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An MRC prospective randomised trial of radiotherapy versus surgery for operable squamous cell carcinoma of the oesophagus

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The objective of the trial was to determine whether there was any difference in survival rates after operable cases of squamous cell carcinoma of the oesophagus were treated by radiotherapy or surgery. It was designed as a prospective, randomised, multicentre trial in the United Kingdom, after staging as potentially operable, and it was planned to enter 100 patients per annum for 4 years, with a minimum follow-up of 5 years, after pre-entry staging of patients under 75 years of age by barium swallow, chest radiographs, oesophagoscopy, biopsy, bonchoscopy and CT scanning.

The protocol was published in July 1986; the trial started in January 1987 and was stopped in June 1988 when only 31 patients from 16 centres were entered, although 30 centres had ethical committees' approval and were willing to start the trial.

Interventions were to be as follows:

1 ***Surgery.* According to the practice of that particular surgeon and classified as (*a*) curative resection if the surgeon considered that no macroscopic tumour was left behind, and (*b*) palliative if incompletely resected.**
2 ***Radiotherapy.* (*a*) Prescribed minimum corrected tumour dose of 5000 cGy with daily dose of 250 cGy in 20 fractions over 4 weeks. (*b*) Prescribed minimum corrected tumour dose of 6000 cGy with daily dose of 200 cGy in 30 fractions over 6 weeks.**

The endpoint was to be survival at 1, 2 and 5 years.

The trial was discontinued after 18 months because of lack of recruitment and thus the question whether operable squamous cell cancer of the oesophagus, staged before treatment with CT scanning, is to be treated by radiotherapy or surgical resection remains unanswered. It is unlikely that a phase III trial will ever have sufficient support from surgeons to find the answer.

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Surgical resection of oesophageal cancer has become a standardised procedure, and most surgeons use the two-stage Ivor-Lewis approach of a right thoracotomy following a preliminary laparotomy *(1)*. McKeown *(2)* developed a three-stage procedure with the gastro-oesophageal anastomosis in the neck to reduce the dangers of anastomotic leakage in the chest and to obtain a greater clearance longitudinally. A further modification aimed at reducing mortality has been blind dissection of the thoracic oesophagus, approaching the tumour from above and below to avoid a thoracotomy and its complications. This was introduced by Grey Turner in 1933 *(3)* and has recently had a revival *(4)*. There is little data to show that the technique is more important for obtaining good results than the general condition of the patient and the staging of the tumour. There is, however, good evidence that the 'experienced' surgeon, doing more than five cases a year, has a lower operative mortality than the 'occasional oesophagectomist' doing one or two *(5,6)*. Postoperative mortality nowadays should be under 15%; this should be expressed as both 30-day mortality and inhospital mortality, because all early deaths must be included in assessing the risks of surgery, and the former figure always understimates the true postoperative mortality. There should be a survival rate of 45% at 1 year, 20% at 2 years and 10% at 5 years; these figures should include all those who have had surgery and not just those who leave hospital after resection. Operative rates should be almost the same as resection rates, because there is mortality and morbidity associated with exploratory procedures.

The results of radiotherapy are difficult to obtain because the staging of the original population is never accurately defined, and most of the literature was pub-

lished before the advent of CT scanning. In a literature review in 1980, the overall survival after radiotherapy was 18% at 1 year and 6% after 5 years *(7)* which is comparable with the mortality of 18% and 4% for all patients with the disease *(8)*. Selection in surgery can improve the results by subdividing according to operable or non-operable, curative or palliative resection, excluding operative deaths, using 30-day hospital mortality rather than total hospital deaths, and applying age-adjusted survival rates. Selection in radiotherapy is similarly variable, and the usual method is to divide patients into those receiving radical or palliative treatment. In 1966 Pearson *(9)*, by excluding all palliative radiotherapy patients, achieved a 44% 1-year and a 22% 5-year survival with radiotherapy. An update of these Edinburgh figures in 1980, presenting the data from 1956–1974 in a different way, showed that with tumours less than 5 cm long a 12% 5-year survival could be achieved *(10)*. A recent series of operable squamous cell cancers treated by radiotherapy alone achieved a 46% 1-year and 14% 5-year survival *(11)*. These patients were deemed operable on a clinical assessment of their tumours, without CT staging, and included many who would be considered non-operable on the basis of their age, over 75 years, and general condition.

From the literature there is no evidence that surgery can achieve better results than radiotherapy, provided the staging of the tumour is stated. Radiotherapy can achieve about the same results as surgical resection when used on a similar patient population to those undergoing surgery. The results of both radiotherapy and surgery are improved in the earlier-stage tumours. There have been isolated attempts to complete a phase II trial of treating operable patients with radiotherapy and these have achieved results comparable to surgery. There is doubt in the minds of some surgeons and radiotherapists as to which treatment is best. That is why the Medical Research Council's Cancer Therapy Committee investigated whether there would be support for a prospective, randomised, phase III trial of radiotherapy versus surgery in operable squamous cell carcinoma staged by pretreatment CT scanning.

Data collection

In the 6 years of its existence, the Working Party tried to collect data for the better analysis of oesophageal cancer treatment. The sources were from central cancer registration and mortality figures, the Hospital Activity Analysis, Regional Cancer Registers, specialist surgical audit such as the UK Thoracic Surgical Register and questionnaires sent out by the Committee. For an industry which does approximately 2000 oesophagogastrectomies and looks after 4000 deaths from oesophageal cancer each year the available accounting system is abysmal. The following represents the data that can be gleaned from all these sources as well as the literature. It is incomplete, and probably inaccurate, but the best that can be obtained at this particular time. It includes much data that was obtained by the Working Party between October 1982, when the MRC decided to find out whether such a trial was feasible, and November 1985 when the MRC gave permission for the trial to proceed.

In the UK with a population of 50 million there are about 4000 cases of oesophageal cancer and 12 000 of gastric cancer each year.

There are 2000 oesophagogastrectomies performed each year.

Out of the 4000 oesophageal cancer cases, 1000 (25%) are resected.

Out of the 12 000 gastric cancer cases, 1000 (7%) are resected with an oesophagogastrectomy, implying that the anastomosis is in the thorax and excluding gastrectomy with subdiaphragmatic anastomosis, otherwise the operation should have been described as some form of gastrectomy.

Of the 2000 oesophagogastrectomies, 50% were performed for a pathological diagnosis of squamous cell carcinoma and 50% adenocarcinoma. This histology represents a rough separation of oesophageal from gastric cancer; but since 3–5% of true oesophageal cancer is adenocarcinoma arising in a columnar cell lined oesophagus, many of the true cardia carcinomas are squamous celled and tumours of all anatomical sites can be anaplastic, the separation between oesophageal and gastric cancer on a histological basis is blurred.

CT staging is the most accurate pretreatment staging we have, but is inaccurate and cannot be completely relied upon for assessing operability.

With these reservations, 5% of all tumours are in stage I with a short tumour and no lymph nodes, 20% stage II with local lymph nodes, and the remaining 75% stage III or IV with spread to the adventitia or beyond and distant lymph nodes.

If the percentage of stage I tumours rises above 5% in any surgical series there has been selection of cases and a bias, because 5% is the true epidemiological percentage.

With oesophageal cancer, only 25% of the tumours are resectable technically and the majority of 75% are non-resectable.

This 25% should, theoretically, be a mixture of 5% stage I and 20% stage II, but frequently stage III and stage IV patients are resected.

This 25% can be divided into those with no macroscopical tumour remaining (curative resection) and those with tumour spread visible but not resected (palliative resection).

The remaining 75% have widespread tumour or a general condition that makes surgery too dangerous and are inoperable. For example 39% of all oesophageal cancer patients are 75 years of age or older.

Surgical decisions in regard to surgery are to assess whether the condition is

(*a*) Operable or inoperable—before surgery.
(*b*) Resectable or non-resectable—at the time of surgery.
(*c*) Curative or palliative—at the time of surgery.

The ratio of operability to resectability should be as near equal as possible, because there is a danger even in first opening the chest of old people. The clinical impression of complete resection should always be checked histologically. There is a difference between macroscopical staging and post-treatment microscopical staging. In any published study these details should be given so that the reader can properly assess the results.

Post-treatment histological staging shows that of all resections, 50% are incomplete because of lateral spread, and 25% are incomplete because of longitudinal spread into an inadequate resection margin *(5,7)*.

Approximately 5% of the total of 4000 cases per year in the UK are stage I tumours with a curative resection possible; 5% of 4000 = 200.

In Japan, where very detailed data for oesophageal surgery is collected, only 150 stage I cases were found in the total of 1490 in a 5-year period *(5,12)*. Japan has a populaton of 100 million with an annual incidence of 6 per 100 000 for oesophageal cancer, which gives an approximate figure of 6000 per annum. The total over 5 years would therefore be 30 000. Even allowing for many cases not collected in that survey, the incidence of stage I tumours in Japan was well below 5% of 30 000, which is 1500 cases.

In Japan, with postoperative histological staging, these 150 stage I carcinomas were resected with an operative mortality of 8% and a 44% 5-year survival rate, excluding those who died postoperatively. Theoretically, no patient is cured of cancer unless there is no evidence of tumour on death. Practically, a surgeon would be happy with survival even though there is asymptomatic tumour present. If the evidence from the treatment of such favourable stage I tumours shows that the tumour cannot be completely eradicated, surgeons should talk about survival rates not cure rates, because cures cannot be offered in oesophageal cancer.

The only people who were, for certain, cured of their oesophageal cancer in the Japanese series were the 8% of the 150 stage I patients who died postoperatively. This emphasises the point that increased survival is always achieved at the expense of an operative mortality.

A survey in the West Midlands with a population of about 5 million showed that there were four surgeons performing six or more operations a year and 120 consultants performed one or less *(6)*. The operative mortality was 42% for the latter group and 22% for the four experienced surgeons.

The Working Party did a postal survey of all general and thoracic surgeons and gastroenterologists. 66% replied with 1617 completed questionnaires; 458 with a combined experience of 2900 cases per year expressed willingness to join a trial. Only 109 consultants in England and Wales saw more than 10 cases a year and accounted for 1700 cases. There are about 1000 general surgeons and 120 cardiothoracic surgeons, so it would appear that the detailed West Midland survey is true for the whole country.

The UK Thoracic Surgeons collect much better data than the general surgeons. There are about 120 cardiothoracic surgeons working in 50 centres. In addition to their cardiac surgery, 10 000 chest operations are done: 7500 pulmonary and great vessel and 2500 oesophageal. Approximately 800 oesophageal resections were done by the thoracic surgeons, which presumably leaves the remaining 1200 oesophagogastrectomies performed by some of the 1000 general surgeons.

In the UK there is no detailed data about the 1000 oesophageal cancer resections and no analysis can be made.

In the UK the majority of resections are done by surgeons doing less than 10 cases a year.

When the figure for surgery is less than 2 per year the operative mortality doubles.

The majority of surgeons are doing so few oesophageal resections that they are not interested in trials, nor can they enter enough patients.

The MRC Working Party sent out a second questionnaire to assess which particular oesophageal cancer treatment trial would have most support, and this was followed up by an open meeting at the Royal College of Surgeons of England. Radical surgery versus radical radiotherapy had the most support, with 800 cases each year promised. Surgery versus surgery plus postoperative radiotherapy or chemotherapy had very little support, so progress on these problems will proceed in one or two centres. Assessment of the quality of life after different procedures was considered as an option. Care was taken to choose a practical trial with as much support as possible, but it was clear that only a minority were actually interested in trials, even though offered different subjects and protocols.

A minority of 30 surgeons out of 1000 general surgeons and 120 thoracic surgeons had some doubt as to what was the best treatment for operable squamous cell cancer and joined the MRC trial. This number was far smaller than calculated from all the preliminary studies, questionnaires and meetings. In general terms only 2% of all patients with cancer enter clinical trials of treatment. This could be interpreted as though the medical profession already has all the answers. But that may not actually be the true interpretation.

Methodology

The aim of the trial was to compare survival rates for patients with 'operable' squamous cell cancer of the

middle and lower thirds of the oesophagus. The individual clinicians were left to decide for themselves their own threshold for 'operable'. Pretreatment eligibility required the following information: histological evidence of squamous cell carcinoma; the site must be between the arch of the aorta and the cardia, but true carcinoma of the cardia was excluded; the patient must be deemed suitable for surgical resection or radical radiotherapy with an upper age limit of 75 years; WHO performance status 0, 1 or 2; no evidence of pulmonary metastases on chest radiograph and no evidence of spread to the trachea or bronchus either by bronchoscopy, chest radiograph or CT scan; no other evidence of metastatic spread; no history or other malignant tumours, except minor skin cancer.

The following facts and investigations were essential: duration of symptoms; weight loss; degree of dysphagia; barium swallow, chest radiograph; oesophagoscopy; biopsy; bronchoscopy; CT scan from suprasternal notch to umbilicus. After signing an informed consent form the patients were allocated to either surgery or radiotherapy.

Surgery was that operation which the individual surgeon normally performed. The approach, the route for reconstruction, the organ for reconstruction and the site of the anastomosis were recorded. The operation was classified as curative or palliative. A detailed pathological report was filled in for staging after surgery.

Radical radiotherapy was given either as schedule A or B according to their preference and the same schedule was used for all the patients treated in the trial by that clinician. Schedule A was a prescribed tumour dose (minimum corrected) of 5000 cGy with a daily dose of 250 cGy in 20 fractions over 4 weeks. Schedule B was a prescribed tumour dose of 6000 cGy with a daily dose of 200 cGy in 30 fractions over 6 weeks. The treatment volume was recorded and all treatment carried out on megavoltage equipment. Any further treatment necessary after surgery or radiotherapy was left to the choice of the individual clinician but recorded. Attention was paid to quality of life with assessment of side effects and the ability to swallow.

Follow-up forms were to be filled in at 3 months, 6 months, 1 year and then annually for the next 4 years, completing questionnaires for weight loss and dysphagia, performance status, evidence of local recurrence and distant metastases.

The endpoints were (*a*) early death in hospital, (*b*) side effects of treatment, (*c*) survival, (*d*) local recurrence and date of diagnosis, (*e*) spread of metastases and the date, (*f*) degree of dysphagia and need for dilatation or intubation.

Results

After 4 years' preliminary work the trial commenced in January 1987 with the aim of recruiting 100 patients each year for 4 years. Forms were ready and 30 surgeons had obtained local Ethical Committee approval. The trial was stopped in May 1988, 16 months after the start because only 31 patients had been entered by 15 surgeons with a range of 1–8 patients each. A proposal to continue on a private basis to reach the symbolic but non-statistical number of 100 patients was not supported. Preliminary market research had shown that 200 patients per annum had been promised by supporting clinicians. The causes of the poor recruitment were not clear but included: (i) dwindling enthusiasm due to the initial delays of market research and protocol writing, (ii) difficulty in finding suitable patients, (iii) discovery of more inoperable tumours due to the use of preoperative CT scanning, and (iv) raising the threshold for advising surgery.

Conclusions

There is an almost total absence of meaningful data about the disease, its staging, histology and treatment. This is an indictment of the efficacy of data collection in the UK whether it be HAA, Körner, OPCS or Regional Cancer Centres, with a few notable exceptions of excellence. No industry in the free world spending as much as the NHS could survive with so little information about its activities.

The treatment of patients with this disease is too dissipated, with failure to specialise and consequently to give better treatment. This applies to any surgeon treating one or two cases a year, whether that surgeon is a general surgeon or a thoracic surgeon. It also applies to the present generation of gastroenterologists, many of whom are slowly learning the mistakes that have been learned by surgeons years ago.

It is doubtful whether phase III trials should be carried out on a disease with an incidence of 8/100 000, because it falls between the very common (eg breast) and the very rare (eg bone sarcoma) which have been centralised. This trial failed to gain support in spite of good market research, because of the rarity of operable oesophageal cancer. Nobody had difficulty obtaining routine CT scanning. However, there was anecdotal evidence that this investigation discovered unsuspected metastases, raised the threshold for 'operability' and thereby reduced the numbers who could enter the trial.

Much more effort should be spent on proper data collection and monitoring, which includes investigation of perioperative deaths, because this may lead to improvement in treatment without the necessity for trials which in any case are only joined by the minority. The aim should be that everyone is treated as well as is possible.

The opinions in this paper are entirely those of the author who was Chairman of the Working Party on Oesophageal Cancer and are not official statements from the Medical Research Council. The MRC Cancer Therapy Committee and staff have provided unstinting expert help and support, especially Professor N Bleehen and Mr L Freeman. The MRC Trials Office in Cambridge have offered invaluable help. The author would like to thank all the members of the Working Party for their hard work during the 6 years of its existence.

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Book review

Neurological Surgery—A comprehensive reference guide to the diagnosis and management of neurosurgical problems edited by J R Youmans. 3rd edition. 5000 pages, illustrated. W B Saunders, Philadelphia. 1989. £425 (£79.95 each volume). ISBN 0 7216 2097 3

It is now over 20 years since the late Mr Douglas Northfield wrote his magnum opus — a single-author, one-volume textbook of neurosurgery. No one has attempted to emulate his feat (in fact it would probably be beyond the capacity of any single individual) and his book, including the recent revision of it, has been replaced by a number of multi-author textbooks. Of these, 'Youmans', a massive American work, has become the best known and most widely used.

This third edition is a huge, six volume affair, involving scores of expert contributors and running to over 4400 pages. Every aspect of neurosurgical practice, including surgical technique, seems to have been covered. The first volume begins with history taking, clinical examination and radiological and diagnostic techniques; the last, appropriately, with rehabilitation and medical ethics. Inevitably there are minor blemishes and some differences in the calibre of the individual chapters, but it would be churlish to draw attention to these, for the final result is probably as good a textbook of neurosurgery as could be produced. It is well written, well organised and well edited. It is up to date and supplied with good references. On the purely technical side the volumes are beautifully produced with fine illustrations, firm binding and type that is easy to read. This reviewer has no major criticisms to make of it, for it fulfils its purpose both for the neurosurgeon in training and for the neurosurgeon in established practice. Although neurosurgery will continue to develop, the third edition of Youmans will probably remain 'in date' for at least 5–10 years. If a neurosurgeon were to possess a single book this should be it.

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