



SEquencing of CChemotherapy and RRadiotherapy in AAdjuvant B Breast cancer

*A large, randomised clinical trial designed to determine
the optimum sequencing of chemotherapy and radiotherapy
in the adjuvant treatment of early breast cancer*



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Synopsis

Adjuvant chemotherapy and radiotherapy following breast-conserving surgery have become standard treatment for many women with early stage breast cancer. Unfortunately, we still do not know the optimum way to sequence these treatments. The available evidence suggests that delaying chemotherapy may have a survival disadvantage, while delaying radiotherapy may increase the local recurrence rate. Giving both treatments simultaneously avoids delaying either, but risks causing an enhancement of both acute and late toxicity from radiotherapy, particularly if a methotrexate or anthracycline containing chemotherapy regimen is used.

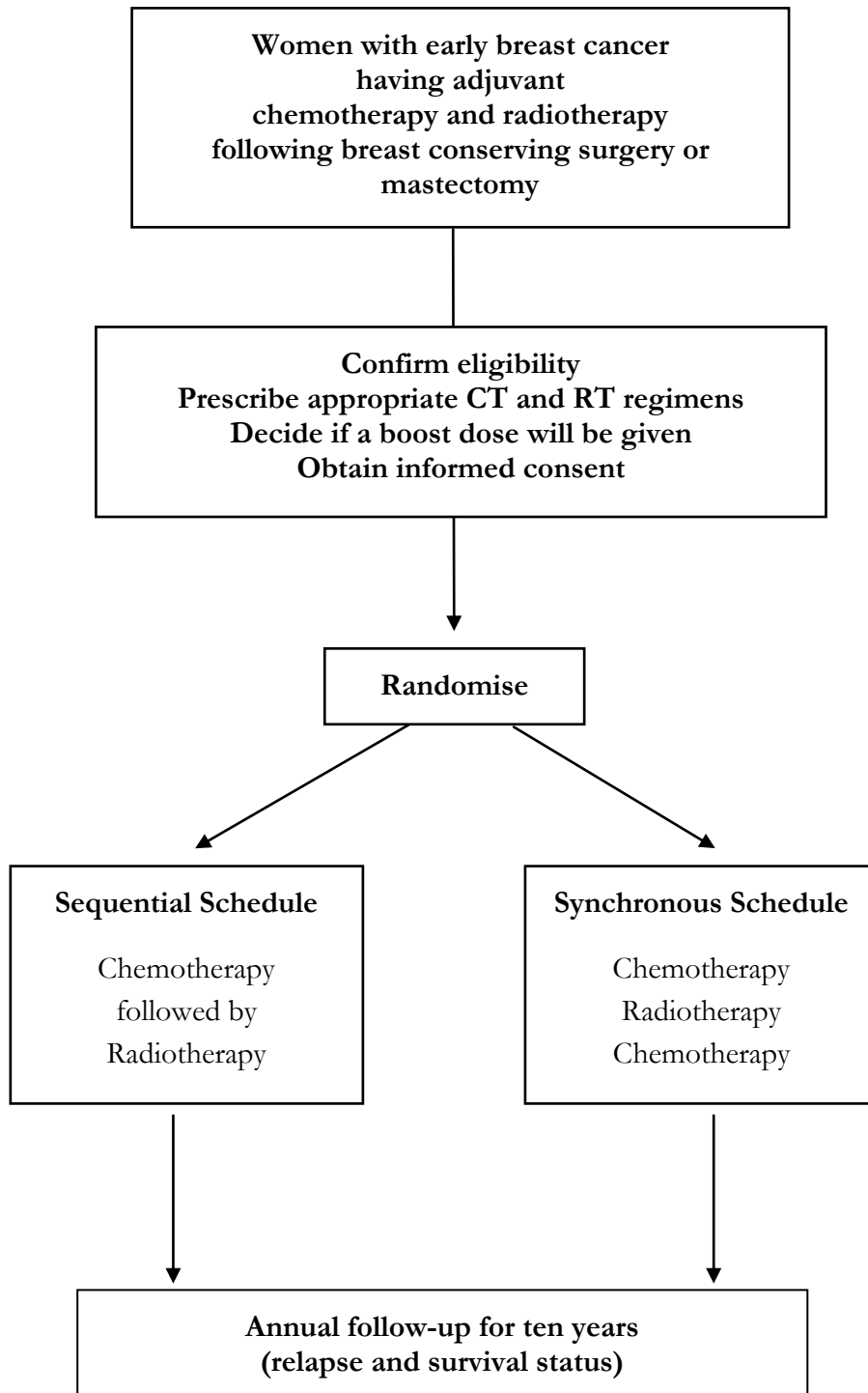
A potentially better option may be to fit the radiotherapy in between the cycles of chemotherapy. This 'sandwich' approach brings forward the start of radiotherapy and so may offer a worthwhile reduction in local recurrence rates, coupled with a shorter treatment time for the patient. However, any benefit in local control must be balanced against the possible higher risk of toxicity, treatment delays or dose reduction in either chemotherapy or radiotherapy, with associated effects on quality of life and cosmetic result.

In the UK, current practice is evenly divided between the 'sequential' (CT→RT) and synchronous (CT→RT→CT) schedules. Hence obtaining a reliable answer to the scheduling question could lead to a significant change in treatment practice throughout the UK. A prospective, randomised trial is needed to compare these sequential and synchronous schedules with respect to local recurrence rates and toxicity.

SECRAB will randomise a minimum of 2250 women with a clear indication for both chemotherapy and radiotherapy following surgery, to receive either 'sequential radiotherapy' given at the end of chemotherapy or 'synchronous radiotherapy' sandwiched in with chemotherapy. The main endpoint is to compare local relapse rates at five and ten years between the two treatment arms. Entry criteria are flexible to accommodate the majority of chemotherapy and radiotherapy regimens in current use, and data collection will be kept to a minimum. A detailed study of toxicity, cosmetic outcome and quality of life will be undertaken in a sub-set of 300 patients.

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1.0 Trial Design



2.0 Introduction

The optimum sequencing of adjuvant chemotherapy and radiotherapy following breast conserving surgery or mastectomy for early stage breast cancer has not yet been defined. This question is important since the number of women considered to have a clear need for both treatments has increased. Post-operative radiotherapy has become standard treatment in the majority of patients having breast-conserving surgery, while chemotherapy is being extensively used in pre and postmenopausal patients, including some who are node negative. Ideally, both therapies should begin soon after surgery to minimise the risk of local and/or systemic failure. In practice, the advantages of early treatment must also be balanced against the risk of enhanced toxicity and the need to maintain good cosmesis and quality of life for the patient.

2.1 Variations in UK Clinical Practice

A survey performed by The Royal College of Radiologists in 1993 found that Fellows of the College were divided in their treatment practice, with a wide range of chemotherapy regimens and radiotherapy schedules in use. Oncologists were divided on how to combine chemotherapy with radiotherapy. Sequential chemotherapy followed by radiotherapy was being offered by 40% of oncologists. Another 40% used various synchronous chemo-radiotherapy schedules, with radiotherapy normally 'sandwiched' between two cycles of chemotherapy to avoid giving both simultaneously. The remaining 20% of oncologists gave radiotherapy before commencing adjuvant chemotherapy. This pattern is reflected in the experience in the West Midlands Breast Group, where half the consultants give the chemotherapy before radiotherapy and the remainder use the synchronous (CT→RT→CT) approach.

The choice of chemotherapy regimen and radiotherapy schedule appears to be independent of the sequence in which they are given. For example, UK centres are evenly divided amongst those using a 3-week radiotherapy schedule versus those using a 5-week schedule, and both are being combined sequentially or synchronously with chemotherapy. In Scotland a four-week schedule is commonly used.

The variation in practice has come to light in the ongoing *NEAT* study where again the choice of giving either sequential or synchronous chemotherapy is split with 39% of patients having synchronous and 61% sequential treatment. This situation reflects the current lack of reliable, persuasive evidence to favour one approach over another.

2.2 Sequential Treatments

A summary of six studies looking at the timing of radiotherapy is shown in Table 1, this suggests that there may be a 5-10% increase in local relapse rate in patients whose radiotherapy is delayed until after chemotherapy. One of the two randomised studies by Recht *et al.* in 1996 in which 244 patients were randomised between chemotherapy followed by radiotherapy (CT→RT) versus the reverse sequence (RT→CT) showed a higher local recurrence if radiotherapy was delivered after chemotherapy compared to the reverse (14% versus 5%). However, the study was not sufficiently large to give a definitive answer, as the difference did not reach statistical significance ($p=0.07$). Furthermore a recent study from the International Breast Cancer Study Group (Wallgren, 1996) failed to show any difference in local control between early or late delivery of radiotherapy. However, data from the latter study is based on a subgroup analysis and in addition there was a >16 week delay in starting radiotherapy even in the early 'sandwich' chemotherapy arm. Clearly, a much larger randomised study is required to answer the question.



Table 1

Author	No. of patients	Study type	Local recurrence (%)	
			Delayed radiotherapy	Early radiotherapy
Recht <i>et al.</i> (1991)	295	Retrospective	12	4
Buchholz <i>et al.</i> (1993)	105	Retrospective	24	2
Slotman <i>et al.</i> (1994)	508	Retrospective	6	2
Hartsell <i>et al.</i> (1995)	484	Retrospective	14	2
Wallgren <i>et al.</i> (1996)	347	Random Subgroup analysis	9	8
Recht <i>et al.</i> (1996)	244	Randomised	14	5

2.3 Sequential Radiotherapy then Chemotherapy

Three studies (Lara, 1989; Dalton, 1987 and Recht, 1996) have suggested that delaying the start of adjuvant chemotherapy by four to six weeks in order to complete definitive radiotherapy may be detrimental in terms of survival. In the Lara *et al.* study, which was a 3-way randomisation between RT→CT, CT→RT or CT→RT→CT, the 10 year actuarial survival rates were 41%, 46% and 57% respectively. In the Recht *et al.* study (1996) the 5-year actuarial rate of distant metastases was significantly higher in patients whose chemotherapy was delayed until after radiotherapy compared to those having chemotherapy followed by irradiation (36% versus 25% p= 0.05). However, there was no significant overall survival difference between the two groups. Other studies have suggested that early initiation of systemic therapy using perioperative chemotherapy may improve survival (Nissen-Meyer, 1978), especially in tumours with a high labelling index (Sertoli, 1990; Pronzato, 1990 and Buzdar, 1982).

Recent data from the Danish Breast Cancer Co-operative Group (Overgaard, 1997) has suggested that the addition of post-operative radiotherapy to adjuvant chemotherapy reduces the loco-regional recurrence rate to less than 10% in those patients treated with chemotherapy and radiotherapy, as opposed to 32% for those treated with chemotherapy alone. In this study the overall ten-year survival of those patients treated with radiotherapy and chemotherapy was 54% compared to 45% with chemotherapy alone. The multivariate analysis confirmed that improvement in survival was independent of tumour size, number of positive nodes and histopathological grade. It should be noted that the radiotherapy in this study was sandwiched in between first and second cycles of chemotherapy. A similar result was seen in the Canadian study of sandwiched radiotherapy (Ragaz, 1997). After 15 year follow up there was a 33% reduction in the rate of recurrence and 29% reduction in mortality from breast cancer in patients treated with combined chemo-radiotherapy, which was significantly better than those treated with chemotherapy alone. However, neither study examined cosmetic result or toxicity.



2.4 Synchronous Chemotherapy and Radiotherapy

The attraction of synchronous chemotherapy and radiotherapy is that neither is delayed. The main concern is the possibility of enhancing the acute and late effects of radiotherapy by giving it in combination. However, the evidence to date suggests that this is very dependent on the type of chemotherapy regimen, radiotherapy technique and the sequence of treatment.

Acute toxicity of CMF-radiotherapy combinations

In a study on 69 patients, Hahn *et al.* (1978) showed an increase in acute erythema in those having concomitant CMF chemotherapy and radiotherapy compared to those having radiotherapy alone. There was no increase in the moist desquamation rate between the two groups. However, Denham *et al.* (1995) who compared a cohort of patients treated with sequential or synchronous CMF-radiotherapy showed no significant difference in acute skin reactions, breast oedema or acute pneumonitis.

Acute toxicity of anthracycline containing combinations

Anthracyclines are known to enhance the effect of radiotherapy, so greater care is needed when giving combined treatment. Anthracycline containing regimens are used routinely in the USA and continental Europe. In the UK, they are still largely reserved for the treatment of 'high risk' patients, with classical CMF combination chemotherapy regimens remaining 'standard'. However, anthracyclines may be expected to come into wider use should the ongoing clinical trials show that they confer a survival advantage over CMF. There have been only a few studies of concurrent adriamycin and radiotherapy. The combination has been shown to increase acute skin reactions to radiotherapy, equivalent to an estimated 10% dose increase (Mayer, 1976 and Penzer, 1989). Severe acute toxicity requiring modification of the treatment plan may have a deleterious effect on local control and possibly survival (Hansen, 1990 and Marks, 1992). Any prospective study must therefore evaluate acute skin toxicity especially if there is a synchronous or sandwich chemo-radiotherapy schedule.

Acute toxicity of methotrexate regimens

Botnick *et al.* (1983) showed that the administration of more than four injections of methotrexate during radiotherapy had a pronounced effect on acute skin toxicity. Conversely a prospective study from the Royal Marsden Hospital, where only two injections of methotrexate was administered synchronously with radiotherapy has shown no significant increase in acute skin toxicity with synchronous chemo-radiotherapy using the 3M regimen (Mitoxantrone, Methotrexate and Mitomycin C) (Fernando, 1996).



Cosmetic and other late effects

There is no doubt that anthracycline containing schedules will significantly enhance late toxicity if given concurrently with radiotherapy (Penzer, 1989 and Hoogenraad, 1992). In addition the Milan study of synchronous adriamycin and radiotherapy had four cases of severe congestive cardiac failure in left-sided lesions (Buzzoni, 1991). Most of the data on late effects of synchronous chemo-radiotherapy using non-anthracycline containing regimens are retrospective comparisons of the cosmetic result (Table 2).

Table 2

Author	No. of patients	Poor cosmetic outcome (%)		Comment
		Synch CT/RT	RT alone	
Abner <i>et al.</i> (1991)	220	24	9	Concurrent only
Rose <i>et al.</i> (1989)	134	24	11	-
Ray <i>et al.</i> (1984)	134	4	5	Concurrent only
Beadle <i>et al.</i> (1984)	255	40	22	-

Overall, patients treated by radiotherapy alone had about a 10% rate of poor or fair cosmetic results compared to 25% in those treated by synchronous chemo-radiotherapy. The studies by Abner *et al.* (1991) and Ray *et al.* (1984) showed no enhancement in either acute or late effects in a subgroup of patients having synchronous 'sandwich' type as opposed to concurrent chemotherapy. Other smaller studies have not shown an increase in longer-term toxicity (Danoff, 1983; Wazer, 1992; Borger & Keijser, 1987 and Denham, 1995). The data are inconclusive and a large prospective randomised study is needed to answer the question of cosmetic result and quality of life.

2.5 Influence of Radiotherapy Techniques

The literature indicates that the risk of acute and late side effects from radiotherapy is affected by both radiotherapy dose and technique. Risk factors include irradiation of the supraclavicular fossa (SCF), exceptionally large breast treatment volumes, overlapping fields and higher doses. Concurrent chemotherapy may increase the risk and severity of the reported effects.

An increase in symptomatic acute radiation pneumonitis in patients having synchronous chemotherapy and radiotherapy was reported by Lingos *et al.* (1991) and confirmed in a study by Wazer *et al.* (1992). Lingos *et al.* showed that the technique of radiotherapy was crucial as the addition of a third 'supraclavicular' field significantly increased the risk of pneumonitis to 8% compared to 2% in those having radiotherapy to the breast alone. Other late effects such as brachial plexopathy (Salner, 1981) and arm oedema (Wazer, 1992) have been shown to increase with the addition of adjuvant chemotherapy to regional nodal irradiation. In both of these studies the SCF was routinely irradiated.

Recent studies have now shown that there is no survival advantage in routinely treating the SCF whereas the risks of sustaining treatment-related toxicity are increased (Fairlamb, 1994). Even in patients treated by radiotherapy alone, factors such as breast size (Gray, 1991) and the use of a third field to treat the SCF have been shown to worsen the cosmetic outcome (Hunt, 1987 and Olivotto, 1989). The latter may relate to the development of matchline fibrosis at the junction of treatment fields.



2.6 Dose Intensity of Chemotherapy

Although most studies (Lippman, 1984) have not shown that the administration of concomitant chemo-radiotherapy results in a reduction in dose intensity of chemotherapy, any prospective study must assess this prospectively as the latter has been shown to be of importance in some reports (Bonadonna, 1981 and Wood, 1994). It should be noted that in the recent Denham *et al.* study (1995) there was a suggestion of reduction in chemotherapy dose in the concurrent chemo-radiotherapy patients. However it is not clear whether consultants used the total white cell count or neutrophil count in deciding when to dose reduce.

2.7 Potential of Newer, 'Synchronous-Sandwich' Regimens

In an attempt to overcome the difficulties reported with simultaneous treatment, a number of 'synchronous-sandwich' regimens have already come into widespread clinical use. In the West Midlands a radiotherapy schedule of 40 Gy in 15 fractions is given over a period of 3-4 weeks (including boost), so that it is possible to 'sandwich' the radiotherapy between two cycles of chemotherapy. Any delay between cycles is minimal, with at most only a 5% reduction in dose intensity of chemotherapy as a consequence of an extra one-week gap between the 2nd and 3rd cycles of chemotherapy (Longo, 1991). Biologically this type of radiotherapy schedule is unlikely to differ significantly from other, longer schedules using daily 2.0 Gy treatments in terms of tumour control and late effects (Yarnold, 1995 and Spooner, 1995).

There are to date, no prospective randomised studies comparing sequential (CT→RT) with the more modern synchronous (CT→RT→CT) schedules, designed to avoid the problems reported with concomitant chemotherapy and whole breast radiotherapy. We believe that the primary question is to ascertain reliably whether the synchronous schedule does indeed result in better overall local control without excess morbidity. If so, an optimum schedule, which also offers a reduced overall treatment duration would have been identified.



3.0 The *SECRAB* Trial

SECRAB will be a prospective, multicentre study randomising a minimum of 2250 women with early breast cancer who have a clear indication for both adjuvant chemotherapy and radiotherapy.

Patients will be randomised to receive either a synchronous or sequential treatment schedule. Entry criteria will be sufficiently broad to address the scheduling question against the background of existing chemotherapy, radiotherapy and scheduling options.

Factors relating to local control and toxicity of therapy (including cosmetic outcome and quality of life) will be examined in a sub-group of 300 women.

3.1 Aims

To answer reliably two questions in the timing of delivery of chemotherapy and radiotherapy in the adjuvant treatment of early breast cancer:

- ◆ Can local control be improved by synchronous delivery of adjuvant chemotherapy and radiotherapy thereby not delaying the administration of either modality?
- ◆ Can synchronous chemotherapy and radiotherapy be given safely without significant enhancement of acute or late toxicity, without compromising on dose intensity of either modality and without adversely affecting quality of life or cosmesis?



3.2 Eligibility Criteria

- ◆ Histological diagnosis of invasive breast carcinoma (unilateral if participating in the Cosmesis Study).
- ◆ Wide local excision or mastectomy with macroscopic complete excision of clinically early stage disease and no evidence of metastases¹.
- ◆ There is a clear indication for both adjuvant chemotherapy and radiotherapy, or the patient has been randomised to these treatments in another study².
- ◆ The intended schedules can be given synchronously³ and the patient is considered suitable to receive either treatment sequence⁴.
- ◆ Medically fit enough to complete chemotherapy and radiotherapy, with adequate cardiac, renal, hepatic and bone marrow function.
- ◆ The patient has given written informed consent⁵.
- ◆ No prior chemotherapy (other than hormone manipulation).
- ◆ No prior malignancy (except skin basal/squamous cell or in situ carcinoma).
- ◆ Not currently pregnant or lactating, no intention of pregnancy during treatment.
- ◆ No other medical or social contra-indication to entry and follow-up.

NOTES :

1. Clinical and staging investigations should follow your normal practice.
2. Patients may first be entered into another trial (Page 26).
3. Suitable combinations are listed on page 9. If chemotherapy has already started, it must be possible to begin synchronous radiotherapy. Treatment choices (including whether to boost radiotherapy), must be declared before randomisation.
4. Precautions to minimise toxicity are discussed on page 10.
5. Women whose first language is not English are eligible for this study and provision of a translator to facilitate this is encouraged.



3.3 Randomisation

Suitable patients should be randomised by calling the Trials Unit. At randomisation you will be asked to provide patient identification details, confirm eligibility and give details of your proposed chemo-radiotherapy treatment plan. The Randomisation Checklist and On Study form contain all of the information you will be asked for. Alternatively, these forms can be faxed to us. Once we have recorded the patient details an immediate treatment allocation to either sequential or synchronous treatment will be made. Written confirmation of the information given, trial number and treatment allocated will be sent to you shortly after.

Call free-phone on
0800 371 969 or 0800 731 7625
or Fax 0800 328 6412
Between 0900 and 1700 hours. Monday to Friday
Ask for *SECRAB* Randomisation

The *choice of both chemotherapy and radiotherapy treatments* and the decision whether or not to give a boost dose **MUST BE MADE** before calling to enter the patient into **SECRAB**. The treatment plan will be recorded before allocation to the sequential or synchronous arms.

If in any doubt about a patients' suitability for synchronous treatment, do not randomise.

3.4 Suitable Chemo-Radiotherapy Combinations

The majority of UK radiotherapy centres will be able to participate in **SECRAB** without changing their existing treatment practice. We have compiled a checklist of regimens known to be suitable for both sequential and synchronous scheduling. These are discussed in more detail under the radiotherapy and chemotherapy sections that follow. Dr. Fernando, the Clinical Co-ordinator for **SECRAB** is happy to discuss alternative schedules and other clinical aspects of the protocol.

Permitted chemotherapy regimens

CMF (iv or oral)
Anthracycline x 4, CMF x 4
Sutton Mitoxantrone and Methotrexate
Mitomycin-C, Mitoxantrone and Methotrexate

Permitted radiotherapy schedules

39 Gy in 13 fractions over 5 weeks
40 Gy in 15 fractions over 3 weeks
42.5 Gy as above, chest wall only, no boost
45 Gy in 20 fractions over 4 weeks
46 Gy in 23 fractions over 4 ½ weeks
50 Gy in 25 fractions over 5 weeks



3.5 Precautions when Planning Combined Chemo-radiotherapy

The chemo-radiotherapy should be tailored to the individual patient and be in line with your normal practice. Investigators should be alert to the fact that patients in the synchronous arm will receive sandwich chemo-radiotherapy, and take reasonable care to minimise toxicity.

Known radiotherapy risk factors:

- ◆ Epirubicin and adriamycin will enhance acute and late skin toxicity from radiotherapy and **MUST NOT** be given concurrently.
- ◆ Patients should be simulated, or a check film taken for radiotherapy to determine the volume of lung within the radiation treatment field. The maximum lung thickness should not exceed 3 cm.
- ◆ Treatment of the SCF may increase the risks of matchline fibrosis, pneumonitis and brachial plexus injury. We advise that the SCF should **NOT** be treated, unless the clinician feels that such therapy is essential in the management of the patient.
- ◆ Intentional internal mammary chain irradiation **IS NOT ALLOWED**.
- ◆ Orthovoltage irradiation to the whole breast **IS NOT** permitted.
- ◆ Toleration is inversely linked to the volume of breast to be treated. Hence women with very large breasts may do worse.
- ◆ Operation wound healing must be complete.

Both chemotherapy and radiotherapy MUST be prescribed before randomisation.

For more detailed information please refer to Section 3.7.



3.6 Surgical Procedures

As the primary end point of the trial is local recurrence, it is important that the surgical procedure undertaken in relation to the axilla is accurately documented. The trial does not require any specific procedure to be undertaken. However, most surgeons adopt a fairly standard policy towards the procedure they undertake in the axilla. The established links between the surgeons and their Clinical Oncologists will ensure that the surgeon informs the Clinical Oncologist when this policy is modified either in an individual case or when there is a change in the protocol.

The two common forms of axillary surgery are axillary sampling and axillary clearance. Sampling is defined for the purpose of the trial as removal of tissue to obtain 4 lymph nodes for histological assessment. This dissection should not normally extend to the level of the axillary vein or medial to the lateral border of pectoralis minor.

Axillary dissection is classified into three groups, level I, level II and level III. The level of clearance is determined by the margins of the pectoralis minor. A level I dissection clears the tissue in front of the axillary vessels and lateral to the lateral border of pectoralis minor. The dissection continues posteriorly to the edge of latissimus dorsi and its neurovascular bundle on the lateral aspect of the axilla and to the site of the nerve of serratus anterior on the medial aspect of the axilla. Clearance of the interpectoral nodes is recommended. A level II dissection continues beneath pectoralis minor to include the tissue anterior to the axillary vessels and below the vessels on to the chest wall. This dissection may be further extended to level III by continuing the dissection to the level of the first rib, beyond the medial border of pectoralis minor, again removing the tissue in front of the vessels and beneath the vessels on the chest wall.

Surgeons whose patients may enter the study are encouraged to classify the procedures they undertake using these guidelines.



3.7 Radiotherapy Planning and Technique

It is important that the radiotherapy is planned and delivered by all participating centres to agreed standards, so that the primary endpoint of effect of scheduling on local control can be reliably assessed. We expect that the treatment given in each centre will conform to the specified criteria below. Please refer to the Royal College of Radiologists' guidelines and the following recommendations:

1. Planning should be performed on a simulator in order to determine the irradiated lung volume. The maximum lung thickness should not exceed 3 cm. If patients are not simulated then a treatment check film must be taken.
2. In patients who have had a level II or III axillary dissection, the breast alone should be irradiated with the patient treated in a supine position.
3. In patients who have had a positive level I axillary sampling then it is strongly recommended that the axilla be irradiated providing a treatment technique is used which minimises any overlap or use of a junction to treat the nodal regions. In order to comply with this treatment of the SCF is not recommended, unless the clinician feels that such treatment is essential in the management of the patient. In addition the treatment of the internal mammary nodes is to be avoided so as to minimise the radiation dose to the myocardium and lung. All patients should be treated in a supine position.
4. A minimum of one transverse outline, taken at the central axis of the length of the tangential fields should be taken.
5. Patients should only be treated with megavoltage irradiation with appropriate wedged fields so that the dose inhomogeneity does not vary by more than 10%. All fields will be treated daily.
6. Centres using orthovoltage to treat the whole breast should not take part.
7. If there are any unplanned gaps in radiotherapy of less than seven days due to any factors other than patient toxicity (e.g. machine breakdown, bank holidays) the missed treatments will be given at the end of the normal radiotherapy schedule, as according to local practice.
8. Bolus may be allowed at the discretion of the individual consultant if this is normal practice. However this must remain standard for all patients entering the study and information with regard to this will be collected before participation in the trial.

Boost dose

A boost to the tumour bed may be delivered at the discretion of the clinician but delivery should not exceed one week and must be standard between the two arms of the study. Investigators will therefore be asked to specify, prior to randomisation, whether or not the boost dose is indicated for a given patient.

An interstitial boost is allowed, if this is part of standard practice. However, the delivery of such therapy must not delay the next cycle of chemotherapy by more than 7 days as stated in the protocol. If a delay of greater than 7 days would result, it is preferable to use an external beam boost.



Standard 3-week schedule and treatment prescription

A 3-week radiotherapy schedule is probably the optimum schedule for use as synchronous therapy with chemotherapy.

A dose of 40 Gy in 15 daily fractions is recommended. This should be prescribed to the 100% at the ICRU reference point to ensure that all whole breast irradiation can be delivered within the three-week gap between chemotherapy cycles in the synchronous arm of the trial.

For patients having chest wall irradiation after mastectomy a dose of 42.5 Gy is allowed providing there is no additional boost.

Standard 4-week schedule and treatment prescription

A dose of 45 Gy in 20 fractions over 4 weeks. The radiotherapy must be delivered according to the recommended synchronous chemo-radiotherapy schedule. When giving synchronous chemotherapy and a four-week radiotherapy schedule, radiotherapy should be omitted on the day that intravenous cytotoxic chemotherapy is administered.

Standard 5-week schedule and treatment prescription

A five-week schedule can be given with slight modification to the synchronous (CT→RT→CT) schedule. A dose of 50 Gy in 25 fractions or 39 Gy in 13 fractions (5 treatments per fortnight) is allowed in centres unable to comply with a three-week schedule. The radiotherapy must be delivered according to the recommended synchronous chemo-radiotherapy schedule. When giving synchronous chemotherapy and a five-week radiotherapy schedule, radiotherapy should be omitted on the day that intravenous cytotoxic chemotherapy is administered.



3.8 Chemotherapy Delivery

Clinicians will be asked to specify their intended chemotherapy schedule(s) on joining the study. The most common regimens are detailed below:

CMF regimens

'Classical' Bonadonna schedules

Patients may be treated by the 'Classical Bonadonna' schedule (or a schedule of equivalent dose intensity delivered intravenously) using the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF).

CMF 'Classical' Oral

Cyclophosphamide 100 mg/m² oral (D 1-14)
Methotrexate 40 mg/m² IV (D 1 + 8)
5-Fluorouracil 600 mg/m² IV (D 1 + 8)
+ Folinic acid 15 mg oral 4 hourly x 6 doses 24 hours after methotrexate administration.

CMF 'Classical' IV

Cyclophosphamide 600 mg/m² IV (D 1 + 8)
Methotrexate 40 mg/m² IV (D 1 + 8)
5-Fluorouracil 600 mg/m² IV (D 1 + 8)
+ Folinic acid 15 mg oral 4 hourly x 6 doses 24 hours after methotrexate administration.

CMF (6-8) IV 3 Weekly (Scottish Breast Group Schedule)

The 3 weekly IV CMF regimen is acceptable providing there is a 3-week gap between cycles.
Cyclophosphamide 750 mg/m² IV every three weeks
Methotrexate 50 mg/m² IV every three weeks
5-Fluorouracil 600 mg/m² IV every three weeks

Anthracycline containing regimens

Combinations of epirubicin or doxorubicin (4 cycles) followed by CMF (4 cycles) (E/CMF) can be used where an anthracycline combination is indicated or if randomised in a clinical trial.

3 Weekly Epirubicin/CMF (Scottish Breast Group Schedule)

Epirubicin 100 mg/m² IV every three weeks for 4 cycles followed by four cycles of:
Cyclophosphamide 750 mg/m² IV every three weeks
Methotrexate 50 mg/m² IV every three weeks
5-Fluorouracil 600 mg/m² IV every three weeks

Epirubicin + CMF (as per NEAT protocol)

Epirubicin 100 mg/m² IV every three weeks for 4 cycles (or doxorubicin dose 75 mg/m²) followed by CMF "Classical" for 4 cycles

Bonadonna Regimen

Adriamycin 75 mg/m² IV every three weeks for 4 cycles, followed by 4-8 cycles of CMF

Mitomycin-C, Mitoxantrone and Methotrexate

Patients may be treated with a combination of Mitomycin-C, Mitoxantrone and Methotrexate (3M) given according to the following schedule:

Mitoxantrone 8 mg/m² IV every 3 weeks for 6 cycles
Methotrexate 35 mg/m² IV every 3 weeks for 6 cycles
Mitomycin-C 8 mg/m² IV every 6 weeks (alternate cycles)
+ Folinic acid 15 mg oral 4 hourly x 6 doses 24 hours after delivery of chemotherapy



Please note tamoxifen should not be given if using this regimen.

Chemotherapy dose modification schedule

Clinicians are strongly encouraged to deliver doses as close to their initial treatment plan as possible, in view of the increasing appreciation of the importance of dose intensity in the adjuvant chemotherapy of early breast cancer (Budd, 1995 and Coombes, 1996). The toxicities of CMF 'classical' are well established and moderate. A pilot study, by the Scottish group, of 4 cycles of Epirubicin followed by 4 cycles of CMF has demonstrated this to be a tolerable regimen. The toxicities most likely to require treatment modification are prolonged myelosuppression, mucositis and neutropenic sepsis.

Myelosuppression

Modification or delay in chemotherapy depending on day 1 blood counts will be in accordance with the clinician's standard practice (or a chemotherapy trial protocol). Every attempt should be made to maintain chemotherapy at full doses.

Mucositis

Grade 3 Mucositis: - (i) Epirubicin: 20% dose reduction
 (ii) CMF: add or prolong folinic acid rescue

Neutropenic sepsis

If this occurs, usually with hospital admission, a 20% reduction in epirubicin or cyclophosphamide is recommended for subsequent cycles.

Prophylactic antibiotics or growth factors

Routine use of these is not recommended but they may be used at the clinicians' discretion:

- ◆ If part of your normal management practice.
- ◆ As an alternative to dose reduction after neutropenic sepsis on treatment.
- ◆ If participating in a clinical trial.

The use of prophylactic antibiotics or growth factors and folinic acid should be recorded on the Chemotherapy Summary Form.



3.9 Serious Adverse Events

SECRAB is comparing two accepted standard treatments, which are in widespread use. The side effects which may be expected, and the precautions needed to minimise risk are summarised in this protocol and may be discussed with the Clinical Co-ordinator or any of the advisory contacts listed on page 49. Clinicians should continue to follow their normal practice for adverse event reporting within the local setting.

Any serious or unexpected adverse events should be reported to the **SECRAB** Trial Co-ordinator without delay. A Serious Adverse Event Form is provided for this purpose. All serious adverse events and adverse events will be reported to the **SECRAB** Data and Safety Monitoring Committee. Unexpected serious adverse events will also be reported to the West Midlands Multicentre Research Ethics Committee and the appropriate Local Research Ethics Committees.

Serious adverse events are those that are fatal, life threatening, disabling, incapacitating, require hospitalisation or the early termination of the planned treatment, or which is a congenital anomaly, a new cancer or an overdose.

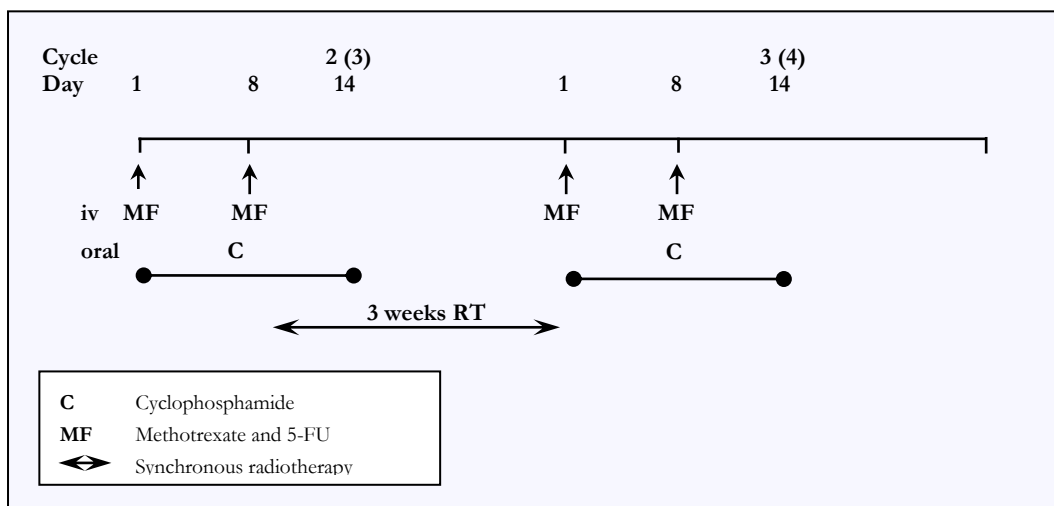
Unexpected adverse events are those which are not discussed in the **SECRAB** chemotherapy and radiotherapy protocols and/or which in the clinicians' judgement merit reporting.



3.10 Scheduling of Synchronous Chemo-radiotherapy

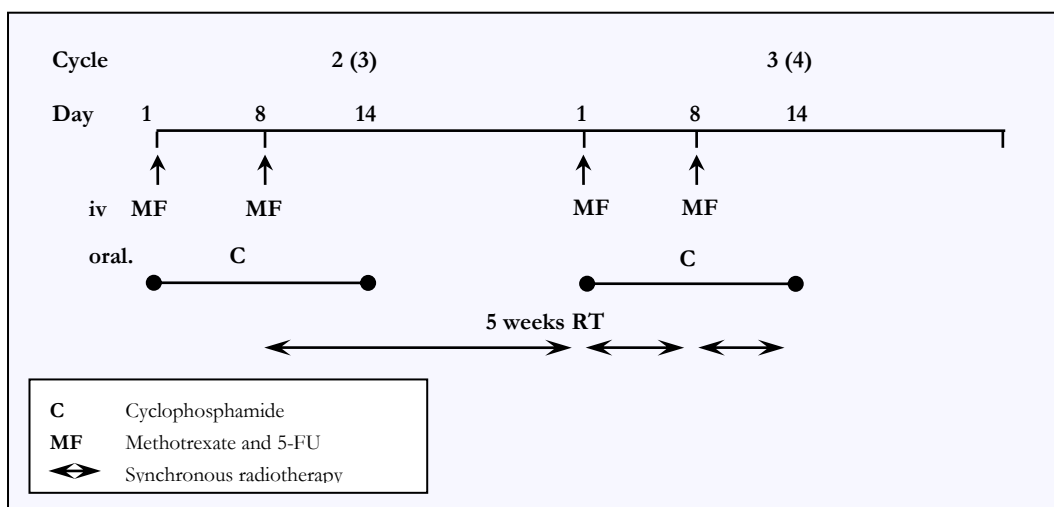
For those patients having a 3-week radiotherapy schedule we recommend that radiotherapy is given during the three to four week gap between cycles 2 and 3. If centres are unable to schedule radiotherapy following cycle 2 it can be given between cycles 3 and 4 so long as whole breast irradiation is complete within 16 weeks of surgery. For patients receiving anthracycline-containing regimens, radiotherapy should be given between cycles 5 and 6. Radiotherapy should be omitted on the days when intravenous methotrexate and 5-FU are given, however simultaneous administration of chemotherapy with the boost dose is allowed but should be recorded for analysis purposes.

Three week schedule CMF 'Classical' Oral



For patients having CMF and a 4 or 5 weekly radiotherapy schedule, we recommend that radiotherapy commences after completing cycle 2 with a standard gap between cycles 2 and 3. If centres are unable to schedule radiotherapy following cycle 2 radiotherapy can commence after cycle 3 with a standard gap between cycles 3 and 4 as long as whole breast irradiation is complete within 16 weeks of surgery. For patients receiving anthracycline-containing regimens, radiotherapy should commence after cycle 5 with a standard gap between cycles 5 and 6 to permit delivery of radiotherapy. However, radiotherapy will be omitted on the days when intravenous methotrexate and 5-FU are given.

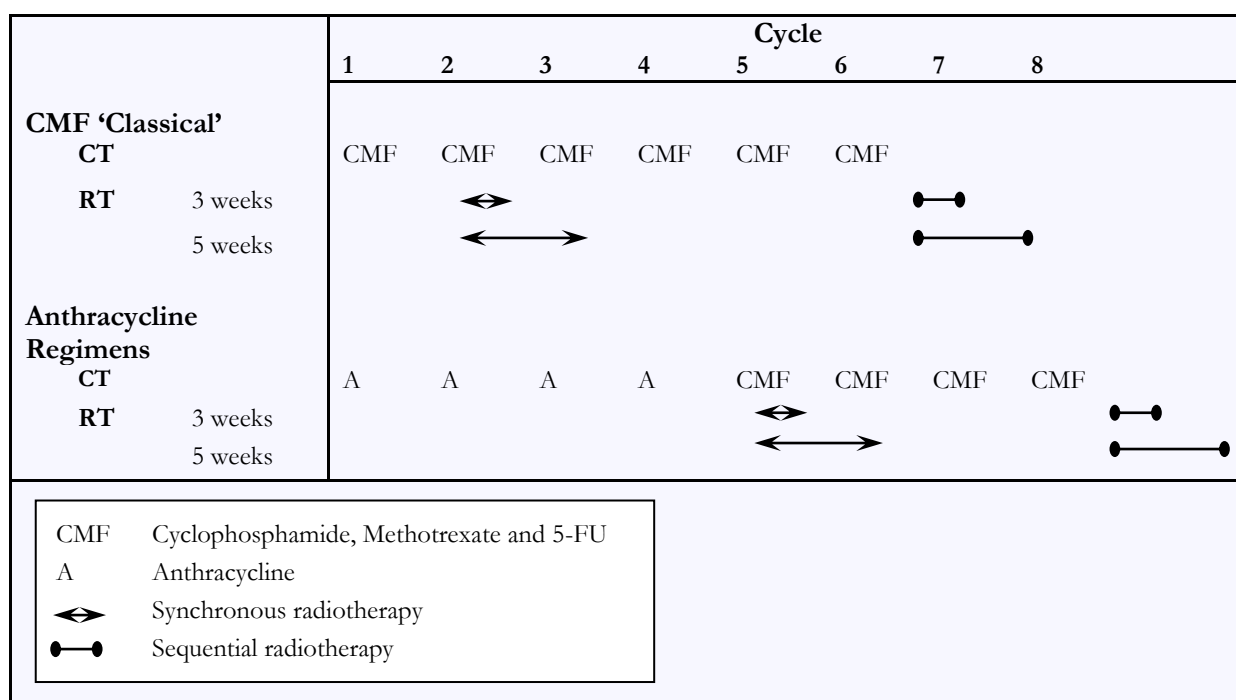
Five week schedule CMF 'Classical' Oral



Administration of the chemotherapy cycles following radiotherapy should not be delayed by more than 10 days unless serious toxicity is seen.



Scheduling diagram



3.11 Concurrent Hormone Therapy

The protocol does not restrict the use of hormone manipulation as part of additional treatment. The majority of women will also be taking tamoxifen 20 mg o.d. and can be registered and subsequently randomised into aTTom, the tamoxifen duration study. Some premenopausal women will also be treated by ovarian suppression (by medical, surgical or radiotherapeutic procedures), and randomised as part of the ABC study. Patients may also be treated according the ATAC protocol (see page 26).

3.12 Follow-up and Action on Relapse or Withdrawal

Out patient follow-up should follow normal local practice. A follow-up report (asking for details of late complications of treatment, date and sites of relapse and death) will be requested annually for a minimum of ten years by the Trials Unit. Subsequently patients will be flagged for follow-up with the Office of National Statistics. The Trial Co-ordinator will welcome updates from centres about significant changes in the patients' status, address etc that occur in the interim.

Patients who relapse will be managed according to the discretion of the responsible clinician.

Patients who withdraw after randomisation will be included in the analysis on an intention to treat basis. The reasons for withdrawal or treatment modification should be recorded and the patient will remain within the trial for the purposes of follow-up.



3.13 Pathology

Pathological details of prognostic significance to the main endpoint of local recurrence will be recorded for all patients for analysis purposes. A copy of the relevant histopathology report(s) should be sent to the Trials Unit, so that the pathology form can be completed. All centres are asked to nominate an interested pathologist willing to act as our local contact. Dr. Rowlands (New Cross Hospital, Wolverhampton) is the Lead Pathologist for the **SECRAB** study.

Data to be collected are based on the breast screening programme recommendations for pathological reporting and include pathological size, tumour grade, presence of vascular and/or lymphatic invasion within the tumour, distance to margins, the total number of axillary lymph nodes removed, and the number that contain metastatic deposits.

3.14 Forms and Data Collection

Data collection has been kept to the minimum necessary. Participants are asked to provide complete information promptly.

- ◆ RANDOMISATION CHECKLIST and ON STUDY FORM. To be completed in full before randomisation.
- ◆ PATHOLOGY FORM. To be completed at the Trials Unit from a copy of the pathology report(s), which should be sent to the Unit.
- ◆ CHEMOTHERAPY SUMMARY FORM and RADIOTHERAPY SUMMARY FORM. The Clinical Trials Unit will send these out as the patient nears the completion of treatment.
- ◆ PHARMACY RECORD (for patients in the Detailed Sub-Study). This will be sent to the pharmacist.
- ◆ ANNUAL FOLLOW-UP FORMS. The Trials Unit will send these out at the appropriate time, annually for a minimum of ten years.
- ◆ SERIOUS ADVERSE EVENT (SAE) FORM. To be completed and returned immediately after an SAE.
- ◆ QUALITY OF LIFE QUESTIONNAIRES and PATIENT DIARY SHEETS (for participants of the Detailed Sub-study). Appendix 2.



4.0 Detailed Sub-study

The secondary endpoints of quality of life, cosmesis, toxicity and dose intensity will be assessed in a sub-study of at least 300 women. These will be recruited from centres with a special interest in studying these questions, and the resources to provide more detailed study data.

Centres taking part should invite all patients who agree to take part in **SECRAB** to give informed consent for the Quality of Life (QoL) and Cosmesis (breast appearance) Study. Patients are free to agree to enter **SECRAB**, yet refuse to take part in the QoL and/or to provide photographs. The aim is to accommodate the women's preferences, and enable centres without access to medical illustration facilities to participate.

Patients who have already started chemotherapy are not eligible to enter the QoL study, since the baseline QoL should be assessed before the start of the adjuvant treatment. Patients entered into more than one trial may only take part in one QoL study. Recruitment to this part of the trial will close once sufficient patients are evaluable (subject to Data and Safety Monitoring Committee approval).

4.1 Quality of Life Study Design

The Quality of Life Study is designed to assess the patient's well being over a two-year period, by use of questionnaires collected at four specified time-points, and patient diary sheets to be completed during radiotherapy treatment (Appendix 2). This time-span allows data collection both during and after chemotherapy and radiotherapy, and should provide insight into the impact treatment has on women's health.

Questionnaires

The EORTC QLQ-C30 (version 2) Questionnaire will be used together with the EORTC-Breast Cancer Questionnaire (EORTC QLQ-BR23) and the Women's Health Questionnaire (Appendix 2).

Questionnaire dates will be calculated from the date of primary breast surgery.

First Questionnaire:	Prior to chemotherapy Baseline assessment
Second Questionnaire:	On completion of both chemotherapy and radiotherapy Questionnaire posted to patient 2–3 weeks later
Third Questionnaire:	One year following surgery Questionnaire posted to patient
Fourth Questionnaire:	Two years following surgery Questionnaire posted to patient
Fifth Questionnaire:	Five years following surgery (for patients participating in the Cosmesis Study only) Questionnaire posted to patient

With each questionnaire a covering letter, Patient Information Sheet and a pre-paid envelope will be sent. This will be repeated a few weeks later if there has been no response.



Diary sheets

The first diary sheet should be completed the day before the start of radiotherapy (or immediately prior to the first treatment). The remaining sheets should be completed on a weekly basis during radiotherapy treatment and for four weeks after. Diary sheets should be completed on the same day of the week throughout (e.g. every Monday) in a routine that suits the patient.

A patient treatment summary sheet is also included in the Diary Sheet Booklet. This should be completed four weeks after the completion of radiotherapy.

4.2 Assessment of Cosmetic Outcome

The extent of the primary breast surgery and reconstruction techniques are expected to be most influential in determining cosmetic outcome. However, the acute and late side effects of radiotherapy may worsen cosmesis, and these may be enhanced when given synchronously with chemotherapy. We therefore intend to obtain an independent assessment of cosmetic outcome, and to compare this with the patients' own perception and satisfaction.

Cosmesis assessment and photographic schedule

To allow independent assessment, photographs will be taken at the following time points:

- ◆ Prior to radiotherapy (to control for the effect of surgery).
- ◆ At the first follow-up visit following the end of all adjuvant treatment.
- ◆ At first, second and fifth annual post-operative follow-up visits.

Two clinical photographs will be taken at each time point, one with arms raised and one with arms lowered.

Photographs will be returned to the Trials Unit for independent, objective assessment of cosmetic result. Photographs will only be identifiable by their trial number to ensure patient anonymity. They will be retained until after final publication. Cosmesis will be scored according to the extent of visible differences in comparison with untreated breast, using the appropriate grading systems given in Appendix 3. Analysis will compare changes in the cosmetic score before and after radiotherapy.

4.3 Assessment of Dose Intensity and Toxicity

The dose intensity of chemotherapy delivery will be recorded in the sub-group only, to ensure that significant dose modification of systemic treatment is not required in patients having synchronous compared to sequential treatment. These data will be captured from pharmacy records. However, information on radiotherapy treatment delay >7 days and chemotherapy dose reduction >20% or delay >10 days will be recorded for all patients. Late effects such as radiation pneumonitis, lymphoedema and brachial plexopathy will be collected on all patients.



5. Statistical Considerations

5.1 Endpoints

Primary endpoint:

- ◆ Local tumour recurrence rates at 5 and 10 years.

Secondary endpoints in all patients:

- ◆ Distant and overall recurrence rates.
- ◆ Survival at 5, 10 and 15 years.
- ◆ Acute toxicity causing significant treatment delay or dose reduction.
- ◆ Other late effects of treatment.

Secondary endpoints in Detailed Sub-study:

- ◆ Reduction in dose intensity of chemotherapy.
- ◆ Acute toxicity during treatment.
- ◆ Early and late cosmetic results and quality of life.

Randomisation will be stratified by Clinical Oncologist, axillary clearance (yes/no), radiotherapy boost intent (Boost, or no Boost) and chemotherapy intent. Analyses will use the log-rank method and include all eligible patients randomised on an 'intention to treat' basis. Local tumour recurrence rates, which will be determined at 5 and 10 years, will be the principle endpoint. Treatment comparisons will be analysed with and without adjustments for the stratification factors. Sub-group analyses will compare treatment schedules separately for those patients receiving CMF and those patients receiving Anthracycline + CMF. In addition a comparison of toxicity between the treatment arms will be adjusted for the duration of radiotherapy treatment (3 weeks versus >3 weeks).

Mandatory information on diameter of tumour, grade, excision margin, presence and number of involved nodes will also be recorded. Treatment delay or gap in radiotherapy of more than 7 days will also be recorded.

Each patient randomised will be followed up annually for ten years from the end of treatment through the responsible clinician. Local and distant recurrences will be documented as will survival. There after patients will be flagged for follow-up via national records.



Number of patients needed

Local recurrence rates are usually reported to be between 5-10% for patients treated with conservation surgery followed by radiotherapy. Thus, recruiting a minimum of 1000 patients into the study will allow the detection of treatment differences in excess of 5%, with an 85% power at the $\alpha=0.05$ level of significance. However, if the differences are slightly lower (3-4%) then these may not be detected unless we double recruitment. Doubling recruitment to 2000 patients would allow a 4% differences to be detected with an 80% power and 3% differences with a 65% power.

To provide sufficient statistical power to perform the sub-group analyses, 1000 patients receiving each of the two principal chemotherapy regimens (CMF and Anthracycline + CMF) will be recruited into the study allowing detection of a 5% difference in local recurrence rates, with 80% power and a 5% level of significance.

In order to recruit sufficient patients to perform both the principal analyses and the sub-group analyses the intention is to recruit a minimum of 2250 patients into the study.

Detailed sub-study

A subset of at least 300 patients (150 in each group) will be assessed in more detail to compare differences in toxicity, treatment delay, dose intensity of chemotherapy and quality of life. Assessments will be taken at the start and at the end of adjuvant treatments, then at the first, second and fifth year's post-operative follow-up visits.

Cosmetic effects will be scored from photographs by an independent observer, using a simple scoring system that has previously been evaluated. Assuming a 10% rate of poor cosmetic score for patients in the sequential arm, this sample will allow the detection of 10% differences in the percentage of patients with poor cosmetic score, with an 80% power at the $\alpha=0.05$ level of significance.

5.2 Data Monitoring

The data will be monitored when approximately 500 patients have been entered into the main study or 100 patients into the Detailed Sub-study, whichever happens soonest, to ensure in particular that there are no cases of excessive acute toxicity in any of the treatment groups. An independent Data and Safety Monitoring Committee will be asked to give advice on whether the accumulated data from this trial, together with the results from other relevant trials, justifies continuing the recruitment of further patients. A decision to discontinue recruitment will only be made if the results are likely to be convincing to a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the Data and Safety Monitoring Committee will advise on the frequency of future reviews on the basis of accrual and event rates.

5.3 Publication

The Steering Committee intends to analyse and publish the study results as soon as possible. Individual clinicians should not publish or present data on **SECRAB** patients pre-emptively or without prior approval. Named authors for the definitive publications will include the Clinical Co-ordinators, Statisticians, Trial Co-ordinator and all collaborators contributing a substantial number of patients from their practice. All other contributors and our sponsor(s) will be acknowledged and provided with reprints.



6.0 Ethical Considerations

A copy of the Local Research Ethics (LREC) Committee approval letter must be sent to the Trials Unit before patients can be entered from a new centre. An 'Ethics submission pack' containing the Multicentre Research Ethics Committee approval documentation will be provided to assist the local submission.

Written informed consent following adequate information should be obtained from the patient before randomisation. Sample Patient Information Sheets and Consent Forms for this study are appended (Appendix 1). These may be adapted to meet your LREC requirements, but a copy of the amended Information Sheet and Consent Forms must be sent to the Trials Unit. The right of a patient to refuse to participate without giving reasons must be respected. After the patient has entered the trial, the responsible clinician(s) are free to give any other treatment or to change the treatment schedule from that allocated in the protocol, if this is considered to be in the patient's best interests. Similarly, the patient is free to withdraw from the trial at any time without giving any reason and without prejudicing further treatment.

Signed informed Consent Forms must be retained in the individual patient record and a copy sent to the Trials Unit.

The patients General Practitioner should be informed that they are taking part in **SECRAB** (with the patient's permission). A General Practitioner Information Sheet is provided (Appendix 1) for inclusion with your initial correspondence with the GP.



7.0 Financial Support and Indemnity

SECRAB is funded by a project grant from the Cancer Research UK. Centres taking part should not incur any extra treatment costs since the trial is comparing the scheduling of existing radiotherapy and chemotherapy in women who would normally receive both. No additional tests or visits are required other than for normal patient care and follow-up.

Funding is available to meet additional medical illustration costs of the Cosmesis Study.

The **SECRAB** trial is being run by the Cancer Research UK Clinical Trials Unit, Institute for Cancer Studies, Birmingham with sponsorship from the Cancer Research UK. It is independent of any pharmaceutical company, and as such it is not covered by the ABPI guidelines on non-negligent liability. The Clinical Trials Unit does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial.



8.0 Other Trials in Early Breast Cancer

Several other ongoing clinical trials are addressing important questions in the management of early breast cancer. **SECRAB** has been developed in discussion with the national Steering Committees of the **NEAT**, **ABC**, **aTTom** and **ATAC** trials. The aim has been to minimise any competition between the trials, and to permit randomisation into other trials wherever possible.

aTTom: Adjuvant Tamoxifen Treatment Offer More? (UKCCCR Trial to Establish the Optimum Duration of Tamoxifen).

We expect that the majority of **SECRAB** patients will be prescribed tamoxifen at their clinicians' discretion. They may be registered with **aTTom** and be randomised to stop or continue tamoxifen in due course.

NEAT: The National Adjuvant Epirubicin Trial.

SECRAB has been designed to run alongside **NEAT**, and we believe that around 60% of patients treated with chemotherapy and radiotherapy are eligible for **SECRAB** only. The remaining 40% who are eligible for both trials may be randomised into **NEAT** first, and then if they consent, can also enter **SECRAB**.

ABC: The Adjuvant Breast Cancer Trial.

Patients randomised in **ABC** to receive chemotherapy and who have a clear indication for radiotherapy may be offered **SECRAB** as a second randomisation.

ATAC: Adjuvant Trial in Post-Menopausal Breast Cancer: Arimidex, Tamoxifen Alone or in Combination.

Patients randomised into **ATAC** are also eligible for randomisation into **SECRAB**.

Significant: Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotics in a Number of Tumours.

Patients taking part in **SECRAB** can subsequently be randomised into **Significant** or visa versa.

TEAM: Tamoxifen and Exemestane Adjuvant Multicentre trial.

Patients randomised into **SECRAB** can be offered **TEAM** as a second randomisation.



9.0 References

- Abner AL, Recht A, Vicini FA *et al.* (1991) Cosmetic results after surgery, chemotherapy, and radiation therapy for early breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 21: 331-338.
- Beadle GF, Come S, Henderson IC *et al.* (1984) The effect of adjuvant chemotherapy on the cosmetic results after primary radiation treatment for early stage breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 10: 2131-2137.
- Bonadonna G & Valagussa P (1981) Dose response effect of adjuvant chemotherapy in breast cancer. *N. Engl. J. Med.* 304: 10-15.
- Borger JH & Keijser AH (1987) Conservative breast cancer treatment: analysis of cosmetic results and the role of concomitant adjuvant chemotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 13: 1173-1177.
- Botnick L, Come S, Rose C *et al.* (1983) Conservative management of breast cancer. Ed Harris J, Hellman S, Silen W. p 321-328.
- Buchholz TA, Austin-Seymour MM, Moe RE *et al.* (1993) Effect of delay in radiation in the combined modality treatment of breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 26: 23-35.
- Budd GT, Green S, O'Bryan RM *et al.* (1995) Short-Course FAC-M versus 1 year of CMFVP in node-positive, hormone-receptor negative breast cancer: an intergroup study. *J. Clin. Oncol.* 13: 831-839.
- Buzdar AU, Smith TL, Powell KC *et al.* (1982) Effect of timing of initiation of adjuvant chemotherapy on disease free survival in breast cancer. *Breast Cancer Research and Treatment.* 2: 163-169.
- Buzzoni R, Bonadonna G, Valagussa P & Zambetti M (1991) Adjuvant chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil in the treatment of resectable breast cancer with more than three positive axillary nodes. *J. Clin. Oncol.* 9: 2134-2140.
- Coombes RC, Bliss JM, Wils J *et al.* for the International Collaborative Cancer Group (1996) Adjuvant cyclophosphamide, methotrexate and fluorouracil versus fluorouracil, epirubicin and cyclophosphamide chemotherapy in pre-menopausal women with axillary node-positive operable breast cancer: results of a randomised trial. *J. Clin. Oncol.* 14: 35-45.
- Dalton WS, Brooks RJ, Jones SE *et al.* (1987) Breast cancer adjuvant therapy trials at the Arizona Cancer Centre using adriamycin and cyclophosphamide. Adjuvant therapy of Cancer V, Ed Grune & Stratton. p263-269.
- Danoff BF, Goodman RL, Glick JH *et al.* (1983) The effect of adjuvant chemotherapy on cosmesis and complications in patients with breast cancer treated by definitive irradiation. *Int. J. Radiat. Oncol. Biol. Phys.* 9: 1625-1630.
- Denham JW, Hamilton CS, Christie D *et al.* (1995) Simultaneous adjuvant radiotherapy and chemotherapy in high risk breast cancer, toxicity and dose modification: a transtasman radiation oncology group multi-institution study. *Int. J. Radiat. Oncol. Biol. Phys.* 31: 305-313.
- Fairlamb DJ & Machin D (1994) Prophylactic supraclavicular fossa radiotherapy in early breast cancer: is it worthwhile? *Clin. Oncol.* 6: 227-231.
- Fernando IN, Powles TJ, Ashley S *et al.* (1996) An acute toxicity study on the effects of synchronous chemotherapy and radiotherapy in early stage breast cancer after conservative surgery. *Clin. Oncol.* 8: 234-238.
- Fernando IN, Ford HT, Powles TJ *et al.* (1996) Factors affecting acute skin toxicity in patients having breast irradiation after conservative surgery: a prospective study of treatment practice at the Royal Marsden Hospital. *Clin. Oncol.* 8: 226-233.
- Gray JR, McCormick B, Cox L & Yahalom J (1991) Primary breast irradiation of larger breasted or heavy women: analysis of cosmetic outcome. *Int. J. Radiat. Oncol. Biol. Phys.* 21: 347-354.
- Hahn P, Hallberg O & Vikterlof KJ (1978) Acute skin reactions in post-operative breast cancer patients receiving radiotherapy plus adjuvant chemotherapy. *Am. J. Roentgenology.* 130: 137-139.
- Hansen R, Erikson B & Komaki R (1990) Concomitant adjuvant chemotherapy and radiotherapy for high risk breast cancer patients. *Breast Cancer Research and Treatment.* 17: 171-177.
- Harris JR, Levene MB, Svensson G *et al.* (1979) Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int. J. Radiat. Oncol. Biol. Phys.* 5: 257-261.
- Hartsell WF, Recine DC, Griem KL & Murthy AK (1995) Delaying the initiation of intact breast irradiation for patients with lymph node positive breast cancer increases the risk of local recurrence. *Cancer* 76: 2497-2503.
- Hoogenraad WJ, Franssen JH & van Turnhout JM (1992) Enhanced toxicity of radiotherapy due to epirubicin containing adjuvant chemotherapy in breast carcinoma patients. *Radiotherapy Oncology.* 24: (Suppl) Abstract 158.
- Hunt MA, Kutcher GJ & Martel MK (1987) Matchline dosimetry of a three field technique for breast treatment using cobalt or 6 MV X rays. *Int. J. Radiat. Oncol. Biol. Phys.* 13: 1099-1106.



- Lara P, Soler M, Asenio C *et al.* (1989) Combined post-operative radiotherapy and chemotherapy in poor prognosis breast cancer patients; comparison of 3 different schedules. *Fifth Eur. Conf. Clin. Oncol.* P-0940, London.
- Lingos TI, Recht A, Vincini F *et al.* (1991) Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 21: 355-360.
- Lippman ME, Lichter AS, Edwards BK *et al.* (1984) The impact of primary irradiation treatment of localised breast cancer on the ability to administer systemic adjuvant chemotherapy. *J. Clin. Oncol.* 2: 21-27.
- Longo DL, Duffey PL, DeVita VT *et al.* (1991) The calculation of actual or received dose intensity: a comparison of published methods. *J. Clin. Oncol.* 9: 2042-2051.
- Marks LB, Halperin EC & Prosnitz LR (1992) Post-mastectomy radiotherapy following adjuvant chemotherapy and autologous bone marrow transplantation for breast cancer patients with ≥ 10 positive axillary lymph nodes. *Int. J. Radiat. Oncol. Biol. Phys.* 23: 1021-1026.
- Mayer EG, Poulter CA & Aristizabal SA (1976) Complications of irradiation related to apparent drug potentiation by adriamycin. *Int. J. Radiat. Oncol. Biol. Phys.* 1: 1179-1188.
- Nissen-Meyer R, Kjellgren K, Malmio K *et al.* (1978) Surgical adjuvant chemotherapy: results with one short course with cyclophosphamide after mastectomy for breast cancer. *Cancer.* 41: 2088-2098.
- Olivotto IA, Rose MA, Osteen RT *et al.* (1989) Late cosmetic outcome after conservative surgery and radiotherapy analysis of causes of cosmetic failure. *Int. J. Radiat. Oncol. Biol. Phys.* 17: 747-753.
- Overgaard M, Hansen PS, Overgaard J *et al.* For the Danish breast cancer cooperative group 82b trial (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N. Engl. J. Med.* 337: 949-962.
- Pezner RD, Lipsett JA, Forell B *et al.* (1989) The reverse hockey stick technique: postmastectomy radiation therapy for breast cancer patients with locally advanced tumor presentation or extensive loco-regional recurrence. *Int. J. Radiat. Oncol. Biol. Phys.* 17: 191-197.
- Pronzato P, Alama A, Rubagotti A *et al.* (1990) Breast cancer cell kinetics: a prognostic parameter in perioperative adjuvant chemotherapy. *Br. J. Cancer.* 62: Suppl 12, Abstract.
- Ragaz J, Jackson SM, Le N *et al.* (1997) Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N. Engl. J. Med.* 337: 956-962.
- Ray GR, Fish VJ, Marmor JB *et al.* (1984) Impact of adjuvant chemotherapy on cosmesis and complications in stage I and II carcinoma of the breast treated by biopsy and radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 10: 837-841.
- Recht A, Come SE, Gelman RS *et al.* (1991) Integration of conservative surgery, radiotherapy, and chemotherapy for the treatment of early stage, node-positive breast cancer: sequencing, timing, and outcome. *J. Clin. Oncol.* 9: 1662-1667.
- Recht A, Come SE, Henderson IC *et al.* (1996) The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *N. Engl. J. Med.* 334: 1356-1361.
- Rose A, Olivotto I, Cady B *et al.* (1989) Conservative surgery and radiation therapy for early breast cancer *Ann. Surg.* 124: 153-157.
- Salner AL, Botnick LE, Herzog AG *et al.* (1981) Reversible brachial plexopathy following primary radiation-therapy for breast cancer. *Cancer Treatment Reports.* 65: 797-802.
- Sertoli MR, Pronzato P, Amoroso D *et al.* (1990) Peri-operative chemotherapy for primary breast cancer: preliminary results of a randomised study. *Proc. Am. Soc. Clin. Oncol.* 9: 21 Abstract.
- Slotman BJ, Meyer OWM, Njo KH & Karim ABMF (1994) Importance of timing of radiotherapy in breast conserving treatment for early stage breast cancer. *Radiotherapy and Oncology.* 30: 206-212.
- Spooner D, Morrison JM, Oates GD *et al.* (1995) The role of radiotherapy in early breast cancer (stage 1). A West Midlands Breast Group prospective randomised collaborative study. (BR3002). British Breast Group. Telford.
- Tureson I & Thomas HD (1989) Repair capacity and kinetics of normal skin during fractional radiotherapy: erythema, desquamation, and telangiectasia after 3 and 5 years follow-up. *Radiotherapy and Oncology.* 15: 169-188.
- Wallgren A, Bernier J, Gelber RD *et al.* for the International Breast Cancer Study Group (1996) Timing of radiotherapy and chemotherapy following breast-conserving surgery for patients with node-positive breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 35: 649-659.
- Wazer DE, DiPetrillo T, Schmidt-Ullrich R *et al.* (1992) Factors influencing cosmetic outcome and complication risk after conservative surgery and radiotherapy for early stage breast carcinoma. *J. Clin. Oncol.* 10: 356-363.
- Wood WC, Budman DR, Korzan AH *et al.* (1994) Dose and dose intensity of adjuvant chemotherapy for stage II node positive breast carcinoma. *N. Engl. J. Med.* 330: 1253-1259.
- Yarnold JR, Price P & Steel GG on behalf of the Clinical Audit Sub-Committee of the Faculty of Clinical Oncology, Royal College of Radiologists, and the Joint Council for Clinical Oncology. (1995) Non-surgical management of early breast cancer in the United Kingdom: radiotherapy fractionation practices. *Clin. Oncol.* 7: 223-226.



Appendix 1. Sample Information Sheets and Consent Forms

Local Hospital Paper

Patient Information Sheet

SECRAB A large clinical trial to determine how best to sequence chemotherapy and radiotherapy treatment for early breast cancer

We would like to invite you to take part in a large national ‘clinical trial’ called the **SECRAB** study. We hope to involve 2,000 women, who like you have recently been diagnosed with breast cancer and need to have chemotherapy and radiotherapy to reduce the risk of the cancer coming back. This sheet tells you about the study, and what joining it would involve. You do not have to decide at once, and you may well want to take this leaflet away and discuss it with your friends and relatives first. If you decide not to take part, simply say so. Your breast care team will respect your decision and your current and future care will not be affected in any way.

Why are we doing the SECRAB study?

Your doctor has recommended that you have both chemotherapy and radiotherapy treatment after your surgery to reduce the risk of the breast cancer coming back. At the moment, some doctors give the chemotherapy before the radiotherapy, while others give the chemotherapy and radiotherapy at the same time. We do not know if the order in which the treatments are given can affect their effectiveness and safety. We are doing the **SECRAB** study to try and find the best way to combine them.

How can chemotherapy and radiotherapy be combined?

In the *Sequential* method the chemotherapy is given first, and when the chemotherapy is finished radiotherapy will start (Chemotherapy → Radiotherapy).

In the *Synchronous or ‘sandwich’* method, chemotherapy is started first and radiotherapy is given in the gap in between the cycles of chemotherapy (Chemotherapy → Radiotherapy → Chemotherapy). This involves the same number of hospital visits as the Sequential method, but because the radiotherapy is started earlier the treatments can be finished slightly sooner.

Why is the SECRAB study important?

We want to find out if the order in which these treatments are given affects their effectiveness and safety. To do this, we need to collect careful information about large numbers of women being treated by both methods. We will be looking for small differences in the chance of the cancer coming back locally (inside the area treated by radiotherapy), and at the intensity of any side effects that the chemotherapy and/or radiotherapy may cause. The results from the study will help doctors to decide how best to treat breast cancer in the future.

What would taking part involve?

Your chemotherapy and radiotherapy will be chosen in the normal way, taking careful account of what is best and safest in your personal case. Your doctor and breast care team will discuss this with you in detail. When both chemotherapy and radiotherapy have been prescribed, only the order in which they will be given remains undecided.



If you agree to take part in the **SECRAB** study a computer will decide whether you should have your chemotherapy followed by radiotherapy (Sequential), or radiotherapy during your chemotherapy treatment (Synchronous). A thousand women will draw Sequential and the other thousand will draw Synchronous treatment. So you have a 50:50 chance of getting either one. Taking part in the study will not change what kind of treatment you are given or involve any extra tests or visits to hospital. Everyone who enters **SECRAB** will be followed up through their doctors at regular intervals for at least five years after treatment has finished.

Your medical records will be kept confidential but they will need to be seen by a member of our research team. They will extract the information we need to collect for the study, and to check that the research data are correct. The research data will also be kept confidential, and nothing that could identify you will be passed to any third party.

Looking at quality of life.

About a quarter of the women who agree to take part in **SECRAB** will be asked if they would also be willing to provide more detailed information about how the treatments affect their quality of life, their experience of any side effects and satisfaction with the breast appearance. If you are one of those being invited to take part, you will be given a separate information sheet about what this would involve.

What are the general side effects of the treatments?

Chemotherapy may cause a sore mouth, some nausea and possibly vomiting, tiredness and hair loss. You may be more at risk from infection. If you have not yet gone through the changes of the menopause, we know that chemotherapy usually stops periods during treatment. This happens for 4 out of 5 women over the age of 40. If you are in this age group you are likely to develop menopausal symptoms like hot flushes during your treatment. You must take care not to become pregnant during the chemotherapy, because of the risk of damage to the unborn child.

Radiotherapy may cause skin reactions such as tenderness, itching, and redness or weeping to the treated area. Fluid retention (lymphoedema) may cause swelling of the arm. The shape and appearance of the treated breast may change. Very rare late side effects include inflammation of the lung, nerve injury affecting the arm and rib fractures.

How do I join the study?

We hope that you will want to take part in **SECRAB**, and we understand that this is an important decision for you to make. You should read this leaflet carefully and ask your hospital doctor or clinic nurse questions if there are things you do not understand. If you choose to join the study you will be asked to sign a consent form. Your doctor will then call the study organizers and enter you into **SECRAB**. You may still change your mind and leave at any time you wish without any problem.

For further information about **SECRAB please contact:**

_____ at _____

on _____

We thank you for taking time to read this leaflet and considering taking part in this study, the answers to which will make it a lot easier for us to advise how best to combine chemotherapy with radiotherapy for future patients with your disease



Patient Information Sheet Quality of Life Study

SECRAB A large clinical trial to determine how best to sequence chemotherapy and radiotherapy treatment for early breast cancer

We would like you to take part in the **SECRAB** quality of life study, but only if you want to. You may want to take this leaflet away and discuss it with your friends and relatives before you decide. You are free not to take part, and if you enter the study you are free to change your mind and leave at any time without giving your reasons. Your team will respect whatever decision you make, and your current and future care will not be affected in any way.

This leaflet explains what taking part in the quality of life study would involve.

Why is the **SECRAB study researching into quality of life?**

At present doctors do not know whether or not the different ways of combining chemotherapy and radiotherapy affects patients' quality of life and general well being. We think it is very important to find out how people taking part in the **SECRAB** study feel, both emotionally and physically and to study any side effects in some detail.

To get reliable information about quality of life, we need about 300 women to tell us more about their treatment experience. We are studying this in two sections: quality of life and breast appearance (cosmesis or cosmetic result). This information will be used to compare the possible advantages and disadvantages of each treatment combination. The results from this study will make it a lot easier to advise future patients what their treatment might involve.

What does the quality of life section involve?

You will be asked to complete a set of questionnaires asking about how you feel physically and emotionally. Questionnaires are given at the start and end of treatment and at your first two annual follow-up visits (if you are taking part in the Breast Appearance Study you will also be sent a questionnaire by the Trials Unit which corresponds with your fifth annual follow-up visit). While you are having radiotherapy you will also be asked to complete a one page 'diary sheet' once every week. The diary sheets will record how you have felt and any side effects you may have experienced during the previous seven days.

What does the breast appearance section involve?

Although surgery probably has the greatest effect on the appearance of your breast, radiotherapy may also affect the final result. We want to study this by taking two photographs (one with arms raised and one with arms lowered). So that you cannot be identified, your face and name will not be shown on the photographs. The photographs will be taken on five occasions - at the start of radiotherapy, at the end of all treatment, at your first two annual follow-up visits, and at your fifth annual follow-up visit.

How important is it to provide all of this information?

In quality of life research it is important to get as complete a picture as possible. If you do take part, please try and complete all of the questions. You can choose to take part in both the quality of life and breast appearance sections or just to take part in one and not the other.

How do I get more information?

Please ask your doctor and the breast care team if you have any more questions. If you have any problems while in the study you can contact Dr. Sarah Bowden at the Clinical Trials Unit on 0121 414 4371.

We thank you for taking time to read this leaflet and considering taking part in this study, the answers to which will make it a lot easier for us to advise how combined chemotherapy and radiotherapy affects quality of life



Patient Consent Form

SECRAB A large clinical trial to determine how best to sequence chemotherapy and radiotherapy treatment for early breast cancer

I have explained the nature of the **SECRAB** study to:

I have described what the study will involve and the implications to my patient and she has agreed to enter the study. I have made it clear that she may withdraw from the study at any time without giving a reason or impairing her treatment. The patient has been given the opportunity to ask questions relating to the study.

Clinician's signature: Date: ____/____/____

Print name:

On the basis of my conversation with the doctor today, and having read the information sheet, I confirm that I am satisfied with the information provided to me relating to the **SECRAB** study. I have had the opportunity to ask questions and I agree to participate in the study. I understand that I may withdraw from the study at any time without giving a reason.

I also understand that my medical records will remain confidential, but will be available to authorized personnel for the purposes of checking the information collected and ensuring that the study has been conducted properly.

Patient's signature: Date: ____/____/____

Witness: Date: ____/____/____

Print name:



Patient Consent Form

SECRAB A large clinical trial to determine how best to sequence chemotherapy and radiotherapy treatment for early breast cancer

The Quality of Life Study

I have explained the **SECRAB** Quality of Life study to:

I have described what the study will involve and the implications to my patient and she has agreed to enter the study. I have made it clear that she may withdraw from the study at any time without giving a reason or impairing her treatment. The patient has been given the opportunity to ask questions relating to the study.

Clinician's signature:

Date: ____/____/____

Print name:

On the basis of my conversation with the doctor today, and having read the information sheet, I confirm that I am satisfied with the information provided to me relating to the **SECRAB** Quality of Life study. I have had the opportunity to ask questions and I agree to participate in the study. I understand that I may withdraw from the study at any time without giving a reason.

I also understand that my medical records will remain confidential, but will be available to authorized personnel for the purposes of checking the information collected and ensuring that the study has been conducted properly.

I would like to take part in the Quality of Life section of this study

Yes No

I would like to take part in the Breast Appearance section of this study

Yes No

Patient's signature:

Date: ____/____/____

Witness:

Date: ____/____/____

Print name:



Patient Re-Consent Form

Patients participating in the Breast Appearance Study only

SECRAB A large clinical trial to determine how best to sequence chemotherapy and radiotherapy treatment for early breast cancer

The Quality of Life Study

I have explained why an additional photograph and quality of life assessment is required for the

SECRAB Quality of Life study to:

I have explained what this will involve and the implications to my patient and she has agreed to have an additional photograph taken and to complete an extra quality of life questionnaire. I have made it clear that she may change her mind at any time without giving a reason.

Clinician's signature:

Date: ____/____/____

Print name:

On the basis of my conversation with the doctor today, I confirm that I am happy to have an additional photograph and complete an additional quality of life assessment for the **SECRAB** Quality of Life study. I understand that I may withdraw at any time without giving a reason.

I also understand that my medical records will remain confidential, but will be available to authorized personnel for the purposes of checking the information collected and ensuring that the study has been conducted properly.

Patient's signature:

Date: ____/____/____

Witness:

Date: ____/____/____

Print name:



General Practitioner Information Sheet

SECRAB A randomised clinical trial to determine how best to sequence chemotherapy and radiotherapy treatment for early breast cancer

Your patient _____ has recently been invited to take part in this study by her oncologist and may approach you for advice before giving informed consent, or for support while in the study. Her consultant(s) will continue to report to you as normal. This information sheet contains supplementary information about the trial, and the possible implications for your patient.

SECRAB is a prospective, multicentre, randomised study comparing two different methods of sequencing chemotherapy and radiotherapy for women with a clear indication for both as adjuvant treatment following curative surgery for early breast cancer. The study is primarily designed to answer safety and efficacy endpoints. Your radiotherapy centre is one of many in the United Kingdom taking part. We plan to randomise two thousand women over a 3-4 year period (1000 in each arm). The two treatment schedules may well prove to be equivalent, hence we are also looking at quality of life and cosmetic outcome in a 300 patient subset.

Why is *SECRAB* an important study?

Oncologists in the UK are uncertain how best to sequence adjuvant chemotherapy and radiotherapy for women who have a clear indication for both treatments following definitive, curative surgery for early stage breast cancer. This question is important since the number of women considered to have a clear need for both treatments has increased. Post-operative radiotherapy has become standard treatment in the majority of patients having breast-conserving surgery, while chemotherapy is being extensively used in pre and postmenopausal patients, including some who are node negative. Ideally, both therapies would begin soon after surgery to minimise the risk of local and/or systemic failure. In practice, the possible slight advantages of earlier treatment must be balanced against the risk of enhanced toxicity and the need to maintain good cosmesis and quality of life for the patient.

A survey performed by Royal College of Radiologists in 1993 found that Fellows of the College were divided in their treatment practice, with a wide range of chemotherapy regimens and radiotherapy schedules in use. Oncologists were divided on how to combine chemotherapy with radiotherapy. Sequential chemotherapy followed by radiotherapy was being offered by 40% of oncologists. Another 40% used various synchronous chemo-radiotherapy schedules, with radiotherapy normally 'sandwiched' between two cycles of chemotherapy to avoid giving both simultaneously. The remaining 20% of oncologists gave radiotherapy before commencing adjuvant chemotherapy. The choice of chemotherapy regimen and radiotherapy schedule appears to be independent of the sequence in which they are given. For example, UK centres are evenly divided amongst those using a 3-week radiotherapy schedule versus those using a 5-week schedule, and both are being combined sequentially or synchronously with chemotherapy. In Scotland a four-week schedule is commonly used. This situation reflects the current lack of reliable, persuasive evidence to favour one approach over another.

Safety and ethics considerations

SECRAB has been independently peer reviewed by our sponsor, Cancer Research UK. The study is being run under the scrutiny of an independent Data and Safety Monitoring Committee and the relevant Ethics Committee(s). Strict confidentiality and good research practices will be observed. The trial will be terminated as soon as clear, convincing risk/benefit evidence becomes available.



Treatment options

The oncologist(s) will prescribe the chemotherapy and radiotherapy regimens following their normal practice. The choice of treatment(s) can be personalised, and will take careful account of the precautions needed to reduce the risk of side effects. Once this is done only the order in which the treatments will be given remains undecided. If the patient consents to enter the trial she will be randomised to either a Sequential or Synchronous treatment schedule.

In the *Sequential* schedule the chemotherapy is given first, and when the chemotherapy is finished radiotherapy will start (Chemotherapy → Radiotherapy). In the *Synchronous or 'sandwich'* schedule, chemotherapy is started first and radiotherapy is given in the gap in between the cycles of chemotherapy (Chemotherapy → Radiotherapy → Chemotherapy). This involves the same number of hospital visits but because the radiotherapy is started earlier the treatments can be finished slightly sooner. The exact time difference depends on the individual treatment regimens, but will probably be in the 3-5 week range.

Possible side effects of chemo-radiotherapy

Patients are likely to suffer the common side effects of chemotherapy. These are nausea and occasional vomiting, tiredness, a higher risk of infections, a sore mouth and hair loss. Other possible side effects include dry gritty eyes, dry skin and sore veins. Menstruation ceases during chemotherapy and patients may develop menopausal symptoms. Your patient must take care not to become pregnant during the chemotherapy, because of the risk of damage to the unborn child. Normal health, including menstruation should be regained after completion of chemotherapy, usually in 2 to 3 months.

Radiotherapy may cause skin reactions such as tenderness, itching, redness or weeping of the treated area. Fluid retention (lymphoedema) may cause swelling of the arm. The shape and appearance of the treated breast may change. Very rare late side effects include inflammation of the lung, nerve injury affecting the arm and rib fractures.

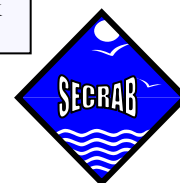
Trial procedures & quality of life study

This research does not involve any extra tests, treatments or visits to hospital. Patients will be actively followed up via the breast care team for the first five years, and then flagged at the national register. Three hundred women taking part in **SECRAB** are asked to provide more detailed information about quality of life, their experience of any side effects and satisfaction with cosmesis. This involves completing a set of questionnaires at four time points during chemotherapy treatment: start and end of treatment, and at the first and second annual follow-up visit to clinic; and patient diary sheets during radiotherapy treatment. Patients also have the option of agreeing to be photographed for assessment of the cosmetic outcome at the same times.

How do I get more information?

If you need to discuss an individual case please contact the consultant responsible or the breast care team. The Trial Co-ordinator will be happy to provide more details about the study, or to put you in contact with an appropriate clinical member of the trial Steering Committee.

Dr. Sarah Bowden SECRAB Trial Co-ordinator Cancer Research UK Clinical Trials Unit Institute for Cancer Studies The University of Birmingham Edgbaston Birmingham B15 2TT		
☎ 0121 414 4371	☎ 0121 414 3700	✉ BT1@bham.ac.uk



Appendix 2. Quality of Life Proforma

EORTC QLQ - C30 (version 2)

We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no “right” or “wrong” answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birth date (day/month/year):19.....

Today’s date (day/month/year):20.....

	No	Yes
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a <u>long</u> walk?	1	2
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2
4. Do you stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4

Please go on to the next page



EORTC QLQ - C30 (version 2)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4

Please go on to the next page



EORTC QLQ-BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week	Not at all	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

Please go on to next page



EORTC QLQ-BR23

During the past <u>four</u> weeks:	Not at all	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4
<hr/>				
During the past week:	Not at all	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g. itchy, dry, flaky)?	1	2	3	4

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Version 1.0

Please go on to the next page



Women's Health Questionnaire

Please indicate how you are feeling now, or how you have been feeling in the last few days, by putting a tick in the correct box in answer to each of the following items:

	Yes definitely	Yes sometimes	No not much	No not at all
1. I wake early then sleep badly for the rest of the night				
2. I get very frightened or panic feeling for apparently no reason at all				
3. I feel miserable and sad				
4. I feel anxious when I go out of the house on my own				
5. I have lost interest in things				
6. I get palpitations or a sensation of 'butterflies' in my stomach or chest				
7. I still enjoy the things I used to do				
8. I felt life is not worth living				
9. I feel tense or 'wound-up'				
10. I have a good appetite				
11. I am restless and can't keep still				
12. I am more irritable than usual				
13. I worry about growing old				
14. I have headaches				
15. I feel more tired than usual				
16. I have dizzy spells				
17. My breasts feel tender and uncomfortable				
18. I suffer from backache or pains in my limbs				

Please go on to the next page



Women's Health Questionnaire

	Yes definitely	Yes sometimes	No not much	No not at all
19. I have hot flushes				
20. I am more clumsy than usual				
21. I feel rather lively and excitable				
22. I have abdominal cramps or discomfort				
23. I feel sick or nauseous				
24. I have lost interest in sexual activity				
25. I have feelings of well being				
26. I have heavy periods				
27. I suffer from night sweats				
28. My stomach feels bloated				
29. I have difficulty in getting off to sleep				
30. I often notice pins and needles in my hands and feet				
31. I am satisfied with my current sexual relationship (please omit if not sexually active)				
32. I feel physically attractive				
33. I have difficulty in concentrating				
34. As a result of vaginal dryness sexual intercourse has become uncomfortable (please omit if not sexually active)				
35. I need to pass urine/water more frequently than usual				
36. My memory is poor				
37. If it is very difficult for you to cope with any of the above symptoms please write the number(s) of the question(s) in the box opposite.				



Patient Diary Sheets

Guidelines for Completion of the Patient Diary Sheets

We are interested in how you feel and what you experience during treatment. To help us do this we would like you to fill in the patient diary sheets contained in this booklet. There is no obligation to complete them and if you decide not to participate your treatment will not be affected in any way. However, it would be useful to us if you could return the diary sheet booklet and comment on why you did not wish to complete them.

The information provided will be of great value to our project and your help is greatly appreciated. All information given will be strictly confidential.

There are ten diary sheets contained in this booklet but depending upon the radiotherapy treatment you have been prescribed by your consultant you may only need to complete eight or nine of these.

Please fill out the sheets at the following times:-

The first diary sheet should be completed **before the start of your radiotherapy treatment**. This is very important as it lets us know how you felt before treatment began.

The remaining diary sheets should then be completed **at the end of each week during your radiotherapy treatment and for four weeks after your radiotherapy ends**.

Please try to complete all of the diary sheets on the **same day** of the week, should you forget then please complete the sheet as soon as you remember.

Fill in the sheet and describe how you felt the week before. There are no “right” or “wrong” answers, just tick the box(es) which best apply to you.

The booklet also contains a patient treatment summary sheet requesting information relating to any supportive care or medication received during your radiotherapy treatment. This form should be completed four weeks after your radiotherapy treatment.

Please return the booklet to the Trials Unit in the prepaid envelope provided.

If you have any questions, please contact Dr. Sarah Bowden at the Clinical Trials Unit on 0121 414 4371 who will be pleased to help you.

Thank you for agreeing to participate in *SECRAB*



Patient Diary Sheet

Your Initials: _____

Date of Birth: ____/____/____

Today's Date: ____/____/____

Diary Sheet No. _____

Please fill in the form describing how you have felt during the past week by ticking the box that best applies to you.

Symptom	Not at all	A little	Quite a bit	Very much	Did it upset you?	
					No	Yes
Have you felt nauseated? (feeling sick)					No	Yes
Have you vomited? (been sick)					No	Yes
Have you lacked an appetite?					No	Yes

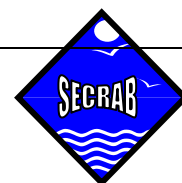
Have you experienced any of the following skin reactions in the area being treated by radiotherapy?

Tenderness					No	Yes
Redness					No	Yes
Itching					No	Yes
Weeping					No	Yes
Pain or discomfort in the breast being treated?					No	Yes
Have you had muscular pain in the chest wall?					No	Yes
Have you felt more tired than normal?					No	Yes
Have you been feeling unusually low?					No	Yes

Please tick one box below that best describes how you have felt this week:-

I have been fully active and able to carry on all my normal activities?	
I have been limited in strenuous activities, such as carrying a heavy shopping bag, but able to carry out light work and move around easily?	
I have been able to move around easily for most of the day and look after myself (such as washing, dressing, eating), but have been unable to carry out light work?	
I have needed help with looking after myself (such as washing, dressing, eating) and needed to rest for most of the day?	

Have you any other comments about the effects of having radiotherapy?



Patient Treatment Summary Sheet

Your Initials: _____

Date of Birth: ____/____/____

Today's Date: ____/____/____

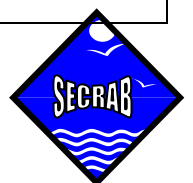
Please could you complete the information on this sheet relating to any supportive care or medication received during and since your course of radiotherapy treatment.

This form should be completed four weeks after your radiotherapy treatment.

<i>Supportive Care</i>			Number
Have you been to see your GP at the health centre or surgery for any reason? If yes, please give the number of visits:-	No	Yes	
Has your GP visited your home for any reason? If yes, how many times:-	No	Yes	
Has a nurse visited you at your home for any reason? If yes, how many times:-	No	Yes	
Has anyone from Social Services or a voluntary organization visited you in your home?	No	Yes	
Has a relative or friend taken time off work to look after you? If yes, how many days:-	No	Yes	
If yes to any of the above, please explain why this was necessary in the space below:-			

<i>Medication</i>
If you are taking any tablets or medication at present, then please write down the name of the drug from the label on the bottle:-
What were the drugs prescribed for?

What part of your treatment has caused you the most problem/difficulty?



Appendix 3. Grading Systems Used

CTC toxicity grading

Toxicity Grade	0	1	2	3	4
Nausea	none	able to eat - reasonable intake	intake significantly decreased, but can eat	no significant intake	_____
Vomiting	none	1 episode in 24 hrs	2-5 episodes in 24 hrs	6-10 episodes in 24 hrs	>10 episodes in 24 hrs or requiring parenteral support
Diarrhoea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools /day, or nocturnal stools	increase of 7-9 stools/day, or incontinence	increase of >10 stools/day, or grossly bloody diarrhoea, or need for parenteral support
Oral (Stomatitis)	none	painless ulcers, erythema, or mild soreness	painful erythema, oedema, or ulcers but can eat	painful erythema, oedema, ulcers, and cannot eat	mucosal necrosis and/or requires parenteral or enteral support
Alopecia	no loss	mild hair loss	pronounced or total hair loss	_____	_____
Constipation	none	mild	moderate	severe	ileus > 96 hrs
Infection	none	mild, no active treatment	moderate localized infection, requires active treatment	severe systemic infection, requires parenteral treatment specify site	life-threatening sepsis, specify site, includes febrile neutropenia
Fatigue	none	mild	moderate	severe	_____



Cosmetic result

Cosmesis following wide local excision (WLE) (Harris, 1979)

Excellent	Identical to other breast
Good	Minor differences to other breast
Moderate	Clearly different to other breast but without severe distortion
Fair to poor	Very different to other breast with severe distortion

Telangiectasia following mastectomy or WLE (Turesson & Thomas, 1989)

Excellent	No telangiectasia
Good	Minimal telangiectasia
Moderate	Moderate telangiectasia in whole breast/breast boost site
Fair to poor	Severe telangiectasia in whole breast/breast boost site

Acute skin reaction to radiotherapy (Fernando, 1996)

Mild	Nil reaction or mild/moderate erythema <5% dry desquamation in field
Moderate	Marked erythema with between 5-10% desquamation (dry or moist)
Severe	Dry or moist desquamation in >10% of field <i>or</i> Treatment gap required due to skin reaction <i>or</i> Incomplete healing 1 month post-radiotherapy <i>or</i> Ulceration 1 month post RT



Contact Details

SECRAB National Clinical Co-ordinator

Dr. Indy Fernando, Birmingham Oncology Centre, Queen Elizabeth Hospital (NHS Trust),
Birmingham, B15 2TH

☎ 0121 472 1311 Ext. 8319

Call free-phone on

0800 371 969 or 0800 731 7625

or Fax 0800 328 6412

Between 0900 and 1700 hours. Monday to Friday

Ask for *SECRAB* Randomisation

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Jane Tovey

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SECRAB Steering Committee

The national Steering Committee is representative of the centres taking part in **SECRAB**. The Trials Unit will be pleased to provide a list of members and their contact details on request.

Links with Related Trials Groups

Scottish Breast Trials Group: OSCAR study

Dr. Ian Kunkler

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