The changing face of oesophageal cancer treatment in Northern Ireland

K McManus, J McGuigan

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SUMMARY

In the late 1970's the options for treatment of oesophageal cancer were limited. When cure was thought possible, resection was performed by the Ivor Lewis or oesophagogastrectomy techniques. Mortality was high, local recurrence rates disappointing, and long-term survival poor. For those patients whose tumours could not be resected, palliative intubation required open operation with high morbidity, and gave poor quality of life. In 1994, selective screening is diagnosing cancers early, more extensive resections are possible with lower mortality, and fewer local recurrences. Adjuvant therapy is increasing the operability rates. Gradually the facade of poor prognosis is being etched away, so that more patients are being given better quality of life, and cure is a distinct possibility. Palliation can be achieved endoscopically by dilatation, intubation or laser ablation combined with local external beam radiation. Mortality for palliative procedures is now considerably reduced.

INTRODUCTION

In 1987 a review of the treatment of oesophageal cancer over the preceding ten years was undertaken at the Royal Victoria Hospital. Of the 401 patients presenting to the hospital, exploratory surgery was performed on 247, and 221 underwent resection. Clear tumour margins were obtained in 112, 82 of whom survived their surgery. Thus only 20 per cent of those who presented for oesophageal surgery left hospital with their disease completely resected. The five-year survival following resection was 13.2% (Fig. 1).

A broad range of factors affecting survival following resection have been examined, and while many were found to be significant, the only independent predictors of survival were sex, involvement of proximal resection margins, curative resection and presence of nodal metastases.

By way of palliation, 113 Celestin tubes were passed at open laparotomy or thoracotomy and 26 Atkinson tubes introduced endoscopically. In nine patients the tumours were bypassed, 21 patients were referred for primary radiotherapy, and 14 were unfit for surgical intervention.

Northern Ireland Regional Thoracic Surgical Department, Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland.

K McManus, BMedSc, FRCSI, Consultant Thoracic Surgeon.

J McGuigan, MB BCh, FRCS, Consultant Thoracic Surgeon.

Correspondence to Mr McManus.

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Following a transition period in 1986-1987, a number of changes have been made in the approach to oesophageal malignancies. Endoscopic surveillance has been introduced for patients with premalignant pathology. Laser ablation has become the treatment of choice for palliating inoperable tumours. For those in whom cure is thought possible, the more extensive total thoracic oesophagectomy operation has been introduced with the aim of resecting more of the proximal oesophagus, performing the anastomosis in the neck. Of the 139 oesophageal resections performed between 1988 and 1992, 73 have involved total oesophagectomy; 20 have been for benign or premalignant disease.

In this paper we describe the changes in our approach to oesophageal cancer, the results of these changes, and outline future plans for treating this difficult disease.

**DIAGNOSIS AND SURVEILLANCE OF OESOPHAGEAL PREMALIGNANT CONDITIONS**

It has become apparent that peptic disorders are associated with oesophageal cancer. In the 1977-86 series, 21.5% of patients had hiatal hernia, and a further 24.3% had other peptic disease. In particular, patients whose oesophagitis has advanced to the stage where the oesophageal lining has changed to columnar intestinal epithelium (Barrett’s metaplasia), have a cancer risk 40 times that of the normal population.\(^1\) In conjunction with our colleagues in gastro-enterology, it is our practice to maintain endoscopic surveillance for all patients with Barrett’s metaplasia. When metaplastic columnar epithelium is found in the
true oesophagus above the oesophagogastric junction, yearly surveillance is recommended. When dysplasia is reported, more frequent and more intense surveillance is required. If any biopsy is reported as containing high grade dysplasia, resection is recommended.

Thirty-three of 112 cancers in the latter series had metaplastic epithelium present in the oesophagus adjacent to the tumour. Six of these had been under surveillance, and the five Stage I tumours have a good chance of long-term survival. In addition, 12 resections were performed for Barrett’s metaplasia without cancer.

More recently we have turned our attention to molecular biology in an attempt to determine which patients are likely to develop tumours. Oncogenes, genetic mutations associated with tumour development, have been identified in oesophageal tumours from a tissue bank set up at the Royal Victoria Hospital (A Ritchie). Mutations of the p53 tumour suppressor gene, which render it inactive, have also been demonstrated in tumour tissue from this bank (K Gleeson, Department of Medical Genetics, The Queen’s University of Belfast). It is hoped that assaying for these mutant genes or their protein products will help indicate premalignant change in patients under surveillance. Oncogenes, being unique to malignant and premalignant cells, would be suitable targets for anti-tumour antibodies, and this treatment modality may be available to us in the future.

RESECTIONS FOR OESOPHAGEAL CANCER

The standard oesophagogastrectomy procedure is usually performed via a left thoraco-abdominal incision (Fig 2). The proximal limit of resection is judged by the surgeon to be a point 5-7 cm proximal to the palpable tumour. The anastomosis is made below the aortic arch within the chest. When the tumour encroaches significantly onto the stomach the resection is extended to include a total gastrectomy. The Ivor Lewis oesophagogastrectomy devised for more proximal tumours, requires an upper midline laparotomy for mobilization of the stomach and a right thoracotomy to resect the tumour, again with a 7 cm margin, the anastomosis being above the level of the azygos vein. The decision as to whether the oesophagogastrectomy or Ivor Lewis approach was used depended on the barium and endoscopic findings.

Total thoracic oesophagectomy is performed using the technique described by Matthews using a left thoraco-abdominal incision, resembling that for the oesophago-gastrectomy but with further dissection of the oesophagus above the aortic arch into the neck from below. The anastomosis is performed via a small cervical incision. This operation is performed whenever there is enough stomach available after adequate tumour resection to reach comfortably to the neck. It is therefore not used for true gastric fundal tumours where an oesophago-gastrectomy or total gastrectomy is performed. The decision on the extent of resection does not need to be made until the tumour is mobilised and is fully assessible.

Mention must be made of the ‘transhiatal’ oesophagectomy approach which is performed via a laparotomy with blunt dissection of the oesophageal tumour and anastomosis in the neck. This operation does fulfill the requirements of total thoracic oesophageal resection with the reduced morbidity of the cervical
anastomosis but avoiding some of the complications of thoracotomy. While recognizing its place in the treatment of benign conditions such as advanced achalasia and Barrett's metaplasia, we have reservations about its use in malignant conditions.

Fig 2. Operative approaches to oesophageal cancer.

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MORBIDITY/MORTALITY

The National Confidential Enquiry into Postoperative Deaths (NCEPOD)\(^3\) for 1992 recognised oesophagectomy as a procedure with risks "worse than that of transplantation and cardiac surgery". This is especially the case in the hands of the occasional oesophageal surgeon.\(^4\) Our mortality for oesophagectomy improved from 39% in 1977 to 11% in 1985. This improvement was maintained with the introduction of the more extensive procedures. The mean mortality for total thoracic oesophagectomy over the first five years was 10.9%, with only one death in the last two years. The mortality for the oesophagogastrectomy procedures was 13.5% in the same period. Much of the improvement over recent years has been a result of better patient selection on the basis of our earlier experience, and also from improvements in postoperative intensive care. An important contribution has been the decrease in anastomotic leaks.

Intrathoracic anastomotic leak has a mortality of over 50%. The incidence has been lowered by the use of mechanical staplers.\(^5\) Cervical anastomotic leak has occurred in two patients (4.3%), with no deaths.Leaks in the neck usually drain via the local incision without mediastinal or pleural contamination. The resulting fistulae drain well and close spontaneously. Non-fatal complications occurred in 23%, being comparable for all procedures.

| Covariate                                    | p value |
|----------------------------------------------|---------|
| Female sex                                   | 0.003   |
| Curative resection                           | <0.001  |
| Nodes free of metastases                     | <0.001  |
| Clear proximal margin                        | <0.001  |
| Tumour confined to oesophageal muscle        | 0.003   |
| Ivor Lewis operation                         | 0.004   |
| Favourable differentiation                   | 0.02    |
| Clear distal margin                          | 0.057   |
| Short symptom duration                       | 0.041   |
| Squamous histology                           | 0.07    |
| Site of tumour (middle third/lower third/cardia) | 0.14  |
| Weight loss                                  | 0.16    |
| Year of operation                            | 0.57    |
| Age                                          | 0.57    |
| Surgeon grade                                | 0.89    |

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SURVIVAL FOLLOWING RESECTION OF OESOPHAEGAL CANCER

The factors affecting survival after resection and discharge from hospital for the 1977-1986 series are summarised in Table I. A multivariate analysis showed that only female sex, curative resection, absence of nodal metastases and clear proximal resection margins were independent predictors of long-term survival. Nodal metastases, the most significant predictor of survival, are indicative of systemic dissemination of tumour. This is reflected by the fact that regardless of the type of operation there is substantial tumour-related mortality in the early months after surgery due to undetected metastatic disease. What is clear is that the future treatment of carcinoma of the oesophagus must include systemic therapy. Many surgeons have now become interested in chemotherapy, in conjunction with surgery. Until recent years, no chemotherapeutic regimes had satisfactory effects on solid tumours, though 5-fluorouracil had some effect in gastrointestinal tract adenocarcinoma.

Success in treating squamous carcinoma of the larynx and lung with cisplatinum logically progressed to trials on oesophageal cancer. 6, 7, 8 The problems of toxicity and patient compliance are now better controlled, and regimes of rehydration, diuretics, sedation and anti-emetics are being standardised. Pilot studies in Belfast have shown the feasibility of such therapy, and patients are being entered in a number of trials of preoperative chemotherapy.

The other main cause of early death is tumour recurrence at the anastomosis. Recurrence is related to the type of operation and particularly the presence of tumour in the vicinity of the proximal resection margin. This is reflected in the survival curves for these two factors (Figs. 3 and 4).

![Survival curves](image)

*Fig 3. Probability of survival following oesophageal resection, RVH 1977-1986. (p = 0.004)*

Operation type. (Operative deaths excluded).
With the introduction of total thoracic oesophagectomy the incidence of proximal limit involvement and anastomotic recurrence has dropped to zero. Despite attempts to gain a greater proximal margin in both Ivor Lewis and oesophagogastrectomy resections, the recurrence rates remain high for these operations (38.5% for Ivor Lewis, 15.8% for oesophagogastrectomy). The distal clearance is similar between all groups though a number of tumours have recurred on the lesser curve of the stomach. The short and medium term survival in the total thoracic oesophagectomy group reflects the improvement in proximal tumour clearance (Fig. 5).

PALLIATION OF UNRESECTABLE OESOPHAGEAL CANCER

Thirty eight per cent of oesophageal cancers present to this hospital in an inoperable state. Palliation, therefore, is a major part of the treatment of oesophageal cancer. Inability to swallow one's own saliva is such an unpleasant end, that aggressive measures are usually employed to restore at least a liquid diet, despite the considerable risks of some of the procedures.

Resection is a major debilitating operation with high risk and prolonged recovery. It is not indicated when metastatic disease is detected during preoperative staging or open exploration, nor when resection is likely to be incomplete and the prognosis poor. Tumour bypass is advocated by some authorities, especially in the case of tracheo-oesophageal fistula. The operation is as extensive a procedure as resection with an anastomosis in the chest. The experience in our 1977-1986 series showed very poor results for bypass.
Intubation of the tumour can maintain a lumen adequate to allow a pureéd diet. An Atkinson tube may be placed at endoscopy, or a Celestin tube at open operation. As the mortality for open insertion was 26% in the 1977-1986, this method is now generally avoided. Mortality from endoscopic placement is low, but the tubes are sometimes poorly tolerated and blockage is not an infrequent complication. Expandible metal mesh stents are now available and claims of lower complication rates have been made.\(^1\) We find that that these stents are relatively easily placed under radiological control but their expense limits their widespread use. They may be over-used in patients who should be offered a chance of a curative resection.

Laser ablation overcomes some of the disadvantages of intubation in that tumours high in the oesophagus can be treated, and a degree of flexibility and motility is maintained in the oesophagus to the extent that a relatively normal diet is tolerated by many patients. It is now the treatment of choice in palliating tumours of the true oesophagus. It is less suitable for tumours of the oesophagogastric junction or for tumours which cannot be dilated to allow introduction of the endoscope carrying the laser. For undilatable tumours one must resort to traction intubation via laparotomy or, in dire circumstances, a jejunostomy.

At present, chemotherapy has no place in the routine palliation of oesophageal carcinoma. Current therapy is not aimed at palliation but rather at preoperative tumour shrinkage as described above, or for patients with a high probability of micrometastatic disease suggested by extra-oesophageal invasion, nodal metastases or residual disease after resection.

\[\text{Fig. 5} \text{ Probability of survival following total thoracic oesophagectomy compared to oesophagogastrectomy (Ivor Lewis and standard) 1988-1992.}\]
Fluid and nutritional balance can be maintained by insertion of a jejunostomy and sometimes a narrow bore nasogastric feeding tube. Neither method relieves the complete dysphagia but has the effect of prolonging life of the patient with the distressing symptom of 'drowning in his own saliva'. The limited uses of these techniques have been as a bridge to surgery, to allow a patient time to arrange his affairs or for specific social reasons. Laparotomy and jejunostomy has a high mortality rate in this setting.

Radiotherapy currently has a role in obtaining local control of tumour, both squamous and adenocarcinoma, in patients who are unfit for surgery. It also has a role in the pain control of metastatic lesions. Unfortunately, when used as palliation for dysphagia in patients with advanced disease, it is less useful. Our 1977-1986 review included a number of such patients referred for dilatation after radiotherapy. The perforation rate was 44% and mortality almost as high. The trend continues in our current practice. We would prefer to palliate dysphagia with laser ablation and then use an endo-oesophageal stent to maintain a lumen. When the disease is regarded as local, radiotherapy may then be used with curative intent.

CONCLUSIONS

Changes made in the approach to oesophageal cancer in the late 1980's have increased the chances of survival. Neoadjuvant chemotherapy and radiotherapy are on trial in an attempt to improve operability and survival. The future direction of the science of oncology will clearly involve tumour manipulation at the molecular biological level. The Royal Victoria Hospital in association with The Queen’s University of Belfast is at the forefront of research into the use of these new technologies in relation to oesophageal cancer. Clinical benefits can be expected in the not too distant future. The surgeon's role is changing from being the sole hope for patients with oesophageal cancer to being one arm of a multidisciplinary approach.

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