



QUASAR1

a UKCCCR study of
adjuvant chemotherapy
for colorectal cancer

Which colorectal cancer patients need chemotherapy?

It now seems likely that adjuvant chemotherapy with 5-fluorouracil and folinic acid can improve survival somewhat in colorectal cancer, with the weight of evidence favouring benefit in Dukes stage C patients. **However, there is still a need for better evidence on chemotherapy for Dukes stage B disease, and for older patients.** All of us realise that adjuvant chemotherapy has significant morbidity and cost implications, so we need to generate much more reliable evidence on the balance of benefits and risks before wide use of systemic chemotherapy becomes firmly established. **QUASAR1** may represent one of the last chances which we have to support an adjuvant trial with an observation only arm.

The **QUASAR1** study has achieved its target recruitment for the 'clear indication' randomisation and so this chemotherapy comparison has closed and will, in time, provide definitive evidence on the relative value of high- and low-dose folinic acid, and on any role of levamisole. However, the 'uncertain indication' arm has randomised only 1100 patients towards a revised target of 2500 - we need to recruit a further 1400 patients to meet our target. **QUASAR1** is therefore continuing, randomising patients with an uncertain indication for chemotherapy between six months of adjuvant chemotherapy and observation only (with chemotherapy considered just for patients whose disease recurs). The chemotherapy used for the remainder of the study will be the low-dose folinic acid and 5-fluorouracil regimen (without levamisole) unless new evidence emerges to indicate any modification is necessary. In **QUASAR1**, any extra work for collaborators is absolutely minimal and folinic acid is provided in convenient treatment packs free of charge. We understand the difficulties around recruiting patients to trials with observation only arms, but we feel that a final push from our collaborative group could see us achieve our objective - a reliable assessment of the worth of systemic chemotherapy in patients for whom the potential benefit of therapy are currently unclear.

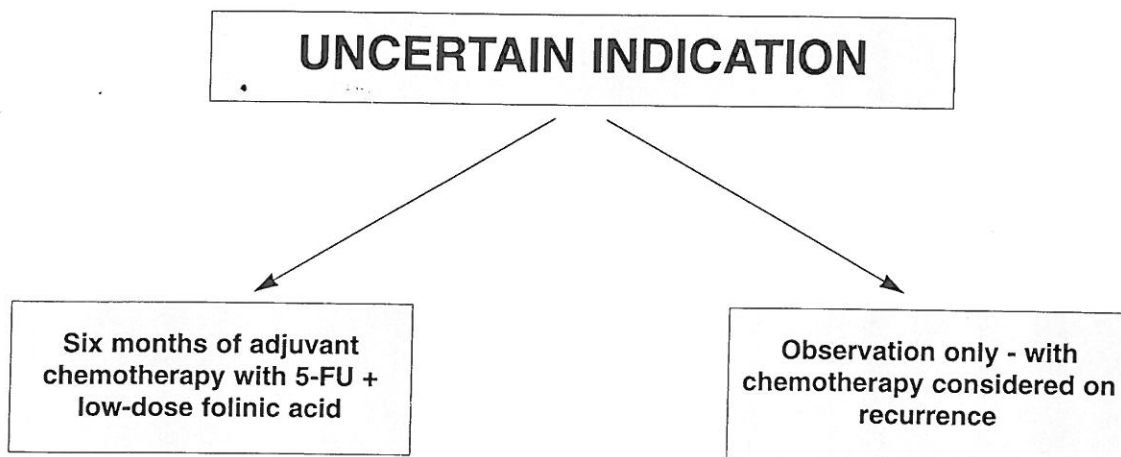
If you would like more information about QUASAR1 or would like to take part in the study
please contact:

The QUASAR Study Office, CTSU, Harkness Building, Radcliffe Infirmary, Oxford, OX2 6HE.

☎ 01865 - 792529 or Fax 01865 - 726003

QUASAR1 randomisation: simple eligibility based on 'Uncertainty'

- Do you consider the indication for chemotherapy to be **UNCERTAIN?**



Simple entry procedures: telephone randomisation

- No entry form is needed and no special tests have to be done
- Obtain patient consent (**QUASAR1** patient information booklets are provided)
- Prepare for telephone questions using the randomisation note pad
- Ring the 24-hour randomisation service ☎(0800 - 585323 or 01865 - 240972)
- In the West Midlands please call ☎(0121 - 414 - 3586 or 0121 - 414 - 3793)

Simple, widely practicable outpatient chemotherapy regimen:

- Patients allocated chemotherapy will be assigned a **QUASAR1** trial pack and case number. The trial pack containing free low-dose folinic acid and treatment instructions will be sent to the hospital pharmacy. Chemotherapy should be started as soon as possible and should continue for six months, unless a clear contra-indication is thought to have developed.
- If the patient is randomised to no systemic chemotherapy, such treatment should be avoided, if possible, and should be considered only if a clear indication (e.g. recurrent disease) is thought to have developed.

Simple follow-up: minimal documentation, no extra investigations

- To make really large-scale recruitment feasible, **QUASAR1** imposes little or no extra workload on participating clinicians, beyond that required to treat their patients
- Once a year, one line of information per patient will be requested detailing any recurrences, and the date and cause of death if the patient has died. No extra investigations or clinic visits are required.



Patient Information Book

Invitation to join an international research study of drug treatment after surgery for bowel cancer.

You have been treated with surgery for bowel cancer and your surgeon thinks that all of the tumour has been removed.

But, there is still some risk that the disease might come back and recent research suggests that giving you further treatment with cancer killing drugs might help, but we are not yet sure which patients need this type of treatment.

To find out, we are taking part in a big international research study, called **QUASAR1**, involving several thousand patients in more than a hundred hospitals in the UK and abroad.

The people who take part in the study will, like you, have had bowel cancer removed with no evidence of any remaining disease.

Some of them will be asked to have a six month course of treatment with cancer killing drugs, and the others will be followed up in the usual way and not asked to have any further treatment unless, later on, some reason emerges why they should do.

Although taking part in this study may not help you directly, it will help others because, through the **QUASAR1** study, we will find out how best to treat people in the future who develop this illness.

New research looking at the tumour tissue removed at surgery may help us understand the question of which patients will benefit from chemotherapy. Tissue samples removed at the time of your surgery will have been stored by your hospital. If you agree, then we may use a part of your tissue for this new research and hopefully this will benefit patients in the future. Your name would remain anonymous and would not be included in any publication or report.

If you do decide to take part in the research study, then neither you nor your doctor will know beforehand which treatment you would receive: that will be determined at random, **after** you've made a firm decision to join the study.

QUASAR 1 is an International study of treatment of bowel cancer organized by the National Cancer Research Institute. QUASAR is funded by the Medical Research Council, the Imperial Cancer Research Fund and Cancer Research UK. It is administered from the Cancer Research UK Institute for Cancer Studies, Queen Elizabeth Hospital, Birmingham.

Introduction

As you know, you have had surgery for cancer of the bowel (also known as the colon or the rectum). The operation has gone well and your surgeon thinks that all of the tumour has been removed. For most people this means that the cancer will not come back. But even when everything appears normal, there is a risk that some cancer might have already spread to other parts of the body. Cancer cells that have broken away from the original cancer can sometimes carry on growing and eventually cause problems. Recent research suggests that treatment with cancer killing drugs (chemotherapy) may reduce the chance that the cancer will return, but we are not yet sure which patients need this type of treatment or which drugs are best.

Chemotherapy

Chemotherapy means the use of drugs to kill cancer cells. It is usually given by a series of injections with rest periods in-between to allow patients time to recover from any side-effects of the treatment. For a number of years the main type of chemotherapy used for cancer of the bowel has been a drug called 5-fluorouracil (5-FU for short). When given on its own 5-FU is not very effective. But, when a vitamin called folinic acid is given along with the 5-FU it becomes more effective. These two drugs are now the standard type of chemotherapy for bowel cancer.

Which patients should be treated with chemotherapy?

This is a difficult question. In the past, chemotherapy for bowel cancer has mainly been used when the disease has spread or started to grow in another part of the body. Chemotherapy for patients with these advanced cancers does seem to help them live longer. However, the tumour eventually becomes resistant to chemotherapy and so the disease is very rarely curable by chemotherapy if it reaches this stage.

Another way of giving chemotherapy is to give it soon after surgery. This is called "adjuvant chemotherapy". The idea of adjuvant therapy is that cancer killing drugs given early on will be more likely to kill off any bits of cancer in other parts of the body while they are still small, before they have a chance to grow and become incurable. But, because it is given to everybody the disadvantage is that many patients who have already been cured by surgery - and so don't need any more treatment - will have an inconvenient and sometimes unpleasant treatment needlessly. If we could predict whose disease is going to come back and whose is not, we could just treat those patients who might benefit. But, at present, we cannot do this.

Because doctors are unsure how best to give chemotherapy, there have already been quite a few studies (called clinical trials) around the world that have compared a policy of giving adjuvant chemotherapy to all patients with a policy of giving chemotherapy only to patients whose disease comes back. Recent studies like this, testing 5-FU in combination with folinic acid, have been

promising and suggest that giving this form of adjuvant chemotherapy may make a moderate but important difference, particularly for those patients who are at higher risk of having their cancer come back. But, these studies were not big enough to tell us whether or not it is better to use adjuvant chemotherapy or to adopt a wait-and-see policy for patients who have a lower risk of recurrence. So, although we are very hopeful about the possibilities, we have to test this new type of chemotherapy properly in order to find out how best to use it. This is why we are taking part in the International **QUASAR1** study.

The QUASAR1 study

We, and many other doctors, from hospitals in this country and elsewhere, are taking part in an international study of bowel cancer treatment, called **QUASAR1**. The purpose of this study is to determine which patients, if any, should receive adjuvant chemotherapy and which should not. We know that chemotherapy will not stop cancers from returning in all patients, but what we need to find out is whether chemotherapy can prevent enough cancers coming back to make the side effects and inconvenience of the treatment worth putting up with. This information will make it a lot easier for us to advise future patients with your disease about the best treatment. It is possible that you might be one of the people who would benefit from adjuvant chemotherapy. However, until it has been tested properly, we can't be sure. This is the reason that we would like you to help by taking part in this research.

Why is the study called QUASAR1?

QUASAR stands for **Quick And Simple And Reliable**. It is called "QUASAR" because its aim is to provide a **quick** answer to the important question of which patients, if any, should be given chemotherapy early after surgery. To do this the trial has been kept as **simple** as possible so that doctors can enter most of their patients and hence the trial should be large enough to provide a **reliable** answer.

Research – clinical trials

Research into new ways of treating cancer is going on all the time. As no current cancer treatment results in the cure of all the patients treated, cancer doctors (oncologists) are continually looking at the possible benefits and drawbacks of new treatments and they do this by using clinical trials like **QUASAR**. Often many hospitals take part in these trials. Usually, clinical trials compare the most promising new treatment with the best available standard treatment. Doctors then seek a pool of volunteers to take part in the study. Half of these people are chosen, at random, to take one of the treatments and the other half take the other. The doctor, or patient, cannot choose the treatment because it has been shown that, if they do, he or she may unintentionally bias the result of the trial. Instead, the decision is made by the central organisers of the study. This type of study is called a randomised clinical trial and it is the only reliable way of testing new treatments. One treatment may turn out to be more effective than the other or they may be equally effective but one has fewer

unpleasant side effects. Hundreds of thousands of patients from all around the world have already taken part in clinical trials and this has been of great help in improving the treatment of their diseases. Before any clinical trial is allowed to take place it is first checked by the hospital's independent Research Ethics Committee – which is made up of doctors, scientists, nurses and non medical people – to make sure that it is properly designed and is in the patient's best interests. Your doctor must inform you about the study and ask for your consent before you are entered into any clinical trial or other research. This means that you must know what the trial is about, why it is being undertaken, why you have been invited to take part, and what the treatments would involve for you.

What would taking part in QUASAR1 involve?

In order to find out which patients should receive chemotherapy, patients in **QUASAR1** will receive EITHER:

Surgery only

Patients in this group will receive the standard treatment for lower risk bowel cancer, i.e. surgery alone without any chemotherapy. Their doctor will continue to see them at regular intervals after surgery (such "follow –up" appointments are usual with all cancer patients). If at any time after surgery their doctor thinks that chemotherapy would now definitely be best for them, then it would not be withheld because they are taking part in the QUASAR1 study.

OR:

Surgery and Chemotherapy

Patients in this group will be given adjuvant chemotherapy, in the hospital's out-patient department, starting a few weeks after surgery. The chemotherapy will be given over a period of about six months.

The decision whether or not you will receive chemotherapy will be made at random and neither you nor your doctor will know which treatment you would receive until **after** you have decided to take part in the study.

QUASAR1 chemotherapy

The two drugs which are being used in the chemotherapy group of the **QUASAR1** study are:

5-fluorouracil - This is the standard drug used in the treatment of bowel cancer. It is given by an injection into a vein in your arm.

Folinic Acid - This vitamin makes 5-fluorouracil more active, and is also given by injection.

Chemotherapy is given for a period of about six months usually in the outpatient clinic. So, if you receive chemotherapy, it will mean you will have to go to the Oncology Centre on thirty separate occasions to be given your injections. The treatment consists of either six five-day courses at four-weekly intervals, or is given once a week, every week, for a total of 30 weeks.

The 5-day, 4-weekly treatment is given in this pattern:

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1	2 injections	2 injections	2 injections	2 injections	2 injections	No treatment	
Week 2	No treatment						
Week 3	No treatment						
Week 4	No treatment						

The injections are given during the first week only. There is no treatment in the second, third and fourth weeks. These four-week courses are repeated five times – one after another- until you have had six courses in total.

As with any treatment given over a long period of time there can sometimes be interruptions because of illnesses, holidays or other social factors. You shouldn't worry if you experience unavoidable interruptions.

There is not much to choose between the two ways of giving chemotherapy. At the beginning of the QUASAR trial most Oncologists thought that the 5-day, 4-weekly treatment was likely to be more effective and so the once-weekly treatment was given just to people who, for work or other reasons, found it difficult to attend the clinic five days running, or at hospitals that only had once-weekly bowel cancer clinics. But, early results of the QUASAR study show that the once-weekly treatment seems just as effective but with less risk of side-effects such as mouth ulcers. So we can't yet be sure which way of giving chemotherapy is best. The QUASAR study will help us find out.

Radiotherapy

Radiotherapy is another treatment sometimes used for bowel cancer. Radiotherapy treats cancer by using high energy rays which destroy the cancer cells while doing as little harm as possible to normal cells. Your doctor will decide whether or not you should receive radiotherapy after taking into consideration a number of factors including your age, general health, and the type and size of your tumour. If you require radiotherapy, then while you are receiving it, you will be given your injections on a once-weekly basis.

Will the chemotherapy have any side-effects?

All drugs can have side-effects, and some patients do experience unpleasant symptoms with this form of chemotherapy although the majority do not.

The side-effects that are most often experienced are diarrhoea, feeling or being sick and a sore mouth. Up to 15% of patients get severe diarrhoea which needs to be treated with fluids and medicines. **You should, therefore, always report any serious problems to your hospital doctors without delay.** A similar number of patients experience mouth ulcers which can sometimes be painful enough to stop you eating solid food for a few days. The risk of developing mouth ulcers can be reduced by sucking ice chips at the time of injection. If you have any of these problems with your first course, then the dose of the drugs will be reduced in the next course to try and avoid them. If you have side-effects that have not cleared up by the time you are due to receive your next course of chemotherapy, then the course is sometimes delayed for a week.

QUASAR1 Pathology Sub-study - A study of tumour tissue to identify which patients benefit most from chemotherapy

When you had your surgery, the tumour that was removed will have been stored at your hospital by the pathologist. This happens for all cancer patients who have surgery in the UK. We would like your permission to collect a small piece of your tumour and use it for some new research. We would like to collect samples from all patients in the QUASAR study and measure the amounts of certain chemicals in them known as "markers". We know that some tumours have higher or lower levels of these "markers" than average. We believe we can predict which patients get most benefit from chemotherapy by studying the levels of the "markers" in different patients and comparing them to how well the treatment has worked. The most important "markers" we will look at are known as p53, Thymidylate Synthase, microsatellite instability and vascular invasion.

The tumour samples we collect will be made anonymous and will not be identified to anybody outside the QUASAR study office. You will not benefit yourself but we believe that this research will help patients in the future because we will know who will benefit from treatment and who will not. Donation of your tumour tissue is entirely voluntary and you will not be affected in any way if you do not give your permission. If you would like to contribute to this new research then please tick the box on the consent form.

What if I don't want to take part?

You do not have to be part of the **QUASAR1 study** or the **Pathology Sub-study** if you don't want to. You have already received the best standard treatment for your cancer and your doctor will be happy to continue to give you whatever treatment seems best for you. Nobody will behave differently towards you if you do not wish to take part in a clinical trial.

Can I change my mind?

If you choose to take part in the **QUASAR1 study** or the **Pathology Sub-study**, but then later change your mind, you are perfectly entitled to do so. Nobody will mind, and your progress will continue to be monitored even when you are no longer taking any study medicines. Whether or not you take part, your care is your doctor's most important concern, and he will always offer you the treatment which he considers is definitely best for you.

Who will have access to my medical records?

If you take part, the doctors in your hospital will pass on details of your condition and initial treatment, in strict confidence, to **QUASAR1** central organisers who consist of other doctors, medical statisticians and administrators. If you agree, a sample of the tissue removed at the time of surgery will be sent to the study's research laboratory for central review. The information will be held in strict confidence and used only for medical research purposes. No information which identifies you, or any other patients taking part in the study, will appear in any publication.

When will the results be known?

At the **QUASAR1** coordinating center the information from all patients is analysed regularly to see if one of the treatments is better. If any clinically important information becomes available from these analyses, doctor will be notified, and the findings will be published in a medical journal, so that all doctors and future patients with bowel cancer can benefit from the new knowledge.

Will my general practitioner know if I take part in QUASAR1?

If you agree to take part, your oncologist or surgeon will write to your GP informing him about the **QUASAR1** study and that you are taking part in it. The research team may also write to your GP to ask about your progress if you are no longer being seen regularly by your Consultant.

When do I have to decide whether or not to take part?

You do not have to make your mind up straightaway whether to take part in **QUASAR1**. You may prefer to discuss it first with relatives, friends or other persons. You can take this booklet with you and wait until your next appointment before deciding.

Who do I have to tell if I want to take part?

You should let your doctor or nurse know, or you can telephone the person on the back cover of this booklet and ask them to arrange it.

SUMMARY

QUASAR1 is a worldwide research study, which aims to provide bowel cancer patients with the best care possible while at the same time trying to find out ways of improving the treatment of this disease. The purpose of this study – called a clinical trial – is to find out whether giving extra treatment with cancer killing drugs after surgery to remove bowel cancer can lead to more patients being cured and, if so, which patients benefit most from this extra drug treatment (called chemotherapy). The drugs being tested are called 5-fluorouracil (5FU for short) and a vitamin called folinic acid and they are given by injection over a period of about six months. Unfortunately, this chemotherapy sometimes causes side-effects which can include severe diarrhoea, painful ulcers in the mouth, nausea, vomiting and an increased risk of infection. We know that this treatment will not make a big difference but we are hopeful that it will stop enough cancers coming back to make the inconvenience and side-effects worth putting up with.

The study is organised by the National Cancer Research Institute and more than a hundred hospitals worldwide are taking part. All centres taking part in the **QUASAR1** study must have first obtained approval from their Local Ethics Committee. At all times the care of each patient is the most important consideration. No-one will be denied any treatment that they definitely need, just because they are in the **QUASAR1** study. We would like you to take part, but patients can only be entered if they give permission and all participants are free to leave the study at any time without any prejudice against them. If you do decide to take part, we will let your GP know and provide information about your disease and progress to the central study office which will be treated in strict confidence in the same way as your other medical records.

You do not have to make your mind up straightaway whether to take part in **QUASAR1**. You may prefer to discuss it first with relatives, friends or other persons. You can keep this booklet and, if you like, make an appointment with your nurse or doctor to discuss the study again. If you have any questions then please feel free to discuss them with the person named below:

Name.....Telephone.....

Next appointment: Time.....Date.....

This booklet is produced in conjunction with BACUP, the cancer information service set up to give cancer patients, and their families, information on all aspects of cancer and its treatment as well as on the practical and emotional problems of living with the illness.

Information about services is available from:

BACUP

3 Bath Place, Rivington Street, London EC2A 3JR

<http://www.cancerbacup.org.uk>

Cancer Information Service

Freephone number 0800 181199