with ER positive breast cancer gives better local control and that primary endocrine therapy should be reserved for patients with significant comorbid disease or who refuse surgery. I would only rephrase the final conclusion – or those who have decided not to have an operation.

5.12 Strengths

- The failure to operate on older women with apparently operable breast cancer to some extent relates to increasing comorbidity in this age group.
- The confounding factors of variations in prognosis and treatment related to socio-economic status, ethnicity, geographical region and breast screening are confirmed.
- By using all available sources the data are more robust than the BCCOM dataset 2004.

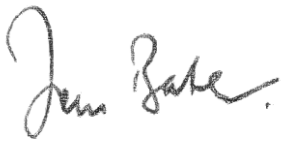
5.13 Weaknesses

- HES Comorbidity data were only available for England.
- HES data are only available for women who have had a hospital admission. In consequence there are no comorbidity data available for most of the women who were not operated on.
- HES data probably under-record the likely number of comorbidities in older women.
- The extent to which patient choice affects the treatment of breast cancer in older women is unresolved.

5.14 Overall contribution

This study documents the incidence of comorbidity of older women with breast cancer, albeit this may be under-recorded or unavailable in those women who were not operated on. The steady rise in the non-operative treatment of breast cancer at 3.1% per year of age from age 70 has not previously been noted. The quality of data from the National Cancer Registration Database has substantially improved on that available to BCCOM for 2002-2004. Finally, the weakness of HES data on comorbidity has been highlighted.

I submit that this body of published work comprises a coherent theme, which examines many of the factors which lead to variation in the management of older patients presenting with potentially operable breast cancer.



Tom Bates

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Appendix 1 Study 1

Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone[61].

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Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone

T. Bates, D. L. Riley, J. Houghton, L. Fallowfield and M. Baum (on behalf of the Elderly Breast Cancer Working Party)

Cancer Research Campaign Clinical Trials Centre, King's College School of Medicine and Dentistry, London, UK

Correspondence to:
Mr T. Bates, The William Harvey Hospital, Ashford TN24 0LZ, UK

Three hundred and eighty-one women with operable breast cancer aged over 70 years were randomly allocated to 40 mg tamoxifen daily and optimal surgery or to tamoxifen alone. At a median follow-up of 34 months there was no demonstrable difference in survival rate or in quality of life between the two treatment groups. More patients treated with tamoxifen alone had a subsequent change of management and this was usually an operation for local treatment failure. This progression to surgery has not been shown to be disadvantageous and the study will continue. Informed consent for randomization was difficult to obtain, leading to the exclusion of eligible patients, and it is therefore proposed to include non-randomized patients in a total cohort study.

The incidence of breast cancer increases with age[1] and a third of new tumours occur in women aged over 70 years[2,3]. Women in this age group have usually been excluded from clinical trials despite expectancy of life at age 70 being 14 years and the increase in the number of elderly women[4].

Current clinical management of elderly women with breast cancer varies. Women with the same stage of disease may be treated in different centres by mastectomy[5,6], by local excision[7] or, more recently, by tamoxifen alone[8–13]. Trials of adjuvant tamoxifen in women undergoing surgery for primary breast cancer have shown a definite survival benefit in postmenopausal women[14]. There is therefore an ethical difficulty in withholding tamoxifen from elderly patients. Evidence from uncontrolled studies shows that tamoxifen is effective as the sole primary treatment of operable breast cancer, and an increasing number of elderly women are treated in this way. It was decided therefore that all patients should have tamoxifen but that one group should undergo the surgical procedure that the surgeon felt best suited to the individual patient.

The premise was that tamoxifen is of value as the sole primary treatment of operable breast cancer in the elderly. The question was whether surgery improves the control of disease, the quality of life or the length of survival.

Patients and methods

The study was a randomized multicentre trial co-ordinated by the Cancer Research Campaign Clinical Trials Centre at King's College Hospital.

All women aged over 70 years with operable breast cancer (diagnosed on Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsy, fine needle aspiration cytology or unequivocal mammography) with normal radiography of the chest, pelvis and lateral lumbar spine were eligible. Exclusions included patients who declined surgery at the outset, those considered unfit for surgery, and those wth Paget's disease, bilateral breast cancer or an impalpable tumour discovered by mammography. Patients were randomly allocated to either surgical or conservative treatment groups.

The surgeon undertook the operation that was considered best for the individual patient (optimal surgery), for example simple excision or mastectomy. The patient received adjuvant tamoxifen, 40 mg daily (either single or divided dose), indefinitely thereafter.

In the conservative group all patients received the same dose of tamoxifen indefinitely and the tumour response was assessed by Union International Contra le Cancrum criteria[15]. Treatment options, including surgery, could change at 6 months or earlier if tumour growth was progressive (≥ 25 per cent increase over initial maximum diameter).

Tumour progression in the conservatively treated group could not be compared with local recurrence in the surgically treated group and the interval to the first change of management was recorded as an indication of primary treatment failure. The length of survival was used as an outcome measure but death from intercurrent disease is common in this age group and difficult to identify[16–18].

Quality of life was assessed in those centres agreeing to the study using a sociodemographic questionnaire and the General Health Questionnaire (GHQ 28 items)[19]. The GHQ-28 was designed for use as a screening instrument to detect psychiatric and social morbidity and a threshold score of five determines dysfunction. Some[20] have suggested that a threshold score of ten is more appropriate in women with breast cancer undergoing cytotoxic chemotherapy. The two self-report questionnaires were sent to patients by post at least 3 months after operation or from the start of medical therapy.

Survival

The majority of patients were 'flagged' at the National Health Service Central Register which provided the trials office with an automatic notification of the death of each patient within about 6 months. In this analysis, therefore, all patients were assumed to be alive at a cut-off date of 31 March 1989 unless a copy of the death certificate had been previously received (for the few patients from Ireland who could not be 'flagged', a cut-off date of 31 December 1988 was selected to provide time for notification of death).

Statistical methods

Comparison of the two groups for both survival rates and time to change of management used standard log rank χ^2 tests.

Results

By 31 July 1989, 381 patients were entered with a median follow-up of 34 months (*Table 1*). Twenty-seven patients were excluded from analysis because they entered after the cut-off date. Ten patients in the surgically treated group did not undergo surgery, eight because they declined and one developed skin secondaries by the time of admission. In one case information is not available. Of these ten patients, seven are still alive, six with no change of management; three have died, two with and one without a change of management.

First change of management: There was an excess of local treatment failure in the conservatively treated group (64 patients) compared with the surgically treated group (33

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Table 1 *Comparison of treatment groups*

	Surgery ($n=171$)	Conservative treatment ($n=183$)
Median age (years)	76·8	76·6
Mean tumour size (cm)	3·5	3·4
Median follow-up (months)	34·8	33

Table 2 *Reasons for first change of management*

	Surgery ($n=171$)*	Conservative treatment ($n=183$)
No operation	10	—
Local recurrence/progression	12 (7·5)	42 (23·0)
Ipsilateral axillary nodes	6 (3·7)	2 (1·1)
Local recurrence/progression with positive axillary nodes	4 (2·5)	7 (3·8)
Distant recurrence	6 (3·7)	6 (3·3)
Other	9 (5·6)	11 (6·0)
Total	33† (20·5)	64† (35·0)

Values in parentheses are percentages. * Percentages in the surgery group are calculated on the 161 patients who had an operation. † Because recurrence occurs concurrently at local and distant sites in some patients, the total number of patients is less than the sum of all the reasons for a change of management

Table 3 *Locoregional recurrence following surgery in 161 assessable patients*

	Surgical group	Local recurrence
Local excision	120	20 (16·7)
Mastectomy	37	1 (2·7)
Quadrantectomy	4	0
Total	161	21* (13·0)

Values in parentheses are percentages. * Excluded from this analysis was one patient whose surgical procedure was not known and nine patients who refused surgery, one of whom now has progressive disease

Table 4 *Tumour response in the conservative group* ($n=183$)

	Percentage of patients responding	
	At 6 months	Best ever
Complete remission	16·1	32·7
Partial remission	9·0	14·6
No change	62·6	46·8
Progression	12·3	5·8
No. of patients not assessable	28	12

patients) (*Table 2*), leading to further surgery in 35 patients and 15 patients respectively, a statistically significant difference ($\chi^2=11{\cdot}35$, $P=0{\cdot}001$) (*Figure 1*). Local recurrence following surgery is detailed for the 161 assessable patients in *Table 3*.

Tumour responses to tamoxifen alone at 6 months and the best ever are shown in *Table 4*.

There was little difference in the mortality rates between the two groups, with 26 deaths in the surgically treated group and 32 in the group on tamoxifen alone (*Figure 2*).

Twenty-three of the 32 clinicians involved used the quality of life assessment questionnaires on their patients. Of 308 women sent questionnaires, 298 were still alive and 237 responded (79·5 per cent compliance). The mean time between operation and questionnaire response was 13·5 months (range 3–33 months) for the medically treated group it was 12 months (range 3–32 months). The two groups were well matched for sociodemographic characteristics (*Table 5*).

Half of the women in each group lived alone. Most were happy living in their current house and the majority felt that they had someone to talk to about any problems. There was no demonstrable difference between the two groups in their ability to manage household tasks. Approximately one-third of all patients experienced significant difficulty. Using the GHQ overall threshold of five, 30 of 117 women (25·6 per cent) in the surgically treated group had problems indicative of the psychiatric morbidity compared with 33 of 120 (27·5 per cent) women in the other group (*Figure 3*). Using the threshold of ten, the respective numbers of women were 17 (14·5 per cent) and 21 (17·5 per cent). The GHQ-28 contains four subscales for physical malaise, anxiety, social dysfunction and depression but there was no significant difference in the psychosocial morbidity between the two groups.

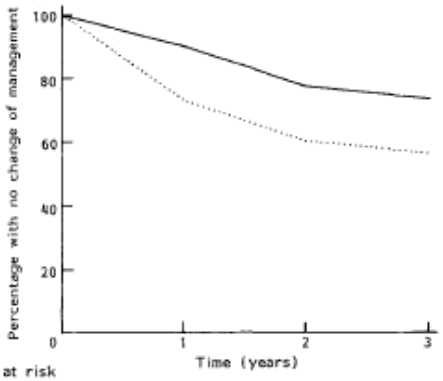

Figure 1 *Log rank comparison of time to first change of management ($\chi^2=11{\cdot}35$, $P<0{\cdot}001$, relative risk = 0·50, 95 per cent confidence interval 0·33–0·75); (——), surgery; (·····), conservative treatment. 'Numbers at risk' represent the number of patients with no change of management at entry and annually thereafter*

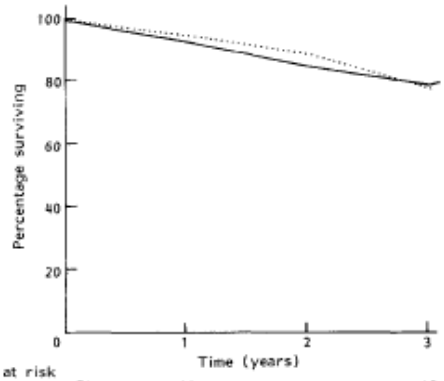

Figure 2 *Overall survival rates ($\chi^2=0{\cdot}25$, $P=0{\cdot}6$, relative risk = 0·88, 95 per cent confidence interval 0·52–1·47); (——), surgery; (·····), conservative treatment. 'Numbers at risk' represent the number of patients alive at entry and annually thereafter*

Table 5 *Social/demographic characteristics*

	Surgery ($n=117$)	Conservative treatment ($n=120$)
Marital status		
Married	37 (32)	43 (36)
Widowed	65 (56)	61 (51)
Single	14 (12)	13 (11)
Divorced	1 (1)	3 (3)
Living alone	59 (50)	61 (51)
Unable to manage household tasks	36 (31)	44 (37)
Not happy living in current house	5 (4)	10 (8)
Someone to talk to about problems	102 (87)	106 (88)

Values in parentheses are percentages

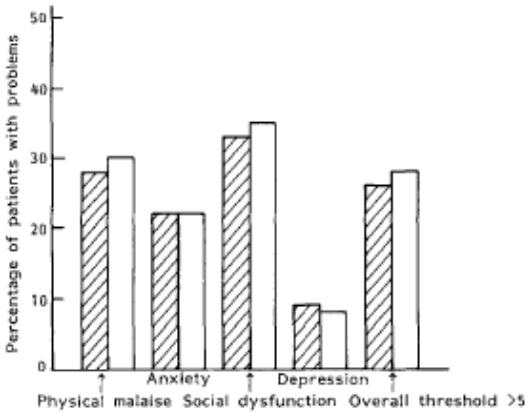

Figure 3 *General Health Questionnaire (GHQ-28);* ■, *surgery and tamoxifen* (n = *117*); □, *tamoxifen alone* (n = *120*)

Discussion

Preliminary reports on two clinical trials of tamoxifen *versus* surgery in the elderly have been published. The St. George's Hospital study[21] had a large proportion of T_3/T_4 tumours, and a 37 per cent locoregional recurrence rate in the surgically treated group led to the conclusion that tamoxifen was the best primary treatment. The Nottingham group studied patients more comparable to those in the present study and found a 43 per cent local treatment failure rate at 3 years with tamoxifen alone: the contrary conclusion was drawn[22]. The discrepancy between the tumour response rates in this and the present study may reflect a difference of interpretation between a tightly controlled single-centre study and a multicentre trial. Two EORTC (European Organisation for Research and Treatment of Cancer) trials of surgery *versus* tamoxifen in the elderly are as yet unpublished. The present study is the only one to examine the effect of surgery with adjuvant tamoxifen in this age group and shows this combination of treatments to be best. Some patients treated with tamoxifen alone require surgery due to local treatment failure but this has not been shown to be disadvantageous so far.

Quality of life is adversely affected by both the diagnosis and treatment of breast cancer but there is no evidence that either treatment in the present study had a more detrimental impact.

If further follow-up in this study demonstrates that the majority of women die from intercurrent disease before symptomatic progression of breast cancer, then tamoxifen alone may be judged to be optimal therapy. If an unacceptable level of local problems persists in those treated conservatively, leading to high surgical intervention rates or locally advanced disease in ageing women less fit to withstand surgery, then a more aggressive initial approach may be justified. Alternatively, new developments in fine needle aspiration cytology with immunohistochemical assessment of oestrogen and other receptors may allow a more selective policy in the future[23–26].

It is felt ethically justifiable to continue with the present study but it has been found difficult to obtain informed consent from some elderly women. An unknown number of potentially eligible women have thereby been excluded and this must raise doubts about the applicability of the conclusions. In future, all eligible patients, after suitable explanation, will be offered the choice of either of the two treatments or of randomization. In this way all patients at risk will be studied[27].

Since 10 October 1990, 40 patients have been entered into the trial and 54 non-randomized patients have been registered.

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Appendix 2 Study 2

Late follow-up of a randomised trial of surgery plus tamoxifen versus tamoxifen alone in women over 70 with operable breast cancer[68].

Randomized trial

Late follow-up of a randomized trial of surgery plus tamoxifen *versus* tamoxifen alone in women aged over 70 years with operable breast cancer

M. Fennessy[1], T. Bates[3], the late K. MacRae[4], D. Riley[1], J. Houghton[1] and M. Baum[2], on behalf of the Closed Trials Working Party of the Cancer Research UK Breast Cancer Trials Group

[1]Cancer Research UK and University College London Cancer Trials Centre, Royal Free and University College London and [2]Department of Surgery, Royal Free and University College, London, [3]William Harvey Hospital, Ashford, Kent and [4]Department of Medical Statistics, Postgraduate Medical School, University of Surrey, Guildford, UK

Correspondence to: Mr T. Bates, Breast Unit, William Harvey Hospital, Ashford, Kent TN24 OLZ, UK (e-mail: bates.tom@virgin.net)

Background: Breast cancer has been considered a more indolent disease in the elderly, who are less tolerant of aggressive therapy. This trial tested the hypothesis that tamoxifen without surgery would provide adequate control of breast cancer for the remainder of life in elderly women, thereby sparing them surgery.

Method: Women aged over 70 years with operable, invasive breast cancer were randomized to receive either tamoxifen alone or surgery plus tamoxifen. Time to treatment failure (TTF), indicating initial primary treatment failure, was the primary endpoint. Overall mortality, and death from breast cancer were also compared between the two groups.

Results: Between 1984 and 1991, 455 patients were included in the trial. The analysis was based on a median follow-up of 12·7 years. The TTF was significantly shorter in the tamoxifen alone group: hazard ratio (HR) 4·41 (95 per cent confidence interval (c.i.) 3·31 to 5·88). Ninety-three (40·4 per cent) of 230 patients randomized to tamoxifen alone underwent surgery for the management of their disease. Both overall mortality and mortality from breast cancer were significantly increased in the tamoxifen alone group, although the survival curves did not diverge for the first 3 three years: HR 1·29 (95 per cent c.i. 1·04 to 1·59) and 1·68 (95 per cent c.i. 1·15 to 2·47) respectively.

Conclusion: Omission of primary surgery in unselected elderly women with operable breast cancer who were fit for the procedure resulted in an increased rate of progression, therapeutic intervention and mortality.

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Introduction

Women aged over 70 years with breast cancer have received less aggressive treatment than younger women[1–4] because of their presumed shorter life expectancy, inability to tolerate active therapy and concern about co-morbidity. Positive findings from observational studies of primary tamoxifen treatment in the elderly[5–7] stimulated three randomized trials that compared primary tamoxifen therapy with surgery alone[8–10]. It was hypothesized that tamoxifen alone might control the tumour over the patient's lifetime and obviate the need for surgery and radiotherapy. The Nottingham trial[8] showed better local control with mastectomy than with tamoxifen. The St George's trial[9], in which surgery mainly comprised wide excision, reported no difference between the two treatments. The European Organization for Research and Treatment of Cancer trial[10] of tamoxifen alone *versus* modified radical mastectomy has recently reported 10-year follow-up; although there was a decreased time to treatment failure (TTF) in patients receiving tamoxifen alone, there was no difference in survival between the two groups.

As data emerged that adjuvant tamoxifen may prolong survival in postmenopausal women, three further trials were initiated that compared primary tamoxifen with

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surgery plus tamoxifen. In the Cancer Research Campaign (CRC)[11] and Group for Research on Endocrine Therapy in the Elderly[12] trials both conservative surgery and mastectomy were permitted. The CRC trial excluded adjuvant radiotherapy as it was hoped that adjuvant tamoxifen would provide adequate local control following breast-conserving surgery. At the time that the trial was designed, it was generally considered that elderly patients tolerated postoperative radiotherapy poorly[3]. Patients were not selected on the basis of oestrogen receptor (ER) status because suitable assays were not widely available. Both trials confirmed that surgery improved local control. A second Nottingham trial[13], that randomized patients with strongly ER-positive tumours, also demonstrated improved local control with mastectomy. None of these studies revealed differences between treatments with respect to the development of distant metastases, breast cancer mortality or overall mortality, but with the exception of the GRETA Trial[12], the sample sizes were small, median follow-up was short or tamoxifen was omitted from the surgical group.

The present study analysed late follow-up in women aged over 70 years with operable breast cancer who were randomized to surgery plus tamoxifen or tamoxifen alone.

Patients and methods

Eligible women were identified in district general hospitals or university teaching hospitals in the UK from routine breast clinic referrals. Included patients were aged 70 years or over, had a palpable breast lesion and histological or cytological evidence of invasive disease, or unequivocal mammographic evidence of breast cancer, and had operable disease. At the time the trial commenced some centres relied on mammography for diagnosis. Operable disease was defined as T1, T2, T3a (less than 10 cm), T4b (local skin involvement only), N0 or N1, and M0. Patients with palpable ipsilateral axillary nodes were eligible if the nodes were mobile in relation to the chest wall. Negative radiographs of the chest, lateral lumbar spine and pelvis were required. Patients with bilateral breast cancer or a previous malignancy, apart from non-melanoma skin cancer or adequately treated *in situ* carcinoma of the cervix, were excluded. Patients were required to be fit for surgery and available for follow-up. Following confirmed diagnosis, patients were randomized to either tamoxifen alone, 40 mg daily (single or divided dose), or surgery plus the same dose of tamoxifen. There was no restriction on the extent of surgery and tamoxifen was prescribed indefinitely.

A computer-generated randomization, stratified by hospital in block sizes of four, was produced and concealed by staff at the CRC Clinical Trials Centre. Eligibility was confirmed and the randomized allocation issued by a telephone call to the trials centre. Patients were reviewed every 3 months for the first 2 years, every 6 months for a further 3 years and annually thereafter. All patients were flagged with the Office for National Statistics for notification of deaths that occurred within the UK. The cause of death, as reported on the death certificate, was compared with information recorded in the clinical data forms and incongruities were resolved by reference to the medical records. The trial protocol was approved by the local research ethics committee. An information sheet was provided and verbal consent required from all patients.

Endpoints

The hypothesis was that tamoxifen alone would provide adequate control of breast cancer for the remainder of life in elderly women, thereby sparing them surgery. The objectives were to compare TTF and overall mortality in patients randomized to surgery plus tamoxifen and tamoxifen alone. The primary endpoint was TTF and the secondary endpoint overall mortality.

Progression in the tamoxifen alone group was based on the Union Internacional Contra la Cancrum criteria for unidimensional tumours[14]. The maximum tumour diameter was measured in a single dimension only, at baseline and each follow-up visit. Using a computerized algorithm, progression was assigned when there was a greater than 25 per cent increase in maximum tumour diameter compared with the smallest recorded diameter, or the appearance of new lesions. To avoid bias, in both treatment groups the date of progression was taken as the date of clinical diagnosis, provided that this was subsequently confirmed by cytology, histology or imaging.

Statistical analysis

It was calculated that a sample size of 350 patients would be enough detect a 10 per cent difference in outcome between the treatments for either endpoint, with 90 per cent power.

All randomized patients, regardless of eligibility and whether they received the assigned treatment, were included in an intention-to-treat analysis. Time intervals for Kaplan–Meier[15] plots were calculated from the date of randomization to the date of the event. Surviving patients who had not had an event at the time of analysis were censored at the time of last known status. For progression and breast cancer mortality analyses, patients who died without experiencing an event were censored at the time of death.

Median time intervals were estimated by the life-table method. Kaplan–Meier plots were arbitrarily terminated

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at 10 years, but statistical estimates included all data. Effect of treatment and independent prognostic variables on these plots was estimated using a Cox proportional hazard model. There were no planned subgroup or co-variate analyses. All analyses were conducted using SAS® version 6·12 (SAS Institute, Cary, North Carolina, USA).

Results

Between January 1984 and October 1991, 27 hospitals in the UK randomized 455 patients into the trial. The analysis was based on a median follow-up of 12·7 years. Follow-up was complete for all but six patients up to September 1999 at least. The trial profile is shown in *Fig. 1*.

Seven randomized patients were ineligible because they had bone metastases, previous cancer, were not fit for surgery, had excision biopsy before randomization or had bilateral breast cancer. Four patients treated by local excision deviated from the protocol by receiving adjuvant radiotherapy. There was an excess of T3a tumours in the tamoxifen alone group and of T4b tumours in the surgery plus tamoxifen group. Otherwise the groups were well matched with regard to prognostic factors and diagnostic procedures (*Table 1*).

Fourteen patients randomized to surgery rejected the allocation and received tamoxifen alone, whereas three randomized to tamoxifen alone elected to have surgery. These patients were analysed as randomized.

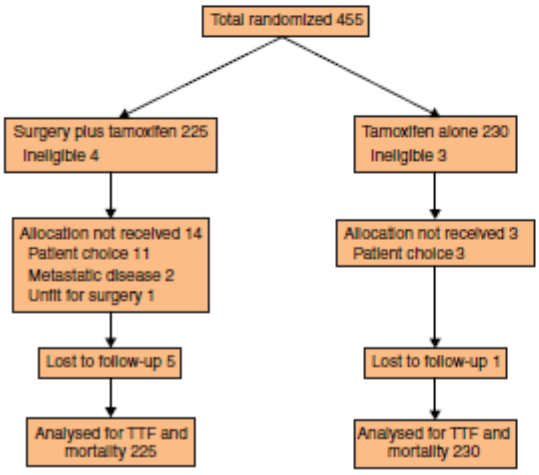

Fig. 1 Trial profile. TTF, time to treatment failure

Table 1 Patient characteristics

	Surgery plus tamoxifen ($n = 225$)	Tamoxifen alone ($n = 230$)
Age (years)*	76 (70–90)	76 (70–87)
Follow-up (years)*	12·4 (0·3–16·2)	12·9 (4·1–16·3)
Tumour stage at baseline		
T1 (≤ 2 cm)	48	38
T2 (> 2 to ≤ 5 cm)	114	130
T3a (> 5 to < 10 cm)	9	16
T4b	54	46
Clinical node status		
No palpable nodes	179	191
Palpable nodes	40	33
Not known	6	6
Method of diagnosis		
Biopsy (+/– cytology, +/– mammography)	131	131
Cytology (+/– mammography)	74	82
Mammography alone	19	17
Not known	1	0
Primary surgery		
Modified mastectomy	10	
Simple mastectomy	42	
Quadrantectomy	12	
Local excision	147	
Surgery not performed	14	
New primary cancers		
Endometrial cancer	4	5
Total	25	24

*Values are median (range).

Disease progression

Fifty-seven patients randomized to surgery plus tamoxifen and 141 to tamoxifen alone had disease progression (*Table 2*). The progression-free interval was significantly shorter in the latter group: hazard ratio (HR) 4·41 (95 per cent confidence interval (c.i.) 3·31 to 5·88) (*Fig. 2*). The median progression-free interval in this group was 1·69 (95 per cent c.i. 1·43 to 1·82) years, whereas the median had not been reached in the surgery plus tamoxifen group. The most frequent intervention following a change of management was hormonal therapy in patients randomized to surgery plus tamoxifen and surgery in those allocated to tamoxifen alone (*Table 3*).

Primary tamoxifen was inferior to both mastectomy (HR 17·24, 95 per cent c.i. 6·41 to 47·62) and breast-conserving surgery (HR 5·99, 95 per cent c.i. 4·12 to 8·70) in achieving local control. Among patients randomized to surgery plus tamoxifen, the risk of local progression was greater in those who had breast conservation than in those who had a mastectomy: HR 2·98 (95 per cent c.i. 1·06 to 8·39). The 5-year rates of local progression were 8 per cent after mastectomy, 18 per cent after breast

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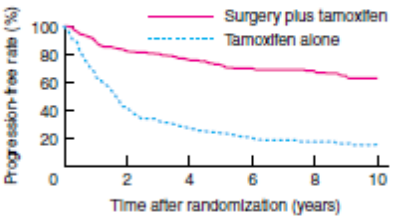
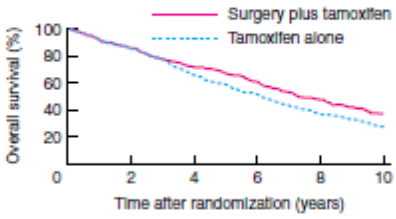


No. at risk

Surgery plus tamoxifen	225	162	133	110	91	58
Tamoxifen alone	230	82	40	26	19	9

Fig. 2 Progression-free interval in trial of 455 women aged over 75 years with breast cancer



No. at risk

Surgery plus tamoxifen	225	192	162	135	107	71
Tamoxifen alone	230	199	152	120	87	57

Fig. 3 Overall mortality in trial of 455 women aged over 75 years with breast cancer

conservation and 64 per cent in women who had tamoxifen alone. Although many more patients in the tamoxifen alone group had local progression, some of whom did not have a subsequent change of management, this did not result in an increased incidence of uncontrolled local disease at death: 11 patients in the surgery plus tamoxifen group and 13 in the tamoxifen alone group. Thirteen and 39 patients in each group respectively had cancer progression without a recorded change of management.

The baseline co-variates age at randomization, clinical tumour size, clinical status of the axilla and involvement of the skin overlying the tumour, along with their interaction with randomized treatment, and randomized treatment itself, were evaluated in a Cox proportional hazards model. Only randomized treatment (HR 4·50, 95 per cent c.i. 3·37 to 6·01) and tumour size (HR 1·14, 95 per cent c.i. 1·04 to 1·24 per cm) were independently predictive of progression.

Table 2 Comparison of treatment failure in the two groups

	Surgery plus tamoxifen	Tamoxifen alone
Recurrence or progression		
Local	24	94
Axillary*	12	21
Distant†	20	14
Stable disease deemed an unsatisfactory outcome	n/a	8
Tamoxifen side-effects	0	1
Other‡	1	3
Total	57	141

*Includes simultaneous confirmation of local and axillary recurrence; †includes simultaneous confirmation of distant and local or axillary recurrence; ‡one patient had a cystic carcinoma resected because of repeated aspiration and three patients developed contralateral breast cancer.

Mortality

Both overall mortality and mortality from breast cancer were significantly increased in the tamoxifen alone group after the first 3 years compared with surgery plus tamoxifen: HR 1·29 (95 per cent c.i. 1·04 to 1·59) and 1·68 (95 per cent c.i. 1·15 to 2·47) respectively (*Fig. 3* and *Table 4*). There were no perioperative deaths following primary surgery. The 5- and 10-year survival rates were 67·4 (95 per cent c.i. 61·3 to 73·5) and 37·7 (95 per cent c.i. 31·2 to 44·2) per cent respectively for the surgery plus tamoxifen group, and 59·5 (95 per cent c.i. 53·2 to 65·9) and 28·8 (95 per cent c.i. 22·9 to 34·8) per cent respectively for the tamoxifen alone group.

As described for disease progression, baseline co-variates were evaluated in a Cox proportional hazard model. Age (HR 1·08 (95 per cent c.i. 1·05 to 1·10) per year) and tumour size (HR 1·17, 95 per cent c.i. 1·09 to 1·27 per cm) were independently predictive of overall mortality. Addition of age and tumour size did not improve the Cox model (adjusted HR 1·30, 95 per cent c.i. 1·05 to 1·60) compared with the unadjusted overall mortality. However, the median tumour size in the mastectomy subgroup was greater than that in the breast conservation subgroup (4 *versus* 3 cm respectively) as was the proportion of T4

Table 3 Therapy following change of management

Intervention	Surgery plus tamoxifen ($n = 71$)	Tamoxifen alone ($n = 144$)
Surgery	28 (39)	93 (64·6)
Hormonal therapy	37 (52)	42 (29·2)
Radiotherapy	16 (23)	24 (16·7)
Other interventions	7 (10)	4 (2·8)

Values in parentheses are percentages. Some patients received more than one intervention.

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Table 4 Causes of death

Cause of death	Surgery plus tamoxifen	Tamoxifen alone
Breast cancer	43	68
Other	116	119
Total	159	187

tumours (16 (31 per cent) of 52 *versus* 32 (20·1 per cent) of 159 respectively).

Discussion

A strong consensus has prevailed that by the time a breast tumour is palpable, dissemination has already occurred and local treatment can only provide local control. Surgery cannot influence the development of distant metastases nor, in turn, mortality from breast cancer. Data from mature randomized trials challenge this belief. Adjuvant radiotherapy decreases overall and breast cancer-specific mortality rates[16–19]. Similarly, trials comparing surgical interventions suggest that the extent of surgery can reduce the rate of distant metastasis[20] and mortality from breast cancer[21]. Results from the present trial contribute not only to the management of early breast cancer in the elderly but add to the accumulating evidence that local treatment offers more than local control by impeding the metastatic process.

The overall mortality rate was increased when primary surgery was omitted, primarily because of an increase in the number of deaths from breast cancer. There were no perioperative deaths and any harm from surgery must have been offset by the local benefit derived from control of breast cancer because the overall mortality curves for the two treatment groups were virtually superimposed for the first 3 years after randomization. It is possible that the increase in mortality from breast cancer in the tamoxifen alone group did not translate into an overall increased mortality rate because of a dilution effect resulting from 'competing' mortality from other causes, such as old age or concomitant illness. Furthermore, recording death from breast cancer is susceptible to bias. In patients treated with tamoxifen who have a palpable unresected primary carcinoma at death, there may be a tendency to attribute the cause of death to breast cancer, despite the lack of confirmed distant disease, especially when the patient died at home or was too frail to be investigated.

A survival benefit was not expected because these women were elderly and at risk of death from concomitant disease. Only a quarter of the women in the surgery plus tamoxifen group received adequate local treatment by current standards, in that those who had breast-conserving surgery did not receive radiotherapy.

The daily dose of tamoxifen 40 mg was the standard treatment for advanced breast cancer at the time of trial design. The duration of treatment was not limited as this would have increased the relapse rate in patients treated with tamoxifen alone. As expected, there was a higher than predicted rate of endometrial cancer, but other studies have shown that this has little effect on survival[22].

About two-thirds of the tumours in this trial would be expected to be ER-positive. It is therefore unlikely that the large differences in tumour progression rates noted between the groups would be eradicated in an ER-positive population, as both treatments would have improved outcome in women with ER-positive tumours[13].

This study showed that tumour excision decreased the mortality rate in an unselected population of elderly women with operable breast cancer who were fit for the procedure. However, for women with an ER-positive tumour who have a short life expectancy, primary tamoxifen therapy is worthy of consideration as it produces an overall survival curve similar to that of surgery plus tamoxifen during the first 3 years of treatment.

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Marsden Hospital, Sutton), J. Rennie (Dulwich Hospital), R. Roxburgh, P. Sauven (Broomfield Hospital), P. Savage (Queen Mary's Hospital), Professor R. A. Sellwood (Withington Hospital), K. D. Vellacott (Royal Gwent Hospital), R. G. K. Watson (Waterford Regional Hospital), T. G. Williams, P. Bentley (Kent and Sussex Hospital).

Members of the Closed Trials Working Party of the Cancer Research UK Breast Cancer Trials Group were T. Bates (Chairman) (William Harvey Hospital), M. Baum (Cancer Research UK and University College London Cancer Trials Centre), D. A. Berstock (Clatterbridge General Hospital), J. Cuzick (Imperial Cancer Research Fund, London), J. Dobbs (St Thomas, Hospital, London), J. Haybittle, J. Houghton (Cancer Research UK and University College London Cancer Trials Centre), K. McPherson (London School of Hygiene and Tropical Medicine), R. Millis (Guy's Hospital), T. J. Powles (Royal Marsden Hospital, London), R. Rubens (Guy's Hospital), R. Sainsbury (University College London Medical School) and A. Wilson (Whittington Hospital).

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Appendix 3 Study 3

Variations in management of small screen-detected breast cancer in the South Thames East Region[104].

Variation in management of small invasive breast cancers detected on screening in the former South East Thames region: observational study

S Moritz, T Bates, S M Henderson, S Humphreys, M J Michell

South Thames East Breast Screening Quality Assurance Reference Centre, King's College Hospital, London SE5 9RS
S Moritz, *data manager*
S M Henderson, *quality assurance administrator*

William Harvey Hospital, Ashford, Kent TN24 OLZ
T Bates, *consultant surgeon*

King's College Hospital, London SE5 9RS
S Humphreys, *consultant histopathologist*
M J Michell, *consultant radiologist*

Correspondence to: Mr Bates bates9304@aol.com

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Abstract

Objective: To examine the variation in surgical and adjuvant treatment of breast cancer of known histology and detected on screening in a large cohort of patients treated by the surgeons of a health region.
Design: Part prospective, part retrospective observational study using the databases of a region's breast screening programme and of the cancer registry.
Setting: The former South East Thames region.
Subjects: 600 women aged 49-79 who presented during 1991-2 with invasive breast cancer up to 20 mm in diameter that had been detected on screening. These patients were treated by 35 surgeons.
Main outcome measures: Mastectomy rate by surgeon and the use of adjuvant treatment (radiotherapy, tamoxifen, and chemotherapy) were compared with risk factors, tumour grade, resection margins, and axillary node status.
Results: The mastectomy rate varied between nil and 80%, although the numbers at these extremes were small (0/13 *v* 8/10). Surgeons operating on more than 20 such cases had a lower mastectomy rate (15%) than surgeons treating fewer cases (23%), but this difference was confounded by variation in casemix. There were also wide variations in mastectomy rates and in axillary sampling rates that were independent of casemix or caseload. There was broad agreement on the use of adjuvant tamoxifen (94%), but few patients received chemotherapy (2.5%). 78 patients (19%) did not receive radiotherapy, including 51 out of 317 patients with unfavourable tumours, and 26 patients did not receive tamoxifen. Whether the patient received adjuvant treatment was more dependent on referral by the surgeon than the risk factors for local recurrence and was independent of caseload.
Conclusion: Mastectomy rates for similar tumours vary widely by surgeon independently of casemix or caseload, but surgeons with a higher caseload tend to have a lower mastectomy rate. Omission of postoperative radiotherapy or tamoxifen after conservative treatment is not related to risk factors for local recurrence or caseload. Confidential feedback of treatment profiles to individual surgeons has been used, but when benefit has been established treatment should be guided by evidence based protocol.

Introduction

Apparent variations in the outcome of breast cancer in England and Wales[1] and across Europe[2] are thought to be due to variations in treatment. Variations in caseload may also be related to outcome,[3,4] but doubt remains about the methodological soundness of some of the studies.[5] The management of breast cancer may vary between teaching and non-teaching hospitals, geographically,[6–11] and according to patient choice,[12] but difference in outcome may be solely due to differences in the severity of disease.[13] Suboptimal treatment of breast cancer could compromise the success of the NHS breast screening programme in the United Kingdom, which started in 1988 with the aim of reducing the mortality in women aged 50-64 by 25% by 2000.[14] The strong quality assurance component of the programme may have lead to a more uniform approach to the management of cancer detected on screening, but Chouillet et al found variations in the treatment of breast cancer across the four former Thames health regions.[15]

Breast conserving surgery followed by radiotherapy is a safe alternative to mastectomy.[16,17] This was confirmed by an overview of world practice,[18] but Van Dongen et al concluded that only 60% of tumours were suitable for breast conservation.[19] The quality assurance guidelines for the NHS breast screening programme state that more than 50% of patients with small invasive tumours should have them locally excised.[20] Radiotherapy after conservative surgery, which reduces the rate of local recurrence,[16,18,21] does not affect overall survival, but adjuvant tamoxifen gives

a clear survival benefit for postmenopausal patients and the benefits outweigh the risk of side effects.[22 23] Chemotherapy may prolong the recurrence-free interval in postmenopausal patients with node positive disease, but this evidence may not have influenced management in 1991-2.[22 23] The implementation of the screening programme in 1988 was precipitous, and the necessary documentation and computer facilities for retrieval and analysis were not in place at the outset so that data collection was in part retrospective.

We examined the management of patients with small invasive breast cancers detected by the South Thames East breast screening programme during 1991-2. Small invasive tumours are mostly detected on screening, and patients are likely to benefit from early detection if treated appropriately.[24]

Subjects and methods

Data on treatment of all invasive breast cancers were obtained from the participating surgeons by the South Thames East Breast Screening Quality Assurance Reference Centre by means of a standard biopsy and treatment form. Operation details were considered to be correct if the data were consistent with details in the pathology report. We could not check the surgeons' data on adjuvant treatment in a similar way, but after a pilot study showed recording errors these data were checked against data from the Thames Cancer Registry. Registry data are collected directly from patients' notes at regular hospital visits by trained staff. Completeness of registration for breast cancer in women aged 50-64 at screening is estimated to be 82% two years after diagnosis and 87.9% after three years (J Lutz, scientific meeting of the Thames Cancer Registry, London, July 1994). Since the registry collects detailed information on adjuvant treatment, including date of starting and dosage, we considered it certain that treatment had been given. However, the registry's records on adjuvant treatment are not complete.[25] When the registry database did not confirm the treatment on the database of the breast screening programme or when cases were not recorded by the registry, further written evidence was sought from the surgeons to confirm adjuvant treatment. We also confirmed with the four radiotherapy units in the region and with one outside unit that patients who were recorded as not having had radiotherapy had not received it.

Tumour diameter was taken as the largest pathological diameter of invasive carcinoma. The clinical palpability of the tumour was not available for the whole cohort, but a percentage has been extrapolated to the whole database for each surgeon. Palpability may depend on knowledge of the radiologically detected tumour site, and for both these reasons the data cannot be regarded as robust.

Data analysis was conducted with the help of the database system of the breast screening programme. This holds details of patient identification, screening, surgery, pathology, and radiology for all women who attended screening who were found to have an abnormality and were subsequently referred for surgical biopsy.

Preliminary analysis showed that some patients with invasive cancer that was not treated by mastectomy did not receive radiotherapy or, in a few cases, tamoxifen. We therefore used the criteria for the second trial of the British Association of Surgical Oncology, in which patients with small well differentiated tumours were randomly allocated in a two by two trial for and against radiotherapy and for and against tamoxifen.[26] We relaxed the criteria to include patients in whom vascular invasion had not been reported and in whom the node status was unknown.

Favourable tumours were defined as those up to 20 mm in diameter that had clear resection margins, that were grade I, and in which axillary lymph node status was negative or unknown.

Cases

A total of 817 women had invasive cancers detected between 1 January 1991 and 31 December 1992; 620 of these cancers had a tumour size of up to 20 mm in diameter. Surgical data were available for 600 cases, which were included in the analysis. A total of 493 patients had the cancer locally excised, of which 460 had full data, including a pathology report. Of these 460 patients, 328 had adjuvant treatment data cross checked against the registry data and 80 were confirmed by the surgeon. We included only these 408 patients whose treatment details could be confirmed in the analysis of adjuvant treatment after conservative surgery.

Breast screening started in the former South East Thames region between 1988 and 1992 so that most of the women in this study were given their diagnosis at their first attendance, the prevalent round of screening. The median age at diagnosis was 59 (range 49-79).

Results

Surgical workload

Thirty five surgeons were concerned with the management of the patients in this study, the number of patients per surgeon varying between 1 and 70 (median 13) (table 1). Five surgeons treated only one patient, and another five surgeons managed five or fewer patients. Eleven surgeons treated more than 20 patients in two years, and 24 treated 20 or fewer.

Casemix and caseload

All tumours were 20 mm or less on largest pathological diameter, but 160 out of 211 (76%) tumours were palpable among surgeons treating 20 or fewer such patients compared with 196 out of 389 (50%) tumours among surgeons with a higher caseload. The data on palpability are not robust, but the mean tumour size for the 408 patients treated by conservative surgery fell from 13.5 mm if they were treated by surgeons with a low caseload (<5 cases) to 11.9 mm if they were treated by surgeons with a high caseload (>30 cases) (table 1). However, among the six surgeons with a high caseload, the mean tumour diameter varied from 10.7 mm for one surgeon who referred all palpable tumours to local surgeons to 13.1 mm for another who treated all referred patients. The mean tumour diameter in patients treated by mastectomy (12.8 mm) was little different from the mean diameter in those treated by conservative surgery (12.3 mm).

The proportion of node negative, or favourable tumours, was no higher among surgeons with the highest caseload (table 1).

Table 1 Variation in casemix of and treatment of breast cancer by surgeons according to caseload

	Caseload (No of invasive cancers <20 mm detected by screening, 1991-2)					
	<5 (n=8)	5-12 (n=8)	13-19 (n=7)	20-30 (n=6)	>30 (n=6)	Total (n=35)
No of patients	13	65	107	138	271	600*
No of patients with palpable tumour	13	51	72	97	119	354
Mean diameter of tumour (mm)	13.5	13.1	13.1	12.7	11.9	12.5
Mastectomy rate (No (%) of cases)	0	21 (32)	21 (20)	32 (23)	33 (12)	108 (18)
No of patients treated conservatively:	13	44	86	106	239	492*
With full data	10	33	57	91	215	408*
With one or more nodes sampled	10	11	31	55	120	227
With positive nodes	0	3	7	4	29	43
Without tamoxifen treatment	1	3	2	10	10	26
Favourable tumours:	2	8	11	20	50	91
Radiotherapy given	2	6	8	15	33	64
Non-favourable tumours:	8	28	46	71	164	317
Radiotherapy given	8	17	40	60	141	266

*Includes 6 patients who were operated on by other surgeons outside the region; 2 of them had a mastectomy and full data were available for 2 of the 4 patients who did not have a mastectomy.

Extent of surgery

Among the 600 patients with an invasive breast cancer of up to 20 mm in diameter the overall mastectomy rate was 18%, but among the 35 surgeons the individual rate varied from nil to 80%. The numbers at these extremes were small (0/13 *v* 8/10), but surgeons with a higher caseload (>20 cases in the two years) had a mastectomy rate of 59 out of 389 (15%) compared with 48 out of 211 (23%) for the surgeons who treated fewer cases (χ^2 test for continuity with Yates's correction 4.86, $P<0.03$).

These variations were partly explained by the variations in casemix, but the mastectomy rate among surgeons with a low caseload (5-12 cases) varied by surgeon from 0 out of 5 and 1 out of 12 (8.3%) to 8 out of 10 (80%) when the mean tumour diameter was 13.8, 13.4, and 14.2 mm respectively. Similarly, among surgeons with a high caseload (>30 cases) mastectomy rates varied between 1 out of 32 (3%) and 10 out of 39 (26%) when the mean diameter was 12.7 and 11.3 mm respectively. These differences could not be explained by knowledge of tumour grade or node status.

Axillary node status

In the 408 patients with complete data on pathology and treatment, axillary node status was determined by histological examination of at least one node in 224 patients (55%), of whom 43 showed metastases (19%). Variations in axillary sampling rates seemed to be independent of casemix in surgeons with both a low and a high caseload. For example, one surgeon who operated on 5 cases sampled axillary nodes in none of them compared with another who operated on 6 cases and sampled nodes in 5, and one surgeon who operated on 28 cases sampled nodes in only 2 compared with another who operated on 34 cases and sampled nodes in 30.

In 84 women treated by conservative surgery in whom data on treatment were incomplete, the axillary sampling rate was similar, the overall rate being 282/492 (57%).

Ninety three of the 108 patients treated by mastectomy (86%) had a node sample taken, of whom 28 (30%) had positive nodes.

Table 2 Numbers of patients given adjuvant treatment for invasive breast cancer that was treated conservatively, according to type of tumour

Treatment type	Favourable tumours (n=91)*	Non-favourable tumours (n=317)†	Total (n=408)
No adjuvant treatment	4	11	15
Tamoxifen only	23	38	61
Radiotherapy only	1	11	12
Radiotherapy and tamoxifen	63	247	310
Chemotherapy only	0	1	1
Tamoxifen and chemotherapy	0	1	1
Radiotherapy and tamoxifen and chemotherapy	0	8	8

*Up to 20 mm in diameter, grade I, clear margins, node negative or nodes not sampled.
†Up to 20 mm in diameter but which do not meet the above other criteria.

Adjuvant treatment after conservative surgery

Table 2 shows the distribution of adjuvant treatment after conservative surgery in 408 patients. Fifteen patients did not receive any adjuvant treatment, and in all of them the axillary lymph node status was negative or undetermined. Four patients had cancers that were grade I and had clear excision margins, 1 patient had a minimal cancer of 1 mm in diameter whose grade and excision margins were not known, and another patient had a grade I tumour which reached the excision margins. Three of the remaining 9 patients had tumours with positive excision margins; in 6 of these 9 patients the tumour was grade II and in 3 the grade was unknown.

Adjuvant tamoxifen was given to 382 of the 408 patients treated conservatively (table 2). Overall, 330 of them received radiotherapy after conservative surgery. Of the 78 patients who were not treated with radiotherapy (table 2), 15 did not receive any adjuvant treatment, 1 received chemotherapy alone, 61 received endocrine treatment alone, and 1 received chemotherapy plus endocrine treatment. In total, 311 of the 408 patients received both tamoxifen and radiotherapy. Chemotherapy was given to just 10 patients. Four of them had lymph node involvement—2 had grade III tumours, 1 a grade I tumour, and 1 an ungraded tumour. Of the 6 patients with negative or unknown axillary nodal status, 2 had grade II tumours, 1 a grade III tumour, and 3 ungraded tumours.

Management of favourable and non-favourable tumours after conservative surgery

Ninety one patients had favourable tumours, of whom 64 (70%) received radiotherapy compared with 317 patients with non-favourable tumours, of whom 266

Table 3 Details of tumours in patients who did not receive radiotherapy for breast cancer that was treated conservatively. Values are numbers of patients

	Favourable tumours (n=27)*	Non-favourable tumours (n=51)
Grade:		
I	27	6
II	0	29
III	0	1
Not available	0	15
Axillary nodes:		
Positive	0	3
Negative	8	21
Not known	19	27
Resection margin:		
Clear	27	37
Uncertain	0	4
Positive	0	6
Not known	0	4

*Up to 20 mm in diameter, grade I, clear margin, node negative or nodes not sampled.

(84%) received radiotherapy (table 2). Of the 22 surgeons who managed patients with favourable tumours, 12 referred all of them for radiotherapy, 8 referred a proportion, and 2 did not give radiotherapy at all. Comparison of the treatment of favourable tumours with that of non-favourable tumours showed no clear differences in management. Twenty two surgeons treated patients from both prognostic groups. Ten surgeons referred all their patients for radiotherapy, 10 omitted the treatment in some patients irrespective of which prognostic group they belonged to, and 2 omitted radiotherapy only in patients with favourable tumours. Of the 78 patients who were not given radiotherapy, 51 had non-favourable tumours and 27 favourable tumours (table 3). The radiotherapy referral rates by surgeon caseload groups are shown in table 1.

Of the 26 patients who were not given tamoxifen, only 5 had favourable tumours, with the node status being unknown in 3. Omission of tamoxifen was not confined to surgeons with a low caseload (table 1). All 10 patients who received chemotherapy had non-favourable tumours.

Management of patients with lymph node positive disease

Of the 43 patients with node positive disease, 36 were treated with radiotherapy and tamoxifen; 3 received radiotherapy, tamoxifen, and chemotherapy; 1 chemotherapy and tamoxifen; 2 tamoxifen alone; and 1 radiotherapy alone. Ten out of 13 surgeons treated all patients with node positive disease with radiotherapy and tamoxifen.

As part of the South Thames East Breast Screening Surgical Quality Assurance Programme data on treatment were confidentially reported to the surgeons every 6 months so that all surgeons are aware of their treatment profile with respect to their peers.

Variation between regions

Recent unpublished quality assurance data from 16 regions in the United Kingdom for 1995-6 showed that South Thames (East) region has the highest number of patients with screen detected cancers operated on by surgeons with a caseload of less than 10 cases per year. Of those regions that provided data, South Thames had the lowest proportion of benign biopsy specimens weighing less than 20 g and had comparatively long waiting times. However, in none of the therapeutic quality standards, which included the ratio of malignant to benign biopsies, preoperative diagnosis, node status, and mastectomy rate, was the region an outlier compared with other regions (J Patrick, British Association of Surgical Oncology Breast Group study day, Solihull, April 1997).

Treatment outcome

Follow up data on this patient cohort is collected prospectively, but the number of treatment failures is as yet too low to indicate whether variation in treatment will result in different outcomes as measured by disease-free interval and overall survival.

Discussion

The introduction of the screening programme meant that for the first time the specificity of radiologists' work was publicly audited, with publication of recall rates and ratios of malignant to benign biopsy specimens for each screening centre. Pathologists set up a process of peer review, with circulation of histological slides so that the boundaries between invasive and in situ disease and between in situ disease and atypical ductal hyperplasia were defined and monitored. The surgeons were issued with guidelines which included quality criteria, each with a quality objective, outcome measure, and target.[20] These were published in 1992 but had been circulated and discussed in draft form during the period of our study. Regular multidisciplinary meetings of radiologists, surgeons, and pathologists concerned with screening were taking place. However, radiotherapists and oncologists had not been drawn into the consultative process on the best management of screen detected breast cancer at this stage, and in many centres the use of adjuvant treatment was dependent on the referral practice of the individual surgeon treating each patient.

Variations in treatment with caseload

Although the overall mastectomy rate in this study was well below the target of 50% for invasive tumours of 15 mm or less set by the surgical quality assurance guidelines,[20] there was considerable variation between surgeons. Surgeons with a higher caseload performed fewer mastectomies than surgeons with a lower caseload. This trend was also noted in Edinburgh,[27] but in our study the lower mastectomy rate of surgeons with higher caseloads may partly be due to differences in casemix since there was a trend for them to treat smaller impalpable tumours. This tendency was further confounded by variation in referral practice for palpable tumours. However, none of the few patients treated by surgeons seeing fewer than 5 cases received a mastectomy, and all these tumours were palpable. There was clearly a difference in clinical practice for apparently similar tumours between surgeons with both high and low caseloads.

The determination of axillary node status again showed variations in individual clinical practice which were not related to caseload, casemix, or mastectomy

rate. Failure to refer patients for postoperative radiotherapy after conservative surgery for invasive breast cancer or to prescribe tamoxifen was not related to caseload but was related to the surgeon and seemed to be idiosyncratic.

The number of surgeons treating women with breast cancer detected on screening was much higher in South Thames (East) region than in other regions. It has been suggested that only breast experts should treat screen detected breast cancer, but should the management of symptomatic cases be any different? In a population of 250 000 served by a district general hospital it is probably appropriate to have two surgeons with a major interest in breast disease; in South Thames (East) region the 15 districts would require 30 surgeons. At the outset there were 37 surgeons treating breast cancer, and with time this has only been reduced to 33—all of whom are members of the British Association of Surgical Oncology Breast Specialty Group. Several of the surgeons treating only a few cases no longer do so, but the pattern established at the outset of the screening programme has tended to persist. Although South Thames (East) region has more surgeons treating screen detected cancer than is considered appropriate, variation in clinical practice and omission of optimal adjuvant treatment is just as prevalent in patients treated by surgeons with a high caseload. Recent comparison of the surgical audits of the former South East and South West Thames regions shows that the same variations may occur with fewer surgeons treating more patients (T Bates, M Kissin, sixth Brighton breast day, April 1996). The mastectomy rate in these two adjacent regions is similar but lower than that in the northern regions of the United Kingdom (J Patrick, British Association of Surgical Oncology Breast Group study day, Solihull, April 1997). Variations in breast cancer treatment can relate to socioeconomic factors.[28] Although there is no suggestion of this in our study, we did not look for such evidence. Variation may also arise from insufficient knowledge of or disagreements with guidelines among physicians,[28] and in a recent British survey half of the surgeons who undertake breast work spend less than a fifth of their time doing such work.[29]

Quality assurance visits to the regional screening centres with an external assessor have only taken place over the past 12 months, but they have highlighted the need for a weekly multidisciplinary meeting attended by a radiotherapist or an oncologist. Such meetings have tended to be sporadic and retrospective rather than to plan treatment. Audit of these data with feedback of individual data every 6 months to surgeons was in place at the time of the study, but these measures seemed to be comparatively ineffective in changing practice. The lack of site visits rather than the number of surgeons may have been more of a problem in keeping variations to a minimum.

Place of radiotherapy and adjuvant treatment

One of the aims of the NHS breast screening programme is to detect breast cancer at an early stage when tumour size allows for less radical surgery. The safety of conservative surgery plus radiotherapy has been established,[18] and the option of breast conservation should therefore be offered to women whenever possible. However, women should not be put at increased risk of local recurrence by not having radiotherapy because the quality rather than the quantity of life must suffer.

It is uncertain whether all patients with early breast cancer require radiation after local excision or whether there is a subset of patients with a good prognosis whose risk of recurrence of breast cancer with conservative surgery is so small that radiotherapy can safely be omitted.[30] In a randomised trial no low risk subgroup could be identified among patients with node negative disease, but tumour size (greater than 20 mm) and high tumour grade were associated with a higher risk of local relapse.[31] The investigators concluded that until an acceptable low risk group for breast relapse could be identified, all patients should be treated with breast irradiation, a view supported in a recent review by Dixon.[32] Schnitt et al have recently reported the abandonment of a trial of radiotherapy after conservative surgery for breast cancer with a good prognosis,[33] but the preliminary results of the second trial of the British Association of Surgical Oncology have not been reported. The separation of tumours into favourable and non-favourable tumours was not intended to condone the omission of radiotherapy after conservative surgery but to examine whether this had been in the mind of the referring surgeon. It seems that this was not the case.

The use of postoperative radiotherapy for favourable and non-favourable tumours was 70% and 84% respectively, but overall comparison of the treatment of favourable with non-favourable tumours showed no clear differences in management. Most surgeons either referred patients from both prognostic groups for radiotherapy or omitted the treatment in a proportion of cases irrespective of which prognostic group they belonged to. Only two surgeons distinguished between prognostic groups and omitted radiotherapy only in patients with favourable tumours. These data suggest that patient management varied from surgeon to surgeon rather than by risk factors for local recurrence. When the best treatment of favourable tumours is uncertain, clinical practice needs to be established by large, well designed, randomised trials rather than by surgical preference.

The best management of favourable tumours may be uncertain, but variation in treatment was also seen in the use of adjuvant radiotherapy when the literature gives clear guidance.[18] Non-favourable tumours carry an increased risk of local and distant recurrence if adjuvant treatment is omitted after conservative surgery, but it is not known to what extent variations in treatment were influenced by patient choice. Patients must be free to refuse adjuvant treatment, having been fully informed of the potential benefits and risk. The reason why 22% of patients did not receive both adjuvant tamoxifen and radiotherapy is unknown, but it may have been patient choice, contraindication, or oversight. These results are similar to the findings in south east England in a study of all four of the former Thames regions, of which South Thames (East) was one.[15] The management of screen detected and symptomatic tumours in 1990 was examined, and only 63% of patients in the screening age group were treated with tamoxifen and radiotherapy. However, there was significant underreporting of adjuvant treatment in this study by the Thames

Cancer Registry—radiotherapy 20%, tamoxifen 23% and chemotherapy 29%.[23] Underreporting of adjuvant treatment has also been a problem in the screening programme, but in this study we confirmed the absence of treatment in each case.

Axillary node status was only determined in 56% of patients treated conservatively, and, although the expected rate of positive nodes is lower in screen detected tumours, this clearly remains controversial.[34 35] The NHS guidelines revised in 1996 state that histological node status should normally be obtained on all invasive cancers, either by sampling or clearance to ensure that all necessary data are obtained for deciding on adjuvant radiotherapy or systemic treatment.[24] The data collection at the time of this study was not sufficiently robust to record the extent of axillary surgery or the number of nodes sampled. Repeated discussion at quality assurance meetings every 6 months indicate that some surgeons strongly disagree with these guidelines. Node status is a powerful predictor of prognosis, but the evidence that it should determine the indications for adjuvant treatment in postmenopausal women was arguable in 1991-2.[22 25] In our study most patients had tamoxifen, and few had chemotherapy. The unpublished data from the 1995 overview of the world literature on adjuvant treatment for breast cancer may lead to an increase in the use of chemotherapy in the United Kingdom, but they are unlikely to resolve the controversy over surgical exploration of the axilla.

Key messages

- In this health region mastectomy rate varied between surgeons, surgeons with higher caseloads tending to be more conservative, but the wide variation in clinical practice was not related to caseload
- The use of adjuvant tamoxifen in postmenopausal women with invasive breast cancer was high (94%) and the use of adjuvant chemotherapy low (2.5%)
- Adjuvant radiotherapy after conservative surgery was omitted in 1 in 5 cases, but the omission was not related to risk factors for local recurrence
- A weekly multidisciplinary meeting is an important safeguard to ensure optimal treatment, and the team should include a radiotherapist or an oncologist
- When benefit has already been clearly established, treatment should be guided by evidence based protocols and audited by regular site visits

Climate of change

At the time of this study some pathologists did not report tumour grade, lymphovascular invasion, or the margin status of invasive breast cancers treated conservatively. This deficiency was independent of workload but has now been resolved by peer pressure.

The introduction of the NHS breast screening programme has undoubtedly changed the treatment of breast cancer in the United Kingdom so that surgeons treating cancers detected on screening have gradually been referred more patients with breast symptoms. Regular multidisciplinary meetings between radiologist, pathologist, and surgeon are now attended by a radiotherapist or an oncologist, a breast care nurse, and the data manager. The frequency and attendance at such meetings has not been uniform across the region, although the regular feedback of treatment data to each surgeon seems to have gradually changed practice. External audit of screening units has now been put in place, and the first site visit took place in June 1996. Initial experience suggests that this latter form of audit is more effective in highlighting variations in the management of breast cancer whether screen detected or symptomatic and in effecting change of practice.

Several lessons can be learnt from this prospective audit, but the guidelines issued to surgeons are also deficient. The 1996 update of the guidelines warned surgeons to take note of tumour margins and insist on axillary node status, but they do not mention tumour grade or lymphovascular invasion. More disturbingly, the weekly meeting of the multidisciplinary team to plan patient management is still not attended by a radiotherapist or an oncologist. Only the contraindications to radiotherapy are specified. Perhaps it is not altogether surprising that the adjuvant treatment of screen detected breast cancer has sometimes fallen below optimal standards.

In the face of variations in the treatment and possibly of outcome,[3 4 36] there has been considerable pressure to centralise cancer care in the United Kingdom,[37] to which the Department of Health has responded with proposals to set up specialised centres.[38] Doubts remain as to whether variations in treatment cause major differences in survival[5] and centralisation should not be essential to improve the quality of care of the many women presenting each year with breast cancer. When there is uncertainty about best management, the question should be addressed by an appropriate randomised controlled trial. When benefit has already been clearly established, treatment should be guided by evidence based protocols and audited by regular site visits.

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Appendix 4 Study 4

Clinical outcome data for symptomatic breast cancer: the breast cancer clinical outcome measures (BCCOM) Project[85].

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Clinical outcome data for symptomatic breast cancer: the breast cancer clinical outcome measures (BCCOM) project

T Bates[1], O Kearins[2], I Monypenny[3], C Lagord*[,2] and G Lawrence[2]

[1]The Breast Unit, William Harvey Hospital, Ashford, Kent TN24 0LZ, UK; [2] West Midlands Cancer Intelligence Unit, Quality Assurance Reference Centre, Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; [3]University Hospital of Wales, Heath Park, Cardiff, CF14 4XW, UK

BACKGROUND: Data collection for screen-detected breast cancer in the United Kingdom is fully funded, which has led to improvements in clinical practice. However, data on symptomatic cancer are deficient, and the aim of this project was to monitor the current practice.

METHODS: A data set was designed together with surrogate outcome measures to reflect best practice. Data from cancer registries initially required the consent of clinicians, but in the third year anonymised data were available.

RESULTS: The quality of data improved, but this varied by region and only a third of the cases were validated by clinicians. Regional variations in mastectomy rates were identified, and one-third of patients who underwent conservative surgery for the treatment invasive breast cancer were not recorded as receiving radiotherapy.

CONCLUSION: National data are essential to ensure that all patients receive appropriate treatment for breast cancer, but variations still exist in the United Kingdom and further improvement in data capture is required.

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Keywords: breast neoplasm; data collection; clinical audit; mass screening; surgery; treatment outcome

The NHS Breast Screening Programme (NHSBSP), which was set up in 1988 based on the strength of the Forrest Report (Forrest, 1986), has had a number of important effects. At that time, the management of patients with breast cancer in the United Kingdom lay in the hands of general surgeons and, although many took special interest in the disease, the concepts of the breast care nurse and the multi-disciplinary team (MDT) were yet to be introduced in most hospitals. With the passage of time, the occasional operator came to accept the fact that the overall management of breast cancer required the attention of a dedicated team working out of a specialty breast unit, and the disciplines required for the screening process of specialist radiologists, surgeons and pathologists gradually took hold. However, the requirement for complete, accurate and timely data took longer to gain acceptance.

The collection of data on screen-detected breast cancer was funded from the outset by the NHSBSP, and has been facilitated by a single, breast screening computer system. In addition, the Regional Breast Screening QARCs (Quality Assurance Reference Centres) have been instrumental in providing good-quality data for audit (NHS Breast Screening Programme, 2008). The feedback on variations in practice at annual audit meetings organised both regionally and nationally, has identified outliers in clinical practice and, although peer pressure has been proved to be a slow process in establishing a consensus, it has been possible to show major changes in clinical practice over time (Sauven *et al*, 2003). The appointment of regional representatives for the screening programme led to the formation of the Breast Group of the British Association of Surgical Oncology (BASO), which in turn developed into the Association of Breast Surgery at BASO (ABS), and the presentation of NHSBSP/ABS audit data at the ABS Annual Meeting has become the main focal point for breast surgeons in the United Kingdom.

As the screening data became more robust, the lack of data for the majority of breast cancers that present symptomatically became more obvious, and with this recognition there was a growing concern that variations in the standard of care and sub-optimal practice might well be obscured. Since then, the lack of a national breast cancer database has been a limiting factor; although a BASO database was initially funded by Zeneca and later by the Department of Health, the software included all breast consultations and focussed on communication with the general practitioner rather than on systematic data collection. As a result, the database was not used widely and support was eventually withdrawn.

In response to these concerns, in 2000, the ABS initiated systematic data collection for symptomatic breast cancers and, with the support of those units with good data collection systems, achieved approximately one-third of the estimated national caseload. However, it became apparent with each year of this unfunded initiative that, as new units began submitting data, many collaborators failed to continue, often because of the withdrawal of funding for data managers. There was also a move by some acute hospital trusts to meet their responsibility to provide cancer waiting times data by extending the duties of established breast

*Correspondence: Dr C Lagord, West Midlands Cancer Intelligence Unit, Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; E-mail: catherine.lagord@nhs.net
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Table 1 Surrogate clinical outcome measures for breast cancer proposed by the BCCOM Project team

Proposed surrogate clinical outcome measures
1. Number and proportion of breast cancers for which complete information is received
2. Number of symptomatic and screen-detected breast cancers treated in a hospital per annum
3. Number and proportion of breast cancers for which there is a pre-operative diagnosis
4. Number and proportion of breast cancers given medical treatment only
5. Number and proportion of breast cancers treated surgically
6. Mastectomy rate by breast size: <15; $\geqslant 15$ and $\leqslant 20$; >20 and $\leqslant 35$; >35 and $\leqslant 50$; >50 mm invasive diameter
7. Number and proportion of invasive breast cancers for which nodal status is known
8. Number and proportion of histologically node-negative invasive breast cancers for which more than seven nodes were harvested
9. Number and proportion of invasive breast cancers treated by breast-conserving surgery and receiving radiotherapy
10. Number and proportion of node-positive patients with invasive breast cancers, aged <60 years, receiving chemotherapy
11. Number and proportion of patients with ER-positive invasive breast cancers, receiving hormone therapy

BCCOM = breast cancer clinical outcome measure; ER = oestrogen receptor.

cancer data managers, which also had a negative effect. Over the same period, the ACGBI (Association of Coloproctology of Great Britain and Ireland) took a similar initiative to collect data on the management of colorectal cancer, and more recent attempts to collect data on oesophago-gastric and thyroid cancers by the respective professional associations (the Association of Upper Gastrointestinal Surgeons (AUGIS) and the British Association of Endocrine and Thyroid Surgeons (BAETS)), have suffered the same constraints, with retrieval rates of little more than a third of the national data.

Therefore, it became clear that requests made to individual clinicians or to units were not the right way forward, and in 2003 it was suggested that the data held by the regional cancer registries could be used to resolve the problem. Fears were expressed that data collection was less than complete in some registries, and it subsequently became apparent that permission for data release by individual clinicians and the requirement for anonymisation might be barriers to progress. It was at this stage that the Breast Cancer Clinical Outcome Measures (BCCOM) Project was established using a subset of the national breast cancer data set for maximising the ability of regional cancer registries to participate. As it is recognised that it takes some years before it becomes apparent whether variations in treatment lead to differences in disease-free and overall survival, a series of surrogate clinical outcome measures or 'key performance indicators' has been developed to monitor the extent to which best practice is followed.

METHODS

A breast cancer data set was designed after consultation with the ABS and the UKACR (UK Association of Cancer Registries). Data on all newly-diagnosed primary symptomatic breast cancers are obtained from the UK cancer registries and include basic demographic details, diagnostic information, tumour characteristics and the type of surgical and adjuvant treatment for each case. Male breast cancers are included, but screen-detected cases are excluded as far as possible. To reduce the contamination of symptomatic cases with screen-detected breast cancers, cases flagged by cancer registries as screen-detected breast cancers (as required in the national cancer registry peer review measures (Department of Health, 2005)) are excluded from the BCCOM data set. Cancer registries were asked to flag cases as having had a pre-operative diagnosis of breast cancer if the case record contained a cytology or core biopsy diagnosis that pre-dated the first therapeutic operation.

To validate the accuracy of data collection, cancer registries send the collected data to the concerned consultant breast surgeon. The surgeons in turn are asked to check the validity of data by comparing them with those held on local systems, to make amendments if necessary and to return the data without patient-identifiable details to the BCCOM Project team at the West Midlands Cancer Intelligence Unit (WMCIU). Surgeons may submit unchecked data if they do not have the necessary support mechanisms or if they are convinced that the quality of the data is high. Cases are not included if the surgeon attends less than six symptomatic cases in the year, chooses not to participate or is unknown.

From year 2 onwards, the initial protocol for data collection was modified to ensure compliance with Section 60 of the Health and Social Care Act 2001. It was observed that, although non-identifiable data were stored in the BCCOM central database, the flow of information at the beginning of the audit cycle, from cancer registry to surgeon for validation, was at an individual patient level. Therefore, the updated protocol requested that cancer registries obtain the written consent of individual consultant surgeons before releasing the data to the lead breast surgeon in each hospital. In year 2, all consultant breast surgeons, whether members of the ABS or not, were invited to participate in the BCCOM audit. The regional symptomatic surgical representatives contacted the lead breast surgeon in each hospital, seeking his (or her) help in collecting their colleagues' written consent to release data. In year 3, the process for data transfer from the cancer registries to the relevant consultant surgeon was altered such that for all registries apart from those in South West, Northern Ireland and Scotland, the data were distributed by the BCCOM team at the WMCIU. In addition, cancer registries provided the BCCOM team with data on all the breast cancers diagnosed in each region for that audit year (2004) so that an accurate denominator could be identified.

The data collected were analysed against the surrogate Clinical Outcome Measures devised by the BCCOM steering group (Table 1).

RESULTS

Recruitment

Table 2 shows participation levels in the BCCOM Project in each region and country. In year 2 (cases diagnosed in 2003), there was a 14% reduction in the total number of cases submitted (14 120 compared with 16 407) and very large reductions in some regions. These decreases are in part because of the more reliable exclusion of ineligible screen-detected cases in year 2, but mainly result from changes in the protocols for data collection in year 2, which required written consent from all surgeons before releasing the data of patients under their care to the lead surgeon in each hospital for validation. In year 3 (cases diagnosed in 2004), the UK cancer registries supplied the BCCOM team with data on all 48 983 diagnosed breast cancers. This provided a denominator of the total number of eligible cases with which participation could be compared (Table 3) and an estimate of the annual breast cancer burden in the United Kingdom could be made. Wales had the highest recruitment of cases at 94%, and the Thames Region, which has the highest number of surgeons and the most number of cases, had by far the lowest recruitment at 29%. Figure 1 shows that, in addition to the 1219 cases (3%), which were excluded in year 3 because the surgeon had treated fewer than six symptomatic cases, a further 21 220 symptomatic cases (54% of the total number of symptomatic cases identified by the cancer registries) could not be included either because the surgeon was non-compliant (15 471 cases) or unknown (5749 cases).

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Table 2 Participation by regions and Celtic countries in years 1, 2 and 3 of the BCCOM project

	Diagnosis year				
Region or Celtic country	2002 BCCOM year 1	2003 BCCOM year 2	2004 BCCOM year 3	2002–2004 Total	% eligible cases year 3
Eastern	1691	997	1507	4195	65
North West	1091	524	1397	3012	41
Northern and Yorkshire	2419	2029	1910	6358	52
Northern Ireland	640	367	432	1439	45
Oxford	1341	1442	899	3682	62
Scotland	934	181	1836	2951	49
South West	3253	1001	2234	6488	54
Thames	1750	2709	1530	5989	29
Trent	408	1588	1453	3449	52
Wales	351	952	1201	2504	94
West Midlands	2529	2330	2340	7199	77
Total	16407	14120	16739	47266	52

BCCOM = breast cancer clinical outcome measure.

Table 3 Participation by surgeons in year 3 of the BCCOM project (cases diagnosed in 2004)

	Eligible surgeons[a]			Eligible surgeons who submitted data			Take up BCCOM year 3	
Region or Celtic country	Number of surgeons	Number of cases	Average, cases/ surgeon	Number of surgeons	Number of cases	Average, cases/ surgeon	% of eligible surgeons	% of eligible cases
Eastern	42	2314	55	15	1507	100	35.7	65.1
North West	66	3442	52	20	1397	70	30.3	40.6
Northern and Yorkshire	55	3692	67	25	1910	76	45.5	51.7
Northern Ireland	16	962	60	6	432	72	37.5	44.9
Oxford	18	1447	80	12	899	75	66.7	62.1
Scotland	46	3767	82	30	1836	61	65.2	48.7
South West	56	4121	74	27	2234	83	48.2	54.2
Thames	77	5283	69	18	1530	85	23.4	29.0
Trent	35	2782	79	15	1453	97	42.9	52.2
Wales	28	1276	46	18	1201	67	64.3	94.1
West Midlands	49	3027	62	35	2340	67	71.4	77.3
Total	488	32113	66	221	16739	76	45.3	52.1

BCCOM = breast cancer clinical outcome measure. [a]Surgeons were eligible if they treated 6 or more symptomatic breast cancer cases in 2004.

In year 3 (cases diagnosed in 2004), 16611 female breast cancers were included and 128 breast cancers were detected in men. Slightly more breast cancers presented in the left breast (52 *vs* 48%). A total of 25% of cases were diagnosed in patients aged <50 years, 28% in those aged 50–64, 9% in those aged 65–69 and 37% in patients aged 70 or older.

Screening flag

In year 3 (cases diagnosed in 2004), of the 48983 breast cancers cases registered by cancer registries, 9805 (20%) were flagged as screen detected (Figure 1). From the NHSBSP/ABS audit of screen-detected cancers, it is known that 14057 cases would have had a date of first offered appointment to screening in 2004, indicating that the cancer registries had accurately assigned only 70% of the screen-detected cases. Those regions that did not have the robust communications between cancer registries and breast screening QA reference centres, which are required to flag screen-detected breast cancers accurately, tended to have the highest rates of non-invasive breast cancers (up to 10% in year 1) and the greatest proportion of cases in the then screening age group (50–64 years) included in their BCCOM cohorts. The proportion of non-invasive breast cancers decreased from 6.3% in year 1 to 5.8% in year 3, but this rate is still higher than that expected from the literature, which suggests that only 3% of non-invasive breast cancers present symptomatically (Blamey *et al*, 2007) compared with 21% (including micro-invasion) of screen-detected cases (NHS Breast Screening Programme, 2008). This provides surrogate evidence of continuing contamination by screen-detected breast cancers in some regions. The recent requirement of the national cancer registry peer review measures for registries to obtain details of screen-detected breast cancers from breast screening QA reference centres has greatly improved the situation compared with that of 2003, and it is hoped that in year 4 (cases diagnosed in 2005), all registries will have correctly identified their screen-detected cases.

Histological type

Of the 47266 breast cancer cases that were submitted to BCCOM during years 1–3, invasive ductal carcinoma was the most common histological type (68%), followed by invasive lobular carcinoma (12%), ductal carcinoma *in situ* (5%), mixed invasive carcinoma (5%), mucinous carcinoma (2%) and tubular carcinoma (1%). These proportions will probably change slightly when all screen-detected cases have been eliminated, but they illustrate how the audit could provide a source of a relatively large number of rarer tumours for research.

Nodal status

Of the breast cancer cases submitted in year 3 (cases diagnosed in 2004), 31.8% were lymph node positive, 34.3% were lymph node negative and 33.9% had unknown nodal status (Table 4). For surgically treated cases, 40.5% were lymph node positive, and the proportion with

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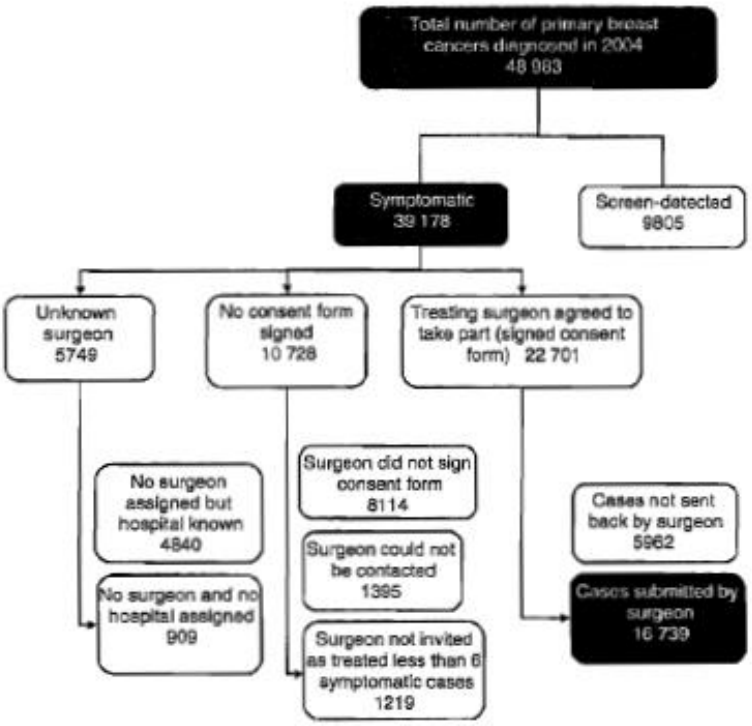

Figure 1 Total number of breast cancers recorded in BCCOM year 3 (cases diagnosed in 2004).

unknown lymph node status was 14.4%. The relatively high proportion of surgically treated cases with unknown lymph node status may be because of the fact that some cancer registries do not record data on lymph node status and tumour size for patients who receive neoadjuvant chemotherapy or radiotherapy. This is because the use of such data to determine the Nottingham Prognostic Index (NPI) (Haybittle *et al*, 1982) or the pathological TNM stage at diagnosis could result in an inaccurate under-staging of the cancer. Recording of the axillary node status increased during years 2–3 of the audit for all age groups, but was higher in those under the age of 50 years (89%) than in those aged over 80 (72%), largely because the latter group are less likely to undergo surgery.

Tumour size

In year 3, for 31.4% of the cancers included in the cohort, the maximum diameter of the invasive tumour component was <20 mm, and for 24.6% of cases the invasive size was unknown. For surgically treated cases, the invasive tumour size was unknown for only 7% of cancers. In most of the latter cases, the invasive size at diagnosis was not recorded either because the patient had received neoadjuvant treatment, which may have reduced the original size at diagnosis, or because the tumour was removed in several pieces from more than one operation.

Tumour grade

In year 3, 12.0% of invasive cancers were classified as grade 1, 41.0% were grade 2 and 33.2% were grade 3. For surgically treated cases, these proportions were 12.8, 43.3 and 37.9% respectively. The grade was unknown for 13.9% of all cases, but this decreased to 6.0% for surgically treated cases. Pathologists are reluctant to report the grade of the tumour after neoadjuvant treatment, which may partly explain the latter shortfall. There was little variation in tumour grade over the 3 years of the study. There was a clear association between nodal status, tumour grade and size; with grade 1 cancers being smaller and more likely to be node negative (Figure 2).

Nottingham prognostic index

In year 3, the NPI score could be calculated for 80% of the surgically treated invasive breast cancers. The NPI could not be calculated in 20% of the cases because of missing grade (6%), size (7%) and/or nodal status (14%). Nodal status was not available in 28% of patients over the age of 80 years. Among those cases with a known NPI, 51% were early breast cancers with an NPI score of below 4.4 and were categorised into the Excellent Prognostic Group (EPG), Good Prognostic Group (GPG) or Moderate Prognostic Group 1 (MPG1). Overall, 49% were categorised into the MPG2 or Poor Prognostic Group (PPG) (Blamey *et al*, 2007). These data are in marked contrast to screen-detected breast cancers. In the NHSBSP/ABS audit of screen-detected breast cancers that were diagnosed in 2004, 83% of cases had an NPI score of below 4.4 (24% in the EPG, 36% in the GPG and 22% in the MPG1), 11% were in the MPG2 and 6% in the PPG. The variation in NPI with age at diagnosis for surgically treated screen-detected and symptomatic breast cancers is shown in Figure 3.

Surrogate clinical outcome measures

The surrogate clinical outcome measures proposed by the BCCOM Project team are shown in Table 1. The number of cases treated in each breast unit cannot be calculated from BCCOM data as not all surgeons agreed to participate in the audit. Pre-operative diagnosis rates varied between 12% in Scotland and 87% in the West Midlands and were 40% or less in five regions. The NHSBSP/ABS

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audit of screen-detected breast cancer has shown an improvement in pre-operative diagnosis from 63% between 1996 and 1997 to 94% between 2006 and 2007 (NHS Breast Screening Programme, 2008). Reliable pre-operative diagnosis data were only available from at most three cancer registries, because many of them record data only from pathology reports for resection specimens and do not record details from any preceding cytology or core biopsy reports. The numbers of nodes reported in what proved to be a negative sample are shown in Figure 4. In those patients treated with breast-conserving surgery, the majority with negative axillae had eight or more nodes reported.

Table 4 Characteristics of the invasive breast cancers included in year 3 of the BCCOM Project (cases diagnosed in 2004)

Invasive breast cancers diagnosed in 2004	All invasive (15 540)			Surgically treated only (11 725)		
	No. of cases	%	% (when known)	No. of cases	%	% (when known)
Nodal status						
Positive	4941	31.8	48	4754	40.5	47
Negative	5332	34.3	52	5287	45.1	53
Unknown	5267	33.9	NA	1684	14.4	NA
Grade						
I	1862	12.0	14	1501	12.8	14
II	6371	41.0	48	5073	43.3	46
III	5152	33.2	38	4449	37.9	40
Unknown	2155	13.9	NA	702	6.0	NA
Invasive size						
<15 mm	2544	16.4	22	2360	20.1	22
15–<20 mm	2340	15.1	20	2220	18.9	20
20–<50 mm	5862	37.7	50	5472	46.7	50
50+ mm	968	6.2	8	849	7.2	8
Unknown	3826	24.6	NA	824	7.0	NA
NPI						
EPG+GPG+MPG1	4896	31.5	51	4816	41.1	51
MPG2 + PPG	4673	30.1	49	4567	39.0	49
Unknown	5971	38.4	NA	2342	20.0	NA
Surgery						
Breast-conserving surgery	5583	35.9	41	5583	47.6	NA
Mastectomy	6142	39.5	45	6142	52.4	NA
No surgery	2034	13.1	15	NA	NA	NA
Unknown	1781	11.5	NA	NA	NA	NA

BCCOM = breast cancer clinical outcome measure; EPG = Excellent Prognostic Group; GPG = Good Prognostic Group; MPG1 = Moderate Prognostic Group 1; MPG2 = Moderate Prognostic Group 2; NPI = Nottingham Prognostic Index; PPG = Poor Prognostic Group.

Surgical treatment

Variations in the treatment of invasive cancers with age at diagnosis in year 3 are shown in Figure 5. The proportion of women not receiving surgery increased with age from 3.5% in women aged <50 years to 47.7% in women aged 80 or more. The proportion receiving breast-conserving surgery decreased with age from 51.4% in women aged <65 years to 41.9% in women aged 65 or more. For surgically treated cases, in each region, the breast-conserving surgery rate was higher in younger patients, but this difference between age groups was most marked in Oxford (58 *vs* 43%) and in Wales (54 *vs* 26%). The proportion of cases receiving breast-conserving surgery was lower than the UK average of 47.6% in Trent, Northern Ireland and Northern and Yorkshire and was higher than the UK average in the Thames Region. Figure 6 shows the regional variation in the operation types recorded for invasive breast cancers with a diameter <15 mm. At 42%, the Trent Region had the highest mastectomy rate for this group of small tumours, and Northern Ireland and the North West Region the lowest (19 and 23% respectively). However, as the proportion of cases with unknown operation type was high in these areas, care should be taken in the interpretation of these reported patterns of care.

Adjuvant treatment

Figure 7 shows, for all breast cancer patients with known adjuvant therapy included in BCCOM years 1–3, how the proportions of cases receiving adjuvant radiotherapy, chemotherapy and hormone therapy vary with age at diagnosis. The recorded use of hormone therapy increases with age, with 85.5% of patients aged 80 years and more receiving hormone therapy compared with 66.4% of patients aged <50 years. This older age group is less likely to receive surgical intervention, and as such hormone therapy may be the only form of active treatment provided. In contrast, the recorded use of radiotherapy decreases with increasing age. In total, 78.3% of the patients aged <50 years received radiotherapy compared with 30.6% of patients aged over 80. The effect of age on recorded treatment modality is most marked for chemotherapy, where 77.2% of patients aged <50 received chemotherapy, but only 21.9% of patients aged 65–79 and 16% of patients aged 65 and more.

In the 3-year period between 2002 and 2004, radiotherapy was recorded as having been received by 68.7% of the 16 487 patients included in the audit who were treated with conservative surgery.

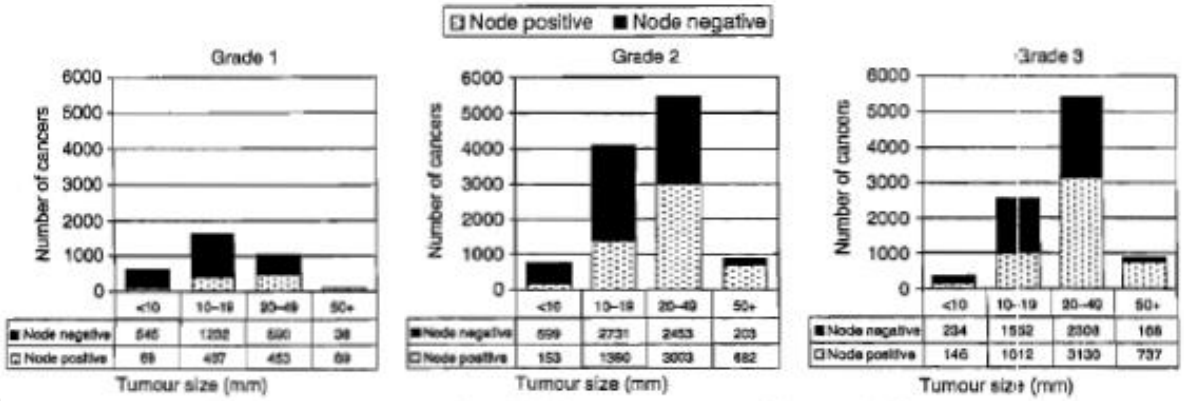

Figure 2 Variation in lymph node status with tumour grade and size for tumours included in BCCOM years 1–3.

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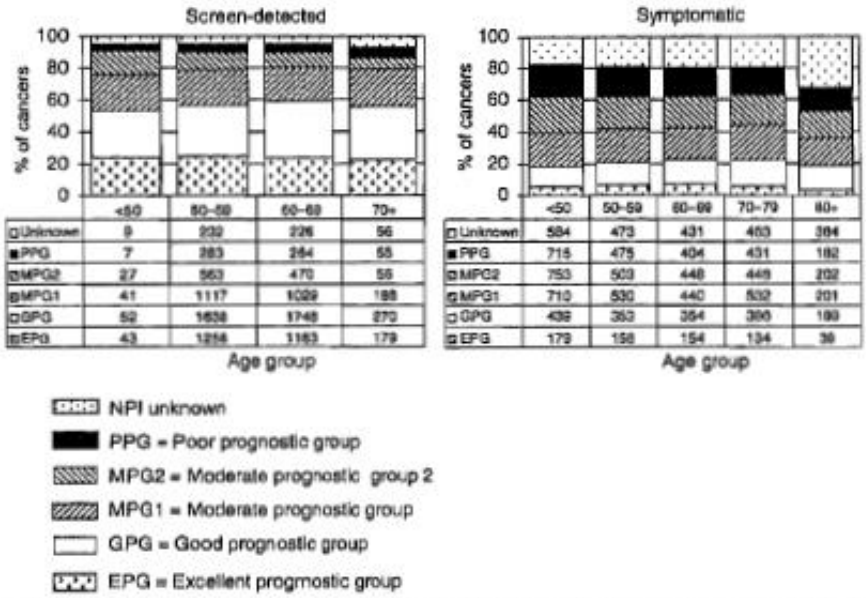

Figure 3 Variation in Nottingham Prognostic Index (NPI) with age group for breast cancers diagnosed in 2004. Sources: screen-detected breast cancers included in the NHSBSP/ABS annual audits (2003–2004 and 2004–2005) of screen-detected breast cancer; symptomatic breast cancers included in BCCOM year 3.

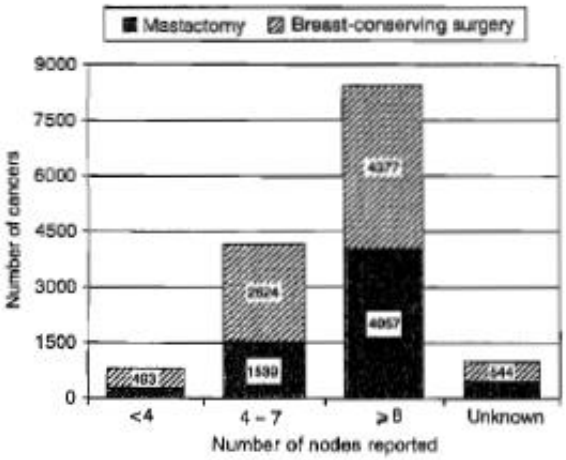

Figure 4 Variation in the number of nodes reported in node-negative patients in BCCOM years 1–3 who received breast-conserving surgery or mastectomy.

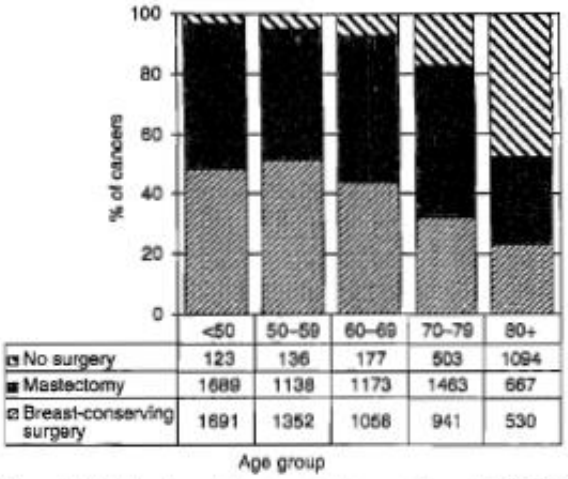

Figure 5 Variation in surgical treatment with age at diagnosis in BCCOM year 3 (invasive cancers diagnosed in 2004).

A total of 1126 cases (6.8%) were recorded as not having received radiotherapy, but for a further 4029 cases (24.4%), it was not known whether radiotherapy was given. Fewer elderly patients were recorded as having undergone radiotherapy after conservative surgery, with the proportion known to have received radiotherapy decreasing from 70% in patients aged under 50 years to 43% in those aged 80 and above.

In the 3-year period of 2002–2004, chemotherapy was recorded as having been received by 53% of the 13 100 patients with invasive breast cancer who were node positive (Figure 8). A total of 2630 cases (20.1%) were recorded as not having received chemotherapy and for a further 3524 cases (26.9%), it was not known whether chemotherapy was given. In node-positive patients under the age of 70 years, the proportion known to have received adjuvant chemotherapy was 68% compared with only 12% in those aged 70 or more.

Of the cases with known hormone treatment that were receptor positive (oestrogen receptor (ER) positive and/or progesterone receptor), 11% (1241 cases) did not receive any form of hormone treatment. For 16% (2418 cases) of the receptor-positive invasive cancers, it was not known whether hormone treatment was given. Only 3961 cases were receptor negative and of these, 9% (367 cases) were known to have been prescribed hormone therapy. Of the 5112 invasive breast cancer cases who did not undergo surgery, 3106 (61%) were recorded as having received hormone therapy, but only 2176 (43%) had known ER status. It would be anticipated that the majority of these mostly elderly patients, who did not

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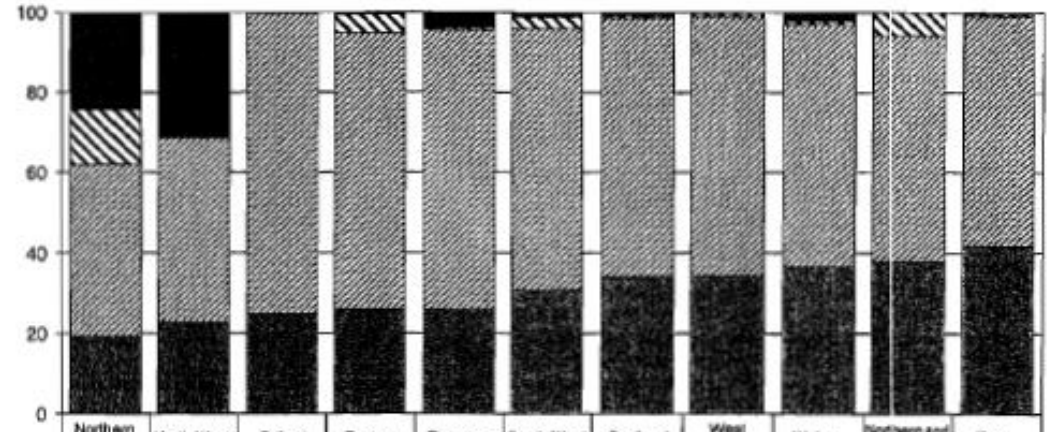

	Northern Ireland	North West	Oxford	Eastern	Thames	South West	Scotland	West Midlands	Wales	Northern and Yorkshire	Trent
■ Unknown	51	147	1	4	40	13	4	2	6	1	1
▨ No surgery	29	1	1	43	5	36	3	11	3	65	2
▨ Breast-conserving surgery	90	215	373	627	733	783	289	745	165	650	214
■ Mastectomy	41	107	125	238	275	365	151	392	100	438	158

Figure 6 Variation with region and Celtic country in the operations recorded for patients with small invasive breast cancers (invasive diameter < 15 mm) in BCCOM year 3 (cancers diagnosed in 2004).

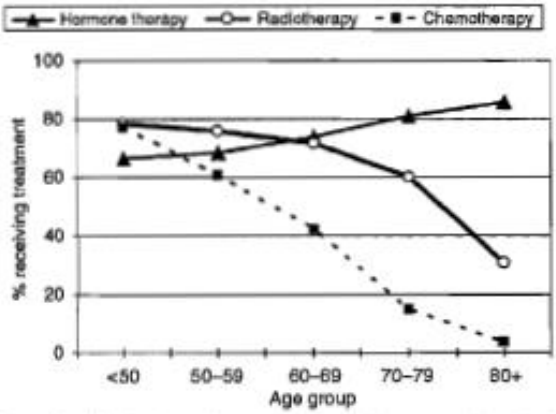

Figure 7 Variation in adjuvant treatment with age at diagnosis for BCCOM years 1–3. Cases for which it was not known whether a patient had received treatment have been excluded. In the elderly patients, hormone therapy was sometimes the sole primary treatment.

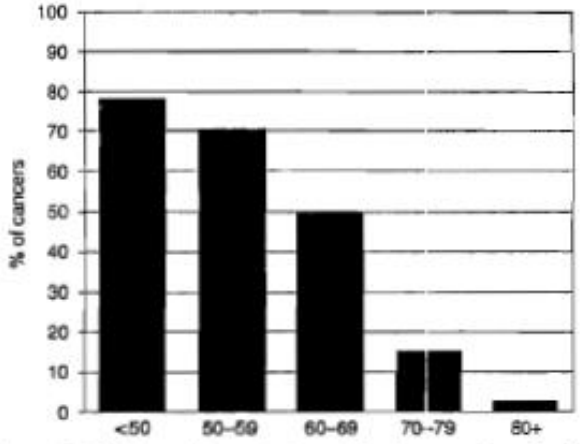

Figure 8 Variation with age at diagnosis in the proportion of node-positive breast cancer patients in BCCOM years 1–3 recorded as having received chemotherapy. Cases for which it was not known whether a patient had received chemotherapy have been excluded.

undergo an operation, would have had strong contraindications to surgery and would have been treated with hormonal therapy. Unfortunately, for all cases for which hormone therapy data are recorded, tamoxifen is not distinguished from aromatase inhibitors and switches are not identified.

DISCUSSION

Participation by breast surgeons in the BCCOM Project is not mandatory, but it is strongly encouraged by their professional body, the ABS. Previous experience with the NHSBSP/ABS audit of screen-detected breast cancers has shown that a regular audit of surgical practice improves standards and highlights outliers, in which local protocols are not in keeping with the accepted best practice (Sauven *et al*, 2003). The regional symptomatic representatives of ABS are encouraged to review participation in their own areas and to identify ways in which this could be improved. Although progress in data collection has been improved by central notification of surgeons in most regions, the data in Figure 1 underline the continuing difficulty in depending on the voluntary and active participation of individual surgeons in the submission and validation of data. The surgeon does not own the data, and although their written permission for the release of patient details under their care has been a prerequisite of the BCCOM audit to date, it seems clear that the collection of cases will not approach completeness on this basis. Furthermore, patients are increasingly managed by a MDT rather than by an individual consultant surgeon, who will be involved in the initial management plan but who may have little or no responsibility for the subsequent treatment.

At a national level, cancer registry data are now matched to data held in national data sets, such as Hospital Episode Statistics (HES). From those cancer registries, which routinely compare their data with those on HES, it has become apparent that the latter can provide

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useful information on operations for which the pathology reports may not have been transferred to or accessed by cancer registries because no malignancy is reported. These include additional operations to remove nodes that are negative for tumour deposits and repeat operations on the breast, such as delayed reconstruction, which have a benign pathological outcome. Most importantly, matching cancer registration and HES data also allows the identification of surgeons and hospitals for each type of treatment if these data have not been collected by the cancer registry, thus increasing the number of cases that can be returned to surgeons for checking.

It has been possible to derive the surrogate outcome measures proposed by the BCCOM Project team for a high proportion of the symptomatic breast cancers included in the audit. The surrogate outcome measures developed to date are restricted, to an extent, by the common data items available from all cancer registries. As yet, quality-of-life data and/or patient-reported outcome measures have been collected on a research basis only, but it is clear that they should become part of the standard outcome measures in the future. The inclusion of reconstruction after mastectomy as a key performance indicator should also be considered, and it is hoped that the inclusion of a surrogate outcome measure for this area will be possible once HES data are obtained for all breast cancer cases treated in England.

Regional variations in surgical practice, especially with respect to mastectomy rates, have been highlighted in the BCCOM audit, but variations in individual clinical practice are more difficult to identify as data were collected by the hospital or unit (Moritz *et al*, 1997). The reasons for regional variations are unclear, but mastectomy rates tend to be higher in rural areas and this association is not confined to the United Kingdom (Craft *et al*, 1997; Gort *et al*, 2007). The data for 2002–2004 indicate that patients with lymph node-negative disease had a large number of nodes removed even when the surgical procedure was conservative (Figure 4). This time period reflects practice before as well as including the wide-scale introduction of sentinel lymph node biopsy (SLNB) for which the audit protocol required a nodal clearance for all patients undergoing SNLB, and future data should show a change in this practice. Variations in practice style by individual surgeons are well recognised (Craft *et al*, 1997; Hawley *et al*, 2006), but in breast cancer, any consequent variation in patient outcomes such as recurrence rates or overall survival rates may take many years to become apparent (Purushotham *et al*, 2001). It is for this reason that surrogate clinical outcome measures have been proposed to reflect best practice, in order that publication of the data may try to persuade outliers to change their practice.

The place of radiotherapy after conservative surgery for invasive breast cancer is well-established (Clarke *et al*, 2005), and yet there is evidence that this treatment has been under-used. There may occasionally be a good reason not to give post-operative radiotherapy but, if the BCCOM data are correct, a third of such patients did not undergo prophylactic treatment and a third of these would be expected to develop local recurrence. The indications for radiotherapy for patients with *in situ* breast cancer are less well defined, but current variations in practice are not always based on the available evidence (Dodwell *et al*, 2007). There is also concern that 20% of patients with node-positive disease under the age of 50 years did not receive adjuvant chemotherapy (Figure 7). There is now a requirement that the treatment of all patients with breast cancer should be considered at a multi-disciplinary meeting, and any failure to consider an appropriate adjuvant treatment should be a thing of the past. Reflection on performance data such as those provided by audits such as BCCOM should assist local breast teams in identifying any non-compliance with national practice in their protocols and for facilitating the targeting of areas requiring modifications to make them consistent with best clinical practice.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix 5 Study 5

A Population Based Study of Variations in Operation Rates for Breast Cancer, of Comorbidity and Prognosis at Diagnosis: Failure to Operate for Early Breast Cancer in Older Women[21].

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A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: Failure to operate for early breast cancer in older women

T. Bates [a,*], T. Evans [b], C. Lagord [b], I. Monypenny [c], O. Kearins [d], G. Lawrence [b]

[a] The Breast Unit, William Harvey Hospital, Ashford, Kent TN24 0LZ, UK
[b] Public Health England, Knowledge and Intelligence Team (West Midlands), Birmingham B3 2PW, UK
[c] Llandough University Hospital, Cardiff CF 64 2XX, UK
[d] Public Health England, Cancer Screening QA Reference Centre, Birmingham B3 2PW, UK

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Abstract

Background: Older women are less likely to have surgery for operable breast cancer. This population-based study examines operation rates by age and identifies groups which present with early or late disease.
Methods: 37 000 cancer registrations for 2007 were combined with Hospital Episode Statistics comorbidity data for England. Operation rates were examined by age, ethnicity, deprivation, comorbidity, screen-detection, tumour size, grade and nodal status. Early and late presentation were correlated with Nottingham Prognostic Index (NPI) groups and tumour size.
Results: The proportion of women not having surgery increased from 7–10% at ages 35–69 to 82% from age 90. From age 70, the proportion not having surgery rose by an average of 3.1% per year of age. Women with a Charlson Comorbidity Index score of ≥1 (which increased with age), with tumours >50 mm or who were node positive, were less likely to have surgery. Although women aged 70–79 were more likely to have larger tumours, their tumours were also more likely to have an excellent or good NPI ($p < 0.001$). Good prognosis tumours were more likely to be screen-detected, and less likely in women aged 0–39, the deprived and certain ethnic groups ($p < 0.02$).
Conclusions: From age 70 there is an increasing failure to operate for breast cancer. Younger women and certain ethnic groups presented with more advanced tumours. Older women had larger tumours which were otherwise of good prognosis, and this would not account for the failure to operate which may in part be related to comorbidity in this age group.
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Keywords: Breast neoplasm; Data collection; Age factors; Comorbidity; Ethnic groups; Socioeconomic status; Surgery

Introduction

The Second All Breast Cancer Report (SABCR), which analysed over 50 000 cases of breast cancer presenting in the UK in 2007, highlighted the increasing evidence that deprivation and older age are associated with late presentation of breast cancer.[1] However, this study confirmed that although older women were less likely to have small tumours and to be treated by surgery, the prognostic features of their breast cancers were otherwise more favourable.[2,3] There is increasing concern that older women may be denied surgical treatment solely on the ground of age,[4] but the actual relationship between age and operation rates for breast cancer is less well documented. It seems likely that comorbidity may be a significant confounding factor[5] and records of operation rates and comorbidity available for England and the 2007 SABCR data for England alone have therefore been further analysed across all age groups.

The aim of this study was to examine age-related operation rates for breast cancer and comorbidity in a large population and to identify those groups likely to present with early or late disease.

* Corresponding author. Lamplands, East Brabourne, Ashford, Kent TN25 5LU, UK. Tel.: +44 01233 750304; fax: +44 01233 750599.
E-mail address: bates.tom@virgin.net (T. Bates).

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Methods

Data for the cohort of women in England included in the SABCR were constructed using the National Cancer Registration Database (NCDR), Hospital Episode Statistics (HES), Breast Cancer Clinical Outcome Measures (BCCOM) audit and NHS Breast Screening Programme and Association of Breast Surgery audit data.

The proportion of patients by age quintile not having an operation was assessed and a chi-squared test for trend was performed in order to identify any statistical significance.

Early breast cancer was correlated to the following prognostic markers, 1) the Nottingham Prognostic Index[6] (NPI) Excellent & Good Prognostic Groups (EPG/GPG) and 2) a tumour with diameter of 20 mm or less. Late detection of breast cancer was correlated to 3) the NPI Poor Prognostic Group (PPG) and 4) not having an operation. Outcomes 1–3 (as defined above) were analysed with the following factors: age group by decade from ≤39 to 80+ years, ethnic group, deprivation quintile, comorbidity as assessed by the Charlson Comorbidity Index,[7] screening status and surgical treatment. Outcome 4 was analysed by age group by decade, ethnic group, deprivation quintile, comorbidity as assessed by the Charlson Comorbidity Index, screening status, tumour size, tumour grade and nodal status. These factors were included as potential explanatory variables in the regression models. To calculate Charlson Co-morbidity Index scores, individual patients were matched to HES data to identify episodes of treatment for comorbid conditions in the 30 months prior to and 3 months post cancer diagnosis. The scores associated with each comorbid[7] condition were then summed to provide an overall score for each patient. Where a patient had similar conditions recorded (e.g. liver disease and severe liver disease) the condition with the highest score was retained. The index cancer and all other cancer diagnoses were removed from the calculation so that a comorbidity score in the absence of cancer was derived.

Charlson comorbidity scores were not obtained for 3996 patients (11%) who could not be matched to a HES record. The proportion of patients without a HES match varied from 8% in the 0–39 age group to 10% in those aged 70–79 and 22% in those aged 80 and above.

Statistical analysis

A number of binary variables were generated based upon tumour characteristics (NPI, grade, nodal status and tumour size), and the presence/absence of surgical treatment in order to distinguish between Early/Not Early and Late/Not Late diagnosis. The likelihood of presenting with early or late presentation breast cancer was investigated using multivariate logistic regression models. The effects of ethnicity, age at diagnosis, surgical treatment, deprivation, co-morbidity, tumour characteristics and method of presentation were included as independent categorical variables in each logistic regression model. The results are presented as adjusted odds ratios. The following were used as the base level for the multivariate comparisons of likelihood, 1–3: age group - 50–59 years; deprivation quintile – average deprivation (quintile 3); ethnicity - white; screening status - symptomatic; Charlson Comorbidity Index score = 0 and surgical treatment – surgery. Early or Late presentation was the dependent variable throughout. For the multivariate analysis of the likelihood of not having surgery (4) the following additional base levels were used: tumour size - ≤20 mm; tumour grade – grade 1; nodal status – node negative. The proportion of patients not having an operation was assessed and a chi-squared test for trend was performed in order to identify any statistical significance.

To account for missing data in the tumour grade, size and nodal status variables, an extra category was coded within that variable. The reasons for this were twofold: a) omitting these from the analysis would have removed valuable data from the regression model and b) the missing data were likely to be of direct interest to the outcome variable, those patients who did not have an operation. The fact that the data were missing might be due to the inappropriateness of collecting that data item (for example if tumour size is mainly assessed following surgery, any patient who does not undergo surgery may by default have an unknown tumour size). Where tumour size was recorded as not assessable this was scored as size unknown.

All analyses were conducted in Stata 11.2 (*StataCorp LP, College Station, Texas USA*). p-Values <0.05 were considered statistically significant.

Results

In 2007, 37 113 women in England presented with primary invasive breast cancer, of whom 30 318 (81.7%) had their first surgical treatment within 6 months of their diagnosis recorded in the NCDR. A further 351 women (1%) had their first surgical treatment within 6 months of their diagnosis recorded on HES and 135 women had their first surgery between 6 months and two years after their diagnosis (0.4%).

The proportion of women aged 35–69 not having surgery was 7–10%. From age 70, this rate rose by an average of 3.1% per year of age to reach 82% ($p < 0.0001$) in those aged 90 or over (Fig. 1). A Charlson Comorbidity Index (CCI) score could be derived for 91% of women aged under 80, but in those aged 80 years and over, a CCI score was available for only 78% of cases. In women aged under 70, where the CCI was available, a score of greater than 2 was recorded for 0.73% of cases, rising to 3.0% in those aged 70–79 and 5.5% in those aged 80 and over ($p < 0.001$). For women aged 0–69, the proportion of cases recorded with a CCI score of 0 was 86% decreasing from 94% (age 0–39) to 82% (age 60–69). Even in those women aged 70 or over, 72% had no recorded comorbidity (CCI score = 0) (Fig. 1). However, the availability of HES data

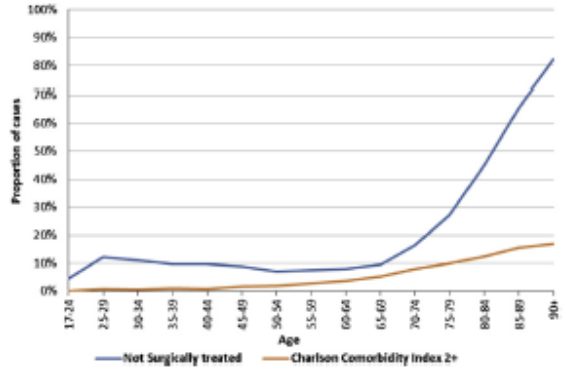

Figure 1. Variation in operation rates for breast cancer with age at diagnosis and the proportion of women with a Charlson Comorbidity Index (CCI) of 2 or more.

is dependent on a hospital admission and it is probable that those women who did not have surgery will have had a higher level of comorbidity.

The following groups were more likely to have a good prognosis EPG/GPG breast cancer; women whose breast cancer was screen-detected rather than symptomatic; women aged 40–49, 60–69 and 70–79 ($p \leq 0.02$). Women of black or Asian ethnicity, women from the most or more deprived cohorts (quintiles 1&2) and women aged 0–39 were less likely to have an EPG/GPG breast cancer ($p < 0.03$) (Table 1).

The following groups were more likely to have a small breast cancer ≤20 mm in diameter: women whose breast cancer was screen-detected, women aged 40–49 and 60–69 ($p \leq 0.02$). Women of black and Asian ethnicity, women from the most deprived cohort, women aged 70–79 and 80 or over and those who did not have surgery were less likely to have a breast cancer ≤20 mm in diameter ($p < 0.02$). The tumour size was recorded as not assessable in only 154 cases (Table 2).

Women of all non-white ethnic groups were more likely to have a poor prognosis PPG breast cancer ($p = 0.02$). Women aged 60–69 and women with screen-detected breast cancers were less likely to have a poor prognosis PPG breast cancer ($p = 0.02$) (Table 3). Tables 1 and 3 document the demographics for the EPG/GPG and PPG groups, the extremes of the Nottingham Prognostic Index.

Women with screen-detected breast cancers were significantly less likely not to have an operation ($p < 0.002$) as were black women ($p < 0.03$) and women aged under 50 ($p < 0.02$), (i.e. were more likely to have an operation than the base level, women aged 50–59) (Fig. 2). Women aged 60 or over were less likely to have an operation, with the Odds Ratio for those aged 60–69 of 1.38 (1.15, 1.67) increasing to 6.07 (5.10, 7.22) for those aged 80 and over. Although tumours between 21 and 50 mm in size showed no increased likelihood of not having surgery ($p = 0.20$), those greater than 50 mm in size were

Table 1
Odds Ratio of presenting with a good prognosis breast cancer (EPG/GPG).

Characteristics ($n = 37\,113$)	Odds ratio (95% CI)	p
Ethnicity ($n = 29\,846$)		
White	Base level	
Asian	0.75 (0.60, 0.94)	0.0118
Black	0.36 (0.25, 0.53)	<0.0001
Other/Chinese	0.89 (0.68, 1.18)	0.4555
Age group ($n = 37\,113$)		
Aged 0–39	0.61 (0.50, 0.76)	<0.0001
Aged 40–49	1.14 (1.02, 1.28)	0.0214
Aged 50–59	Base level	
Aged 60–69	1.14 (1.06, 1.24)	0.0006
Aged 70–79	1.21 (1.09, 1.34)	0.0002
Aged 80+	1.10 (0.94, 1.29)	0.2097
Surgical treatment ($n = 30\,540$)		
Surgery	Base level	
No surgery	0.75 (0.44, 1.29)	0.3085
Deprivation ($n = 36\,952$)		
Most deprived	0.84 (0.75, 0.93)	0.0017
More deprived	0.89 (0.80, 0.98)	0.0254
Average deprivation	Base level	
More affluent	0.92 (0.84, 1.01)	0.1096
Most affluent	0.96 (0.87, 1.05)	0.4377
Comorbidity ($n = 33\,117$)		
Charlson score = 0	Base level	
Charlson score = 1	1.01 (0.92, 1.11)	0.7259
Charlson score = 2	0.99 (0.81, 1.21)	0.9805
Charlson score = 3	0.73 (0.47, 1.13)	0.1638
Charlson score ≥4	1.28 (0.74, 2.22)	0.3685
Screening status ($n = 37\,113$)		
Symptomatic	Base level	
Screen detected	4.78 (4.43, 5.16)	<0.0001

significantly less likely to have surgery (OR 3.05, $p < 0.0001$). An increased likelihood of not having surgery was observed for node positive tumours ($p < 0.03$) and for grade 2 tumours ($p < 0.0001$) but not for grade 3 tumours. The likelihood of not having surgery increased progressively with Charlson Comorbidity Index score from 1.28 (1.11, 1.48) for a CCI = 1 to 7.6 (4.79, 12.0) for a CCI greater than or equal to 4 ($p < 0.001$) (Fig. 2). As expected where tumour size, grade or nodal status was unknown there was a greatly increased likelihood that the patient did not have an operation ($p < 0.0001$).

Discussion

This study has shown in a large population that operation rates for invasive breast cancer show little variation with age until the age of 70 is reached. From that age there is a progressive increase in the proportion of women who do not have surgery, so that by age 90 only a fifth of patients have an operation for apparently operable breast cancer. The prognostic indicators for breast cancer at presentation vary with socio-economic status, ethnicity, screen detection and age. As well as with age, the primary operative treatment varies with screen detection, comorbidity and tumour size, grade and node status. There is a wealth of evidence in the literature that older women with breast cancer receive less

Table 2
Odds Ratio of presenting with a small breast cancer ≤20 mm.

Characteristics ($n = 37\ 113$)	Odds ratio (95% CI)	p
Ethnicity ($n = 29\ 846$)		
White	Base level	
Asian	0.76 (0.63, 0.91)	0.0027
Black	0.74 (0.59, 0.94)	0.0150
Other/Chinese	0.81 (0.64, 1.03)	0.0915
Age group ($n = 37\ 113$)		
Aged 0–39	1.10 (0.96, 1.26)	0.1532
Aged 40–49	1.12 (1.02, 1.23)	0.0137
Aged 50–59	Base level	
Aged 60–69	1.09 (1.01, 1.18)	0.0197
Aged 70–79	0.84 (0.77, 0.92)	0.0002
Aged 80+	0.67 (0.60, 0.76)	<0.0001
Surgical treatment ($n = 30\ 540$)		
Surgery	Base level	
No surgery	0.79 (0.66, 0.94)	0.0091
Deprivation ($n = 36\ 952$)		
Most deprived	0.89 (0.81, 0.97)	0.0154
More deprived	0.97 (0.89, 1.06)	0.5367
Average deprivation	Base level	
More affluent	1.03 (0.95, 1.12)	0.3578
Most affluent	1.00 (0.92, 1.09)	0.8363
Comorbidity ($n = 33\ 117$)		
Charlson score = 0	Base level	
Charlson score = 1	0.97 (0.89, 1.05)	0.5500
Charlson score = 2	0.97 (0.82, 1.14)	0.7451
Charlson score = 3	0.87 (0.63, 1.21)	0.4320
Charlson score ≥4	0.76 (0.48, 1.17)	0.2207
Screening status ($n = 37\ 113$)		
Symptomatic	Base level	
Screen detected	3.96 (3.69, 4.24)	<0.0001

Table 3
Odds Ratio of presenting with a poor prognosis breast cancer (PPG).

Characteristics ($n = 37\ 113$)	Odds ratio (95% CI)	p
Ethnicity ($n = 29\ 846$)		
White	Base level	
Asian	1.77 (1.42, 2.21)	<0.0001
Black	2.57 (1.93, 3.42)	<0.0001
Other/Chinese	1.45 (1.06, 1.98)	0.0173
Age group ($n = 37\ 113$)		
Aged 0–39	1.13 (0.96, 1.35)	0.1331
Aged 40–49	0.91 (0.81, 1.03)	0.1596
Aged 50–59	Base level	
Aged 60–69	0.87 (0.78, 0.97)	0.0173
Aged 70–79	0.96 (0.85, 1.08)	0.5749
Aged 80+	0.90 (0.77, 1.06)	0.2148
Surgical treatment ($n = 30\ 540$)		
Surgery	Base level	
No surgery	1.27 (0.80, 2.00)	0.3018
Deprivation ($n = 36\ 952$)		
Most deprived	1.03 (0.91, 1.18)	0.5582
More deprived	1.09 (0.97, 1.23)	0.1200
Average deprivation	Base level	
More affluent	1.02 (0.91, 1.14)	0.6803
Most affluent	1.02 (0.90, 1.14)	0.7302
Comorbidity ($n = 33\ 117$)		
Charlson score = 0	Base level	
Charlson score = 1	1.07 (0.95, 1.19)	0.2269
Charlson score = 2	1.01 (0.79, 1.28)	0.9288
Charlson score = 3	1.39 (0.88, 2.21)	0.1540
Charlson score ≥4	1.37 (0.75, 2.49)	0.2969
Screening status ($n = 37\ 113$)		
Symptomatic	Base level	
Screen detected	0.20 (0.18, 0.22)	<0.0001

aggressive treatment for operable breast cancer in terms of surgery,[4] radiotherapy[8] and chemotherapy.[9] The question that remains unanswered is whether they are disadvantaged mainly on the basis of their age or whether individual circumstances including patient choice indicate that conservative management may be in their best interests. Women of lower socioeconomic status or of certain ethnic origins[10,11] may be particularly at risk of suboptimal treatment outcomes and there is increasing evidence that comorbidity has to be considered in the multidisciplinary management of patients.[12] The simple proportional values for no surgery for those under age 50 shown in Fig. 1 would appear to be higher than the rates in Fig. 2 but the latter are odds ratios which take account of all the variables.

The First All Breast Cancer Report on symptomatic and screen-detected breast cancers in the UK presenting in 2006, showed that in England those known to be of black ethnicity were more likely to present with larger, poor prognosis tumours and at an earlier age than the white population.[11] In the present study all non-white ethnic groups were more likely to present with poor prognosis tumours but black women were more likely to have an operation than other ethnic groups. The Second All Breast Cancer Report on symptomatic and screen-detected breast cancers in the UK presenting in 2007, confirmed that screen-detected cancers were smaller and of a better prognosis and, as with most studies, that although tumours in older women were larger, they were biologically less active.[1–3,13,14] This is consistent with the findings in the 70–79 year old age group in the present study. Social deprivation has been associated with more advanced tumours and worse survival[1,9] but although more affluent women were more likely to present with tumours of good prognosis socio-economic status did not significantly affect operation rates. Operation rates in women below the age of 70 varied between 90% and 92% (Fig. 1) with the exception of the lower rate in women aged 25–29 where the poor prognosis in this age group may indicate prolonged neo-adjuvant or non-surgical therapy. The slightly increased rate in women age 50–60 probably reflects the large proportion of screen-detected tumours in this age group.

An international study of operable breast cancer in the elderly which compared surgical treatment and outcome in 6 European countries and the US between 1995 and 2005, found a wide disparity in surgical rates with Ireland having the highest non-operative rates for all age quintiles over age 75, very comparable with the present findings and Switzerland the lowest rates. However there was little difference in the 5-year survival, with Ireland paradoxically having the highest relative survival. Survival data were of course not available in the present cross-sectional study of 2007.[15]

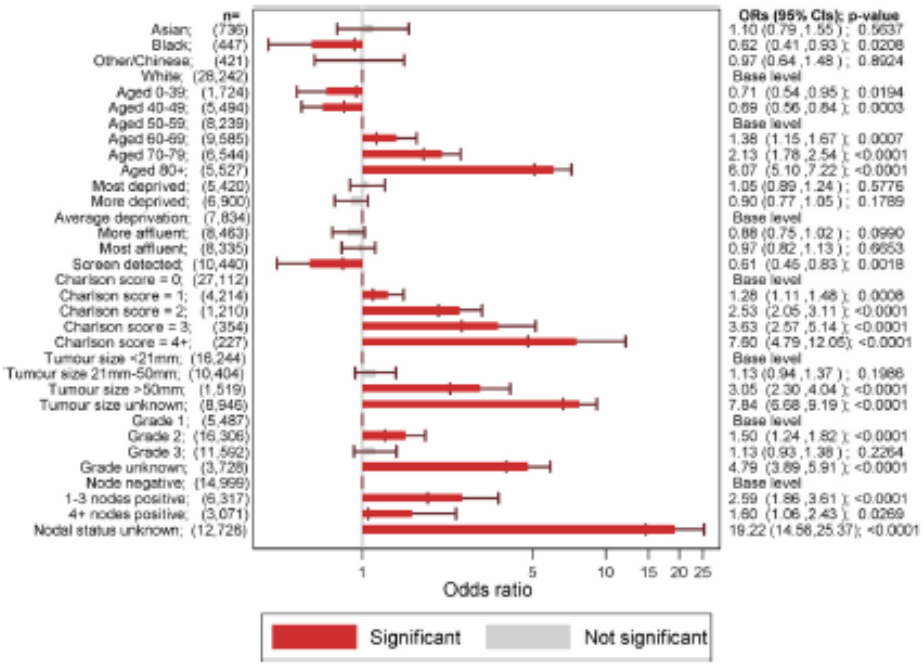

Figure 2. Odds Ratio of not having a surgical operation.

The present study reanalysed the 2007 data collected for England alone since comorbidity data were not available for the rest of the UK. This additionally shows that women with a CCI score of 1 or more have a significantly increased likelihood of not having surgery for their newly diagnosed breast cancer and this likelihood increases the higher the score. Older patients are shown to have a higher prevalence of significant morbidity (Fig. 1) but, of those aged 70 or over, 72% had no recorded morbidity (CCI score = 0) and, of those aged 80 and over, only 5.5% had a CCI score of more than two. Jacobs et al. have shown that comorbidity rapidly increases from age 78 so that at age 85 the rate is triple that of those aged 70.[16] Only 41% of the 80+ year age group in the present study had surgical treatment and, although it is likely that comorbidity is only a contributory factor for the very low rate of surgical treatment for operable breast cancer, most of those who did not have surgery will not have a HES record of comorbidity. It is also evident that the level of comorbidity recorded on HES is significantly under-recorded.[17,18]

Nevertheless, the currently available information shows that this is a significant factor in the very low level of operative treatment. Deviation from treatment guidelines in the elderly is commonly reported in association with comorbidity and patient preference,[19] and it would seem that patient preference and clinical preference[20] for non-operative primary treatment in the elderly may be the prime cause of what might appear to be suboptimal care.

Most published studies on comorbidity show that patients who receive less aggressive treatment fare worse.[12,21] Age and comorbidity are closely inter-related and the latter becomes more severe with increasing age but in patients aged over 80, treatment is less aggressive and age is the stronger determinant.[22] Surgical treatment in the age group 70–79 is rather less than in those aged under 70 but the picture for patients aged 80 or over is very different, with much lower rates for both surgery[4] and adjuvant therapy.[23] Racial differences in comorbidity, apart from deprivation are mostly related to an increased prevalence of hypertension and diabetes in black women[24] but cardiovascular disease and mental illness are the most important factors in European populations.[21] Patients aged 0–39 were less likely to present with favourable tumours which is not unexpected, but conversely, those aged 40–49 had a better outlook. Women in the age group 60–69 were more likely to have good prognosis tumours than those aged 50–59, which might be explained by an increased proportion of screen-detected tumours detected in the incident (subsequent) screening round versus the prevalent first screening round.

Several studies have shown that intercurrent disease outpaces breast cancer as the leading cause of death in the elderly.[25–27] Comorbidity makes a greater difference to survival in patients with low risk breast cancer[19,25] and with increasing CCI score the risk of dying of breast cancer advances as well as death from intercurrent disease.[5] However a review of the ATAC trial at 10 years showed that the risk of recurrence increased with age, and the risk of death without recurrence increased with age and comorbidity score.[28]

There are several randomised trials which compare surgery with or without Tamoxifen versus conservative hormone treatment alone for operable breast cancer in the elderly, but

only one trial has shown a modest overall survival advantage for the surgical removal of the tumour.[29] Nevertheless, a Cochrane Review concluded that surgery for the elderly with ER positive early breast cancer gives better local control, and that primary endocrine therapy (PET) should be reserved for patients with significant comorbid disease or who refuse surgery.[30,31] When PET is used in the appropriate setting the outcome is satisfactory, and although Hille et al. found that, of those patients initially considered unfit for or who declined surgery, 39% eventually had an operation,[32] that was not the finding in the present study.

With increasing age, patients with operable breast cancer who are offered an informed choice between primary endocrine therapy (PET) and surgery, up to half may opt to avoid or delay operative treatment.[33] A cancer-specific geriatric assessment of functional capacity predicts overall survival and may be useful in guiding decision making,[34] but to involve patients in the decision making is important.[35] The updated recommendations of the combined geriatric and breast specialty societies state that surgery is the standard of care for the elderly with operable breast cancer and suggest that an abbreviated geriatric assessment be used as the screening method to identify patients who would benefit from a more time-consuming comprehensive assessment.[36] From the patient's perspective, if offered a choice between an operation and perhaps trying the effect of hormone treatment first, the latter option may be very persuasive, even if the possible downsides of avoiding surgery have been spelt out. From the clinician's viewpoint, Stotter has found that the patient's frailty may be overestimated and their life expectancy underestimated. Furthermore the difficulty of communicating the options is greater than in a younger person.[35] Clearly comorbidity is a factor which may weigh against surgery in the elderly, but to what extent this consideration is responsible for the best option to be declined is uncertain.

Patients at the extremes of age, deprived patients and certain ethnic groups may present with more advanced tumours. Conversely screen-detected breast cancers present earlier. That elderly patients present with larger tumours may be related to lack of screening in this age group but this may influence against surgery for otherwise good prognosis tumours.

However, the failure to operate for early breast cancer in the elderly may also in part be related to comorbidity.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2014.06.001.

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Appendix 6 - Nottingham Prognostic Index[88,89] (NPI)

Nottingham Prognostic Index: Definitions		
NPI = Grade + Nodes + Size (cm) x 0.2		
Nodes Positive: Nil = 1 1-3 +ve = 2 ≥4 +ve = 3		
Excellent Prognostic Group	EPG	≤2.4
Good Prognostic Group	GPG	>2.4 – 3.4
Moderate Prognostic Group 1	MPG1	>3.4 - 4.4
Moderate Prognostic Group 2	MPG2	>4.4 - 5.4
Poor Prognostic Group	PPG	>5.4

Appendix 7 Publications

Publications (Peer reviewed or invited*)

1. **Bates T**. Paraplegia following resection of abdominal aortic aneurysm. Br J Surg. 1971; 58: 913-6.
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Book Chapters

Bates T. The place of research in Surgical Training (General Surgery). ASIT Handbook 1992; 48-50.

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Thrush S, **Bates T**. Epidemiology, Screening and Clinical Trials in Breast Cancer. In Advanced Surgical Practice ed Majid A, Kingsnorth A. Greenwich Medical Media Ltd London 2003: 441- 454.

Video

Bates T, Keller T. Microdochectomy: the operation of choice for a solitary intraduct papilloma. Published by the Royal College of Surgeons of England. Association of Surgeons Annual Meeting, Birmingham, April 25/26th 2001.

Appendix 8 Signed Statements of candidate's contribution

The individual signatures of the 15 co-authors who are still alive have been scanned and inserted below. Original copies and scans of signed Statement of Contribution documents are held on file by the University of Warwick.

Paper to be considered as part of the PhD by Published Work (1)

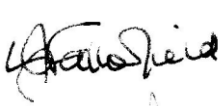
1. Bates T, Riley DL, Houghton J, Fallowfield L, Baum M. Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. Br J Surg 1991; 78: 591-4.

Study circumstances:

In the setting of uncertainty on the use of tamoxifen as a sole primary treatment for operable breast cancer in older women, 3 RCTs were set up in the 1980s in the UK, at St George's, at Nottingham and the present multicentre Cancer Research Campaign (CRC) study centred at King's. The trials at Nottingham and St George's both compared surgery alone with Tamoxifen alone but it was felt that there was an ethical difficulty in withholding tamoxifen from one group of patients in view of the mounting evidence of benefit from primary endocrine therapy. As principal investigator and in collaboration with Michael Baum at the CRC Unit, I therefore set up a multicentre RCT to compare Tamoxifen alone with Tamoxifen together with optimal surgery in women over the age of 70 with operable primary breast cancer.

Contribution of candidate: Tom Bates took a lead role as principal investigator in the design, conduct and evaluation of this RCT in collaboration with Professor Baum and the CRC Unit at Kings. He wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.

I agree that Tom Bates made the aforementioned contribution to this publication.

Name	Signature	Date
Di Riley		13.03.2015
Joan Houghton		11th March 2015
Lesley Fallowfield		5/3/15
Michael Baum		5/3/2015

Paper to be considered as part of the PhD by Published Work (2)

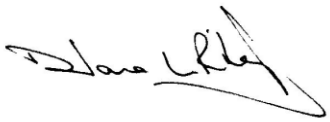
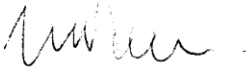
2. Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M. Late follow-up of a randomised trial of surgery plus tamoxifen versus tamoxifen alone in women over 70 with operable breast cancer. Br J Surg 2004; 91: 699-704.

Study circumstances:

In view of the short three year follow-up of our CRC study it was decided to carry out a late review of overall survival at a median of 12.7 years. A final analysis was undertaken on the 455 patients from 27 hospitals who were randomised between 1984 and 1991. As in the earlier analysis there was an early and marked separation of the progression-free survival curves with the maximum event rate now extending to the first two years of follow-up. Statistical analysis was by intention to treat and both overall and cancer specific survival rates were now significantly prolonged in the surgical group of patients. In a subsequent Cochrane review and meta-analysis surgery plus Tamoxifen gave a highly significant advantage to progression-free survival, but overall survival advantage did not reach statistical significance. This CRC Trial is the only RCT to demonstrate a significant overall survival benefit from surgery plus Tamoxifen in the long term.

Contribution of candidate: Tom Bates in collaboration with Professor Baum decided that a long-term follow-up of this trial was important and Michael Fennessy accessed and analysed the archival data. Tom Bates wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.

I agree that Tom Bates made the aforementioned contribution to this publication.

Name	**Signature**	**Date**
Michael Fennessy	Unavailable	
Di Riley		13.03.2015
Joan Houghton		11th March 2015
Michael Baum		5/3/2015

Paper to be considered as part of the PhD by Published Work (3)

3. Moritz S, Bates T, Henderson S, Humphreys S, Michell MJ. Variations in management of small invasive breast cancers detected on screening in the former South Thames East Region: observational study. BMJ 1997; 315: 1266-72

Study circumstances:

With the introduction of the breast screening programme (BSP) it soon became apparent that there were considerable variations in the treatment of breast cancer and one of the first hurdles to address was the ownership of the data. To get the agreement of one's surgical colleagues to release their patient data required some tact but also a change of culture. This paper reports one of the first surgical audits of the management of patients with screen-detected breast cancer. The Key Messages included: in the South East Thames Region, the mastectomy rate varied between surgeons. Those with higher caseloads tended to be more conservative, but the wide variation in clinical practice was not related to caseload. When benefit has already been clearly established, treatment should be guided by evidence based protocols and audited by regular site visits.

Contribution of candidate: As the Surgical Coordinator for the Region Tom Bates was responsible for the surgical aspects of the BSP and audited the process. Sabina Moritz collected and collated the data. TB wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.

I agree that Tom Bates made the aforementioned contribution to this publication.

Name		
Sabina Moritz	Signature S. Moritz	Date 2 March 2015
Sue Henderson	S. M. Henderson	Date 6.3.15
Steve Humphreys	Unavailable	
Michael Michell	M J Michell	9th March 2015

Paper to be considered as part of the PhD by Published Work (4)

4. Bates T, Kearins O, Monypenny I, Lagord C, Lawrence G. Clinical outcome data for symptomatic breast cancer: the breast cancer clinical outcome measures (BCCOM) project. Br J Cancer 2009; 101(3): 395-402

Study circumstances:

Although an annual national audit of the screening programme had become well established by 1998, it became increasingly apparent that it was not possible to audit the majority of breast cancers (80%) which were not screen-detected but mostly presented to general practitioners with symptoms. This study documented the first national audit of the management of Breast Cancer which presented symptomatically. The outcome of suboptimal breast cancer treatment may take several years to become apparent and for this reason a series of surrogate key performance indicators (KPI) was set up to indicate what was considered best practice. There were major variations in clinical management with age and in data capture and recording by Regional Cancer Registries. There were also professional problems in the validation and release of clinical audit data.

Contribution of candidate: The need for this audit was identified by Ian Monypenny, Tom Bates and Gill Lawrence and they drew up the surrogate KPI's. The data were collected and analysed by Olive Kearins, Catherine Lagord and Gill Lawrence. TB checked the data and wrote the manuscript in liaison with the co-authors.

I agree that Tom Bates made the aforementioned contribution to this publication.

Name	**Signature**	**Date**
Olive Kearins		18/3/15
Ian Monypenny		19/3/15
Catherine Lagord		04/03/2015
Gill Lawrence		19/03/15

Paper to be considered as part of the PhD by Published Work (5)

5. Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: Failure to operate for early breast cancer in older women. Eur J Surg Oncol 2014; 40(10): 1230-6.

Study circumstances:

This study expanded on the 2007 data published in the Second All Breast Cancer Report and evaluated comorbidity data using Hospital Episode Statistics (HES) data for England. At this time, comorbidity data were only available for England. The Charlson Comorbidity index (CCI) was calculated removing all cancer comorbidities. It was not possible to calculate the CCI in most women who did not have surgery and therefore no HES data .Failure to operate for breast cancer rose by 3.6% per year of age, from age 70.

Contribution of candidate: The data were collected by Olive Kearins, Catherine Lagord and Gill Lawrence. The data were analysed by Tim Evans who calculated the CCI values. TB checked the data and wrote the manuscript in liaison with the co-authors and responded to reviewers as the corresponding author.

I agree that Tom Bates made the aforementioned contribution to this publication.

Name	**Signature**	**Date**
Tim Evans		4/3/15
Olive Kearins		16/3/15
Ian Monypenny		16/3/15
Catherine Lagord		04 March 2015
Gill Lawrence	Gill Lawrence	19/03/15