Clinical Oncology: Part One

Uptodate: Cancer Research Today, Programme 9

A series of Programmes from the Institute of Cancer Research

With Dr R L Morgan, Mr J A McKinna and staff of the Royal Marsden Hospital.
Participants: Dr McDonald; Mr D Eaton; Dr Levene.

University of London Audio-Visual Centre, 1974.

Made for British Postgraduate Medical Federation.

Black-and-white
Duration: 00:58:06:17

00:00:00:00

<**Opening titles**>

<Dr Morgan to camera>

The previous eight programmes in this series have been concerned with the more fundamental aspects of the cancer problem. Physicists, chemists and biologists have described recent advances in the understanding of the mechanisms and properties of the malignant process. And some new techniques for the detection and localisation of tumours have been discussed. I am sure that the value of a multidisciplinary approach has become obvious.

In the last three programmes of the series, we will be concerned with the clinical aspect of human cancer and some recent advances will be discussed, illustrating again the value of a multidisciplinary approach. Control of human cancer and the survival of the patient depend primarily on two factors: firstly, the sensitivity of the primary tumour to the treatment chosen, whether it be surgery, radiotherapy or

chemotherapy; secondly, the presence or absence of widely disseminated metastases and their amenability to effective therapy. It is therefore clear that it is essential, firstly, to determine the correct diagnosis, secondly, to have an accurate knowledge of the full extent of the disease, an assessment of the full extent both of the primary tumour and of any possible metastatic spread. It may be that in some tumours, a knowledge of the natural history will suggest that widespread metastases, on a microscopic scale, occur quite early in the disease. And it may be better in such tumours to assume widespread metastases and deal with the problem accordingly.

It was emphasised in the first programme that perhaps 75% of the natural history of human tumours was spent in a subclinical phase, where the disease is occult. The importance of more accurate detection of subclinical tumours is clear, and methods of detection and the possible role of tumour marker substances has already been discussed. There is no doubt that in general small tumours are more easily curable than large tumours, whatever treatment modality is chosen. Historically, surgery was the first treatment of choice, radiotherapy was considered palliative and chemotherapy was ineffective. In the past four or five decades, radiotherapy has been recognised as having a more radical curative role and chemotherapy has become more effective. Again, in the past few years, the value of a combined approach in the management of malignant disease has become obvious. In skin cancer, for example, either surgery or radiotherapy alone can produce a cure rate of 90 to 95%, but with combined surgery and radiotherapy, the cure rate can approach 100%. In stage 1 tumours of the larynx, again, 70 to 75% of patients can be cured with surgery or radiotherapy alone. Radiotherapy preserves the human voice, albeit a changed one compared with a pre-treatment voice. But surgery destroys laryngeal speech and postoperative training in oesophageal speech is necessary. This will be discussed again in the last programme of the series. However, combined surgery and radiotherapy can improve the cure rate to something of the order of 80 to 85%.

00:04:44:01

It has been the dream of oncologists for many years to discover a substance which is toxic to malignant cells wherever they may lurk. And the proliferation of radioactive

isotopes produced artificially after World War II stimulated the search for an isotope which would be selectively concentrated in tumour cells and thereby destroy them. The search has not been very successful, but radioiodine has been very effective in the control of some types of papillary and follicular tumours of the thyroid. The treatment itself is simple. The patient is given repeated drinks of a radioiodine salt. In the first introductory programme, Professor Symington illustrated the clinical problem with a diagram of the cancer atom bomb. It is of value to look at this again.

<Morgan narrates over diagrammatic slide showing cancer atom bomb>

The problem presents clinically in stages 2 and 3. And in these stages, it is clear that the disease is already widespread. Neither surgery or radiotherapy can hope to cure those patients in whom the disease is widespread. In the second clinical programme, Dr McElwain will discuss the successes of chemotherapy in the leukaemias and lymphomas and point to the possibilities of the use of chemotherapy in the so-called solid tumours. If at this stage, 2 and 3, combinations of surgery, radiotherapy and chemotherapy and, indeed, perhaps immunotherapy may well offer the best possibilities of better tumour control. In stage 3, the tumour is large and clearly almost certainly widespread, and similar considerations apply but in even greater force.

The main advance we should hope for, however, will probably occur in stage 1. Complete control of human cancer will only be possible in stage 1, but we will have to develop new techniques of detecting subclinical disease and develop more effective methods of dealing with small numbers of tumour cells which are, however, widespread in the patient's body.

I would now like to introduce a small film illustrating the problems of diagnosis and management of a patient with cancer of the oesophagus. These problems will be concerned with the problems of diagnosis and the use of combinations of therapeutic techniques in order to achieve tumour control.

<Film featuring a male patient, who has had cancer treatment, being interviewed by an unnamed doctor. Doctor is off-screen throughout interview and camera remains on patient>

<Doctor>

You're a 60 year old ship's chandler whose illness started about a year ago.

<Patient>

That's right, sir. It started on the 28th of June last year. Sitting down to an evening meal, I had hiccups, and this hiccups for the next night was again. And it gradually got so that every meal I had, I had hiccups with. And so I went to see a specialist locally in Shoreham and had a barium meal. And they decided there was a tumour there which they thought was cancer and thought it was malignant, and from that I came to the Royal Marsden Hospital here.

<Doctor>

Were you apprehensive about coming into hospital for an operation?

<Patient>

Well, as I'd never really been ill in my life and never been in a hospital, I was apprehensive, but once I got here and got the team round me, now I felt very confident.

<Doctor>

And your operation, in November, we did through three incisions. We explored your abdomen through the incision on your …

<Patient indicates site of incision. Camera pans down to abdomen>

<Patient>

Tummy, down here.

<Doctor>

That's right. And then we explored your chest.

<Patient indicating incision, camera pans in on chest>

That one across there.

<Doctor>

And then we opened your neck.

<Patient indicating incision, camera pans in on neck>

That one just there.

<Doctor>

And we were able to remove the whole of the gullet from your chest and replace it with stomach. Stomach was mobilised and taken up through the chest and joined to the upper end of the gullet in the neck. Have you had difficulties with swallowing after the operation?

<Patient>

No, no difficulties at all in swallowing. I'm eating very well. I'm eating less at a time. I'm eating more meals in a day, you know, I have sort of 6 meals a day instead of 3 meals a day. And other than that, no, no problems at all.

<Doctor>

We gave you a short course of X-ray treatment before the operation. Did that upset you?

<Patient>

Not in any way, no.

<Doctor>

And that didn't hamper our operation. Since the operation you've had a cruise and a holiday and now you're coming in once a month for 5 days for chemotherapy treatment.

<Patient>

That's right, sir.

<Doctor>

Does that upset you?

<Patient>

Not in any way at all, no, sir.

<Doctor>

And your life at home is getting back to normal, is it?

<Patient>

Yes, I think so. I think you can say it's practically back to normal again.

<Doctor>

Are you working as hard as before?

<Patient>

Oh no, I'm really not working very hard at all, I must admit that. I'm only working really about 2½ days a week.

<Doctor>

And were you frightened about knowing that you had cancer, were you frightened that perhaps this meant that you were going to die?

<Patient>

I think the first, when I was first told, yes, I was very scared and thought, you know, well, this is the end, but once I got here and realised how much was being done, and how much advance had been made since my mother died of cancer, then I had no fears at all. I'm quite sure knowing helped me. If I hadn't have known, I wouldn't have fought so hard.

<End of film clip>

00:10:44:11

<Cut to studio, Mr McKinna to camera>

That patient described to you very briefly some of the problems which face patients with malignant disease and which Dr Morgan has already mentioned to you that face

clinicians who attempt to treat patients with cancer in a combined disciplinary way. He had symptoms for a very short time, really fairly trivial symptoms, and he was referred by his general practitioner to a surgeon who arranged for him to have a barium swallow X-ray. This showed a narrowing […]

<McKinna narrates over oesophageal X-rays, using indicator stick, interspersed with talk to camera>

[…] at the lower end of the oesophagus, just above the diaphragm. This was an irregular narrowing and oesophagoscopy under general anaesthetic confirmed the presence of a tumour at this site, 30 cm from the mouth. Histology of the biopsy taken at the oesophagoscopy showed that this was an adenocarcinoma of the oesophagus. Adenocarcinomas of the oesophagus, unlike squamous cell tumours occurring in the middle and upper thirds, are not radiosensitive, but we gave this patient preoperative X-ray treatment, not with any effort at cure but with the attempt to reduce tumour viability <*next X-ray*> at the edge of the tumour and perhaps thereby reduce local recurrence. This was only done after preliminary clinical examination had failed to demonstrate the presence of any metastases.

At laparotomy, unfortunately, although the liver was clear, there were numerous lymph node deposits around the coeliac axis and, therefore, any further surgery became palliative rather than curative. However, he had had dysphagia for 2 or 3 weeks before his operation and it seemed, therefore, worthwhile to pursue oesophagectomy and this was done through the right chest and the mobilised stomach was taken up and anastomosed <*next X-ray*> to the lower end of the cervical oesophagus at the level of the sternoclavicular joint.

<McKinna to camera>

Following his operation, this patient is now having regular, intermittent, cytotoxic chemotherapy. And he has already demonstrated evidence of disseminated disease: two subcutaneous nodules of tumour have been excised and he also has a deposit in

the left eye which is being palliatively irradiated to prevent further deterioration of his vision.

All this has occurred within less than a year of the onset of his symptoms and this really is one of the unfortunate problems that face clinicians, that of aggressive, unrelenting malignant disease, almost in spite of treatment. And fortunately, for us and for the patients, not every tumour behaves in this way. It is the relation between tumour type and its behaviour and probable development that continually poses a challenge for the clinician in estimating what may happen to the patient, the prognosis and in planning correct treatment. Dr Morgan has already told you that correct treatment can only be based on the appropriate histological diagnosis and on as careful as possible an estimate of the extent of spread of the disease within the patient.

<McKinna narrates over diagrammatic slide showing path of spread of tumour in the breast>

The next chart diagrammatically represents the spread of a primary tumour in the breast: from the breast, the organ of origin, to the regional lymph nodes and thence through the blood stream to distant sites. And of course, the clinical problem is really that this spread does not occur in the logical anatomical and chronological way in which it's demonstrated on this chart. The spread from organ of origin, primary tumour, to distant sites may well occur in the patient long before the primary tumour is clinically apparent.

00:15:34:15

<McKinna narrates over slide showing TNM classification of breast tumours>

In the next chart, we have a diagrammatic representation of the description that we give to physical findings in carcinoma of the breast. These have been described by the International Union Against Cancer and this is the TNM – tumour, node, metastases – method of classifying and staging the spread of any tumour. And here

we see that the diagrammatic representation of its application to the breast. T1 is a small tumour; N0, no palpable nodes in the axilla; T2, a larger tumour; N1, with a palpable mobile node in the axilla; and so on with increasing extent of local aggression of disease, local spread, regional spread within the nodes, and M is the presence of distant metastases.

<McKinna narrates over graph showing 10 year survival rates with female breast carcinoma>

And if we look at the next chart: this shows figures from the Memorial Hospital in New York that show the 10 year follow-up from patients treated by radical mastectomy for carcinoma of the breast in various stages. And you'll see that for T1N0 patients, small tumours with no palpable axillary lymph nodes, this operation is virtually curative. When the tumour enlarges or the lymph nodes become involved then the prognosis is much less hopeful.

<McKinna narrates over slide showing statistics on prevalence of breast cancer>

<Slide>

30 women die every 24 hours

48 women diagnosed every 24 hours

50 - 60% of the new cases will have locally advanced or disseminated disease

The next slide shows the size of the problem of breast cancer that faces us in this country.

<McKinna to camera and then over slide>

And it is this particular problem which faces surgeons in particular. Patients with tumours, not only breast tumours but all tumours, are often referred to surgeons. And one of the things that the surgeon must do before prescribing treatment and, of course, this applies to the physician or radiotherapist, is he must attempt to stage the extent of spread of disease. <*Slide*> And the aims of classifying, if we look at the slide are to help us plan appropriate treatment: treatment which is appropriate for the patient and the tumour. We hope that this information will also indicate the prognosis and, of course, if we use the same language all the time, this enables us to describe our results and exchange information between other centres.

<McKinna to camera>

Historically, the surgical contribution to the treatment of malignant disease expanded enormously in the first half of this century and this was by the demonstration of the fact that a radical operation that excised the organ of origin of the tumour together with wide margins of normal tissue and including the regional lymphatic lymph drainage, this would reduce quite considerably the likelihood of tumour recurrence. And the surgeon, in particular, has always been concerned with removal of tumour and prevention of its recurrence. In future, of course, the surgeon has got to be more ambitious and he's got to be concerned, as we all have to be concerned, with the long-term survival of the patient and with the treatment of disseminated disease.

The surgical names that one remembers in relation to the development of radical surgery are, of course, in this country Ernest Miles in connection with excision of the rectum, Sampson Handley with operations for carcinoma of the breast, Halsted in the States in connection with radical mastectomy, Wertheim in connection with excision of the uterus, ovaries and vagina for extensive squamous cell carcinoma of the cervix. And the improvements that occurred during the first half of the century were really due to increasing surgical expertise, considerable developments in anaesthesia and in postoperative care. We're much better able to look after the patients after the operation than we used to be and, of course, this has contributed to some of the solutions of the cancer problem, but it has also led to the development of more patients who have metastatic disease that requires treatment.

00:20:31:11

The extent of a surgical operation is one of the problems which faces us at the moment. Particularly as a result of combining forms of therapy, it has been suggested that the extent of a surgical operation can be reduced thereby limiting the maiming, the handicap that one gives to a patient. Removal of a woman's breast is a terrible, terrible shock to her and to her family, to her husband, and there are many people now concerned, for example, with the possibility of conserving the breast in patients with breast cancer. The difficulties that we face in this particular field in trying to define, and very carefully, the safe reductions of radical operations which will not lead to any loss of any effect of the operation is in the correct assessment of the patients. And I draw your attention to a quotation from Professor McWhirter from Edinburgh.

<No narration over slide>

<Slide>

> **"Failure to take account of the extent of the disease has probably caused more confusion in the assessment of the value of different methods for treatment than any single factor."**
>
> **McWhirter**

<McKinna to camera>

Now, Professor McWhirter has led the field in the field of breast carcinoma in suggesting that radical mastectomy is no longer needed and the patients can be just as well treated by a simple mastectomy followed by postoperative radiotherapy. The difficulty in breast cancer as in the clinical assessment of many patients with cancer is in the assessment of the regional lymph nodes.

<McKinna refers to diagram and draws on it while narrating>

And if we look at a pathological 1 cm tumour in the breast, we can anticipate that positive nodes will be present in 30% of the axillae. If we look at tumours of 1 to 2 cm, bigger tumour, then here we're up to 45 or 50% involvement, spread from the breast to the axilla. And a 2 to 3 cm tumour has a likelihood of having a 55% involvement in the axilla. The clinician is particularly bad at assessing this. The pathologist does it very much more accurately than the clinician.

<McKinna to camera and then narrates over slide comparing outcomes of radical and simple mastectomy>

And if we look at the next chart, we see a trial going on at present in Edinburgh to demonstrate what Professor McWhirter has already shown but not in the way of a clinical trial. Patients with operable breast cancer, that is, T1, T2, N0 and N1 tumours in the breast, are submitted to the trial and randomly allocated to two forms of treatment, either radical mastectomy or simple mastectomy and postoperative radiotherapy. And in the figures which he published in 1972, they were preliminary figures, but you'll see that there are nearly 400 patients in the trial.

Now if we look further down, we see that these two groups of treatments have been divided into R1 and R2, and S1 and S2. The patients in group R1 and in group R2, in fact, have the same treatment, that is, radical mastectomy. The patients in S1 and S2 have the same treatment, that is, simple mastectomy and postoperative radiotherapy. And you'll see that there are nearly 100 patients in each group. And that at 4 years, the survival rate of each of those groups of patients was 86%, 75%, 73% and 80%.

Now, if we just look at R1 and R2, 86 and 75 are quite different figures. It would be tempting if one was looking at this trial and suggesting that R1 and R2 were different methods of treatment to imply that R1 was the method of treatment of choice. And I show this slide really to emphasise the point that in clinical trials in human malignant disease, it is vitally important to ensure that like is compared with like. And you'll see that the numerical randomisation of women doesn't, in fact, produce two like groups which can be adequately compared.

00:25:35:20

<McKinna to camera>

Now, clinical trials are one of the ways in which advances are going to be made in the treatment of human malignant disease and I've shown you one example. Another trial is going on at Guy's Hospital concerned with the possible preservation of the breast: wide local excision of the tumour and radiotherapy as compared with radical mastectomy and radiotherapy. And the preliminary results of that trial have shown that it is not safe to conserve the breast when there is clinical evidence that the disease has spread to the axilla. There is a national breast cancer trial centred on King's College Hospital and Addenbrooke's Hospital at Cambridge which is described in the next slide.

<McKinna narrates over slide>

And here you'll see that they, in this trial, are undertaking to admit 2000 women to the trial in the hope that they will have comparable groups on each side of the arm. This is a different kind of trial because the surgical treatment is standard for each patient. They each have a simple mastectomy for operable carcinoma of the breast. And this is followed by randomised radiotherapy or watching policy to the chest wall and postoperative and the regional node areas.

The thought underlying this trial, this study, is the possibility that if the regional lymph nodes are involved by tumour, the patient probably has disseminated disease and therefore local treatment to those lymph nodes with radiotherapy will not influence the prognosis.

<McKinna to camera>

Secondly, if the radiotherapy is given to patients who do not have nodal disease, then it is probably harmful to their immune response and this may, in fact, reduce the

chances of their recovering well from the operation. This is a big trial, it's going on, the results will not be available for several years. This is one of the problems of clinical trials in human malignant disease, the results are not easily and readily available and they require long years of patient input and then further long years of follow-up study.

Other advances are going to be made with the use of new diagnostic aids and you've heard about some of those in the earlier programmes: mammography, for example, soft tissue X-raying of the breast, which has led to the most elegant Strax screening programme in New York which has actually shown that mammography can save the lives of women with early, probably a bad word, minimal breast cancer. Patients with minimal breast cancer may require less treatment, they certainly live longer after conventional treatment. And if, in the long run, patients who are likely to get a malignant disease can be examined by special ways, then earlier disease, minimal disease, may be detected, simpler treatment may be applied, and we may have patients living longer and perhaps with less evidence of subsequent disseminated disease.

One good example, of course, of new diagnostic aids in this respect is the fibre optic oesophagoscope and gastroscope. And this has been put to enormous use in Japan where carcinoma of the oesophagus and carcinoma of the stomach are common diseases, and routine screening of the population by oesophago-gastroscopy detects small tumours that are amenable to minimal surgical treatment and good postoperative results.

00:29:42:43

Dr Morgan will shortly tell you about improvement in the diagnosis of lymph node metastases. Other investigations include isotopes and ultrasound scanning and you've already heard about these. And these are all aimed at the earlier diagnosis and therefore the earlier treatment of either minimal local disease or, we hope, minimal metastatic disease which will be more amenable to treatment.

New surgical treatments are in the careful application of the existing surgical techniques but also there are some physical methods being applied. For many years heat has been used as a method of destroying tumours, diathermy. Pressure is now being applied within the bladder to destroy bladder tumours. Superficially spreading bladder tumours can now be destroyed with an intravesical balloon which is raised to a pressure above the diastolic blood pressure. And this treatment by Helmstein in Scandinavia has shown some very promising early results.

Cold is a new method of destroying tumours and I would like to show you a very short film, not of a tumour being treated but of a piece of beef steak being treated, with a cryosurgical probe because this is a new useful method of treating either small tumour curatively or bulky vascular tumours, perhaps which are painful, in a palliative way and considerably reducing the tumour bulk without, in fact, damaging surrounding normal tissues in anything like the extent required by major surgery or radical radiotherapy. And this film will now show you the probe attached, the cold probe, cooled by liquid nitrogen, attached to the meat.

<McKinna narrates over film showing cryosurgical probe applied to piece of meat>

Here you see the white, cold probe, cooled by liquid nitrogen, and the ice ball of cold, frozen tissue around it, extending around the tumour. When the probe is warmed, by stopping the flow of liquid nitrogen, then the ice on the probe disappears and very quickly the probe may be disconnected from the tumour and applied to another area.

<Film cuts to McKinna in pathology laboratory speaking to camera>

We've spoken about the importance of making an accurate pathological diagnosis on which to prescribe treatment and we've come from the studio, via the operating theatre, to the pathology laboratory, and I've brought a biopsy specimen, an incision biopsy specimen, from a breast tumour in a patient who is at the present in the operating theatre, and I've going to ask Dr Levene, the surgical pathologist, if he will make a frozen section examination of this tissue so that we can determine whether

or not she should have mastectomy. Frozen-section rapid histology is often of vital importance to the surgeon in determining treatment. Dr Levene.

<Dr Levene moves into shot. He removes biopsy specimen from dish and fills out patient information form. Levene then cuts a section from the specimen. McKinna narrates>

It's important at this stage, I think, to make a note of the patient's name and a description of the tissue. What happens now, Dr Levene, to that tissue?

<Camera pans out to show a scientist assisting Dr Levene. Camera follows scientist preparing cryostat section>

<Levene>

Well, this is frozen in the cryostat, here, in subzero temperature and thin shavings are made, sections of about 10 mu or less. They are mounted on a coverslip, rapidly stained with haematoxylin and eosin and then we examine them.

<McKinna off-camera>

And this will give me, as a surgeon, as accurate a diagnosis as a paraffin section would […]

<Levene>

Yes.

<McKinna off-camera>

[…] which takes perhaps 24 / 48 hours.

<Levene>

Yes, it's very little inferior in quality to a paraffin section.

<McKinna off-camera>

And this is useful obviously when we suspect malignancy. It's also useful in the breast when we want to prove that malignancy is not present. Are there hyperplastic conditions which can be mistaken for neoplasia which may be difficult to interpret on frozen section?

<Levene off-camera>

Yes, the group of florid cystic hyperplasia, sclerosing adenosis, form a difficult group to distinguish from cancer of the breast. The group of in situ cancers of the breast, intraduct and intralobular, are also difficult to diagnose, but the advantage of the cryostat is it provides a high quality section, so whereas one may have been in doubt on the old machine which was just called a freezing microtome and sections used to come out at about 15 mu, there's usually little doubt on a modern cryostat section.

<McKinna off-camera>

And, of course, if there is doubt, then the surgeon will not proceed with the operation.

<Levene off-camera>

No.

00:35:53:10

<Camera pans back from scientist to McKinna in conversation with Levene>

<McKinna>

Other circumstances come to mind: one opens an abdomen, finds an inflammatory mass in the colon, it's hard – is this inflammation or is it tumour? Can you help me there?

<Levene>

Yes, usually the differential in histological appearances is so great between adenocarcinoma of colonic origin, say, and inflammation that it's a very simple diagnosis to differentiate histologically.

<McKinna>

Sometimes the specimen of tissue which the surgeon sends you will be very small. Is it then helpful to carry out a frozen section examination?

<Levene>

Of course, it's helpful if the indications are correct. The one you gave, for example, small nodule in the peritoneum in a case where one's carrying out a laparotomy, but it's wrong and unjustifiable […]

<Camera pans back to scientist continuing with preparation of cryostat section>

<Levene off-camera>

[…] to do it on a laryngeal fragment where the patient is not a known case of laryngeal cancer. And the biopsy is precious, unique and it may be destroyed in this process of preparing it. Indeed, all section work is destructive of tissue, and the smaller the amount of tissue, the more one wants to preserve it for definitive paraffin section work for reasons of sparing the patient yet another operation.

<McKinna off camera>

Yes, indeed. So sometimes it's important if we're sure that more tissue is available to use this method to ensure that we've got representative pathological material.

<Levene off-camera and then camera pans back to him in conversation with McKinna>

Yes, yes. When one is doing an operation to make a diagnosis of the pathological changes present, one wants to make sure that the correct piece of tissue has been selected. And it's quite easy, particularly where relatively large volumes are available, to send a piece down to the pathologist and say, are we in the tissue that I'm interested in?

<McKinna>

Yes.

<Levene>

You've probably discussed it with him in advance.

<McKinna>

Yes. And sometimes in lymph node work, this may help you to advise the surgeon that an inflammatory condition is present and bacteriological examination should be carried out.

<Levene>

Yes. In general there is never any harm done in sending tissue down for frozen section provided the indication is correct and provided that the tissue is not so small and so precious that it can't be put at risk in frozen section work.

<McKinna>

Yes. Is it of help now, can you help me in determining the adequacy of an operation, the extent of an operation? We saw a patient earlier who'd had an oesophagectomy. Can you help me as a pathologist to determine the extent of clearance? Does frozen section help?

<Levene>

Yes, there are two roles it has. One is in preliminary scouting of tissues; for example, if a radical ablation of the viscera of the neck is contemplated, it is unjustifiable to do it if preliminary scouting, shall we say, in the retrosternal area or in the posterior triangle low down, indicates that malignant disease is present. That's one way in which frozen section work assists the surgeon in the extent of his operation. And the second one, of course, is when the specimen is provided, inspection and frozen section work on it will indicate the margin of clearance if this is required. For some surgical procedures, the margin of clearance is an irrelevance; for example, in the case of malignant melanoma if the tumour is cut out and then it is confirmed as a melanoma, the subsequent excision is so wide that there's no point at all in saying am I clear. If you're clear by several centimetres, you can see by naked eye.

00:40:18:00

<McKinna>

Yes. In the oesophageal specimen, we spoke of, that patient also had lymph node disease and you said that examination of the lymph nodes is helpful to […]

<Levene>

Yes.

<McKinna>

[…] determine the presence of cancer. Is it helpful after irradiation? Sometimes the head and neck surgeon doing the radical ablation in the neck, that you've spoken of, will come across a hard lymph node and he wants to know, I imagine, whether this is tumour or radiation disease.

<Levene>

Yes, histology is much more accurate than clinical impression here. The histology itself can be difficult because after irradiation, gross tissue changes occur with the development of cells called irradiation fibroblasts which are large, hyperchromatic and irregular in outline and they simulate malignant cells, but particularly in an institution like this where we are well experienced with this picture, it doesn't present a problem. Certainly if a hard nodule in the neck is sent down with a written request – is metastatic squamous carcinoma here or not? – we can give an answer on the spot.

<McKinna>

Thank you. I think the slide is ready. Shall we inspect that?

<Levene>

Yes.

<Levene and McKinna walk across to microscope. Levene examines specimen through microscope and writes notes>

<McKinna>

While Dr Levene is looking at the slide, we spoke a moment ago about examination of the lymph nodes by histology. I think it's important to recognise that there are other methods of examining the lymph nodes – clinical examination, and in the last 10 to

15 years lymphography has been introduced. And in the next part of this programme, you're going to see a patient having a lymphogram and, in addition, Dr Morgan is then going to describe the applications of lymphography in relation to carcinoma of the cervix.

<Levene>

Well, this is a carcinoma of the breast. A banal carcinoma, a polygonal cell with a fibrous stroma and that surprised me from the naked-eye appearances of the tissue. However, there it is, it's unequivocal.

<McKinna>

I think the biopsy was an incision biopsy taken at the edge of the tumour because it was deep in the breast and excision of the whole tumour might have made the next operation more difficult.

<Levene speaks while McKinna looks down microscope>

Yes, if you have a look at that you'll see there are great masses of cells growing in a haphazard fashion in the fibrous tissue which is stained up a pale pink here. The cell nuclei pick up a blue and there's no vestige of normal acinous structure. This could not be confused with any inflammatory or hyperplastic condition of the breast.

<Cut to Doctor (unnamed, possibly Dr McDonald) seated, examining the foot of a patient lying supine on a hospital bed. The patient is undergoing a lymphogram procedure. Doctor narrates to camera and then over close-up shot of foot. He indicates catheter tubes using tweezers>

Mr McKinna mentioned that you will be seeing a patient having a lymphogram. This lady is now in the midst of the investigation and here you can see the incision on the foot with dye passing along the catheter into the fine needle. The dye, blue dye, has been injected into the foot here to demonstrate the lymphatic which is normally

transparent. A weight is used to force the dye through the tubing because it is viscous and normally takes nearly an hour to be injected. This is the apparatus with the weight forcing the 10 cc of contrast into the foot. Although we take pictures to ensure that the dye is going in correctly, the final pictures to show the nodes are taken on the following day and these are the lymphadenogram films which we will see shortly.

00:44:35:14

<Cut to Morgan to camera. An X-ray of an abdomen is displayed on the wall behind him>

In the earlier part of this programme, it has been made clear that the effectiveness of the management of cancer depends primarily on an accurate knowledge of the full extent of the disease including the disease of the primary site and a knowledge of the position of any involved lymph nodes. Mr McKinna has already suggested that the examination of the lymph nodes involves not only a clinical examination but can also involve an X-ray examination using the technique of lymphography which you have just seen performed.

<Camera pans in on X-ray films and Morgan narrates over these using indicator stick>

The films on the viewing box demonstrate the sort of films that one can obtain 24 hours after the injection of the dye and after an intravenous pyelogram has been performed. The dye has been concentrated in the lymph nodes and you will see that the lymph nodes in this area, and along the periaortic chain, are enlarged and have filling defects in them, suggesting that those nodes are involved with the active cancer. The intravenous dye has been concentrated in the kidneys and outlines the renal pelvis and the ureters and the bladder itself.

This patient is a patient who had a carcinoma of the cervix, and as a result of the lymphographic examination of the lymph nodes in the pelvis and the periaortic chain,

we gave her treatment designed to treat not only the primary tumour, in the region of the cervix, but also the lymph nodes which were outlined and seemed involved with disease. The X-ray picture on the right-hand side shows the appearance immediately after the end of treatment where you see the lymph nodes are now normal in size and have no suggestion of very marked filling defects, suggesting that our treatment was effective in controlling the disease at the primary site and in the lymph nodes.

The next slide in position demonstrates that the lymph nodes are normal in appearance on this film, which was taken several months after the end of treatment. The lymph nodes in the pelvis are normal in size and show no suggestion of involvement with tumour as also are the nodes in the lower part of the periaortic chain. But the nodes in this area are larger than in the film immediately after treatment and, in fact, show filling defects, suggesting that this group of lymph nodes on the left-side of the upper periaortic chain are, in fact, beginning to be involved with tumour again.

The importance of lymphography is clearly seen in this pair of films because the dye can, in fact, remain in the lymph nodes for periods of up to 2 years after the initial injection. And follow-up films of this sort can be extremely useful in first detecting the presence of further active disease, long before the patient has any obvious clinical signs or symptoms.

<Morgan hangs chart over lightbox and narrates over this>

The value of lymphography in determining the extent of disease can, in fact, be demonstrated on this chart. A 190 patient with cancer of the cervix were seen from 1965 to 1972 and a 144 lymphograms were done in all patients. Of the stage 1 patients, there were 57 of them and 44 of them had lymphograms. Now stage 1 of the cervix is a disease which is clinically confined to the cervix itself and there is no clinical indication that the disease has spread to any lymph nodes. Yet of those 44 patients, 12 of them showed evidence that the tumour had spread to lymph nodes. 9 showed involvement of the pelvic nodes and 3 showed involvement of the periaortic nodes. In 44 patients, therefore, with clinical stage 1 disease, 12, that is over 25% of

them, showed, in fact, involvement of the nodes. The disease was far more advanced than was clinically detectable.

All stages –190 patients, 144 lymphograms – and of those 62, 62 out of 144 had disease involving the lymph nodes. 48 of them had disease involving the pelvic nodes and 13 had unsuspected disease in the periaortic chain. So that the lymphogram has enabled us to stage the disease into position and detect the position of involved nodes much more easily.

00:49:53:01

<Morgan to camera>

Now, in the past, the techniques of treatment of cancer of the cervix have involved the introduction of radioactive sources into the vagina and the cervix. The usual radioactive source used in the past has been radium, but in recent years, because of its long half-life of 1700 years and its high energy, it has become clear that the use of radium has involved some radioactive hazard to members of the staff engaged in this form of treatment.

<Camera pans out as Morgan narrates while walking forward to show radioactive source store and dispenser. He is joined by Mr David Eaton>

My colleague Dr Jordan Baker and Mr David Eaton, of the Royal Marsden Hospital, in the past decade or so have designed a radioactive source store, or safe, and dispenser, using caesium as the radioactive source in order to reduce the radioactive hazard to members of the staff. And I would now like to ask Mr David Eaton to demonstrate this machine to you. Mr Eaton.

<Morgan walks off screen. Eaton to camera and then narrates over demonstration of radioactive source store and dispenser>

Thank you. This machine, which we now use in the operating theatre, has been made mobile. This enables us to enter the theatre and actually carry out the work on sites. In the centre of the machine, we have a lead safe. And in the centre of the lead safe, we have a source wheel. This wheel has three rings of holes. In the inner ring, we can contain forty 25mg sources. In the centre, we can have forty 15mg sources, and in the outer ring forty 10mg sources. If I now place the model on the machine, you can see very clearly the relationship of the source wheel to the machine. Coming from the centre of the source wheel, we have a steel shaft. This projects beyond the lead protection and carries four further wheels. Three of these wheels are counters so that as you eject a source each one of these counters will register that a source has been ejected. And similarly, if you return a source to the safe, they will again register that fact. The fourth wheel is a selector wheel. When this wheel is rotated, it will bring a radioactive source in line with the exit holes of the safe. Beyond the selector wheel, we have the probe wheel. This consists of a nylon rod which is wound around the wheel. As the wheel is rotated, the nylon rod is pushed through the selector wheel, the counter wheels, the lead safe and the source wheel, and will eject a source into the loading block.

In the loading block, we have a jig. This jig will contain the applicator. The jig is able to move in and out of the loading block and will thus enable us to select each position of the applicator before we load the source into it. On the front of the machine, we have a lever. When this lever is rotated, it will raise and lower the loading block to bring the applicator in line with the exit holes of the safe.

<Eaton narrates indicating applicators on display board>

At the present time, we have in use five applicators. We start off with a large vaginal packet which is able to have four sources contained inside. Further along we have a smaller packet which can contain two sources. In addition, we have three uterine tubes, and depending on the length of the uterus of the patient, we can select a tube which will suit her. The longest tube will contain three sources, the centre tube two sources and finally, one source.

When the applicators are inserted in the patient, the uterine tube is put firstly into the uterus and the vaginal box is located onto the tube. On the cap of the tube, we have a small peg. This peg enables the box to mate with the tube and prevents it from slipping out of its level. When the applicators have been removed from the patient, they are put into a lead pot which is then returned to the caesium room. The applicators are washed and cleaned and we can then reload the sources back into the safe.

<Morgan walks into frame>

<Morgan>

David, this caesium dispenser and safe has, in fact, an arrangement where this portion of the unit here can have accessories put into it which will wash and sterilise and unload the caesium tubes before they are actually inserted back into the safe.

<Eaton>

Yes, we have a system which, when this lid is removed and a further lead block put onto the machine, we can unload the box and tube, the sources will go into a small tray, where they are removed one at a time for inspection for cleanliness and for damage before they are returned to the main safe.

<Morgan>

The important points about this caesium dispenser is the fact that the machine is mobile, it can contain a large quantity of radioactivity, but because the energy of caesium is lower than that of radium, it is perfectly safe for people who are working in the operating theatre itself and who are conducting this form of treatment. Thank you, David.

<Eaton walk off-screen. Morgan to camera and then refers to chart and narrates over it>

Now, over the past 9 years, this form of treatment has been used at the Royal Marsden Hospital and the results are of some interest. This slide, this chart, demonstrates the results that we have obtained from 1965 to 1972 in the treatment of cancer of the cervix. And there are one or two points I would like to bring out to you. The first, stage 1 cases: 57 cases treated, 5 year survival of almost 90%, compared with a pre-1965 result of between 65 and 70%. All stages: a 5 year survival of 60%, compared with a survival of 35 or 40% for all stages treated before 1965. The not inconsiderable improvement in the survival of the cervix can be attributed, I think, to the use of lymphography in the determination of the full extent of the disease before treatment has occurred.

<Morgan to camera>

Now, in the next programme, you will have an introduction to the improvements in radiotherapeutic techniques which are possible given by Professor Michael Peckham. And the question of chemotherapy and the management of malignant disease will be discussed by Dr Tim McElwain.

<End credits>