SYMPOSIUM ON CANCER OF THE OESOPHAGUS – A MAJOR REVIEW WITH A SCOTTISH FOCUS*

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The recent two-day conference on oesophageal cancer held jointly by the Royal College of Surgeons of Edinburgh and the Royal College of Physicians of Edinburgh heard several distinguished speakers describing recent innovations which offer the prospect of earlier detection, improved treatment selection and the provision of more effective treatment of the condition, based in particular on multi-disciplinary and multi-modal therapeutic approaches. These improvements are welcome in view of the current poor prognosis for most patients with oesophageal cancer, though it is important to distinguish innovations with proven benefit from those still under evaluation and to determine whether new procedures and treatments of established benefit have been, or should be, incorporated into everyday clinical practice. By linking the conference with the first presentation of data from the Scottish Audit of Gastro-Oesophageal Cancer (SAGOC), participants were able to identify some aspects of the care of oesophageal cancer in Scotland that need to change and to identify others requiring further scrutiny.

A changing pattern of incidence of oesophageal cancer is evident in many regions of the world. Most of the published Western series show that the incidence of adenocarcinoma of the lower oesophagus is increasing steadily, whereas the incidence of sqaumous carcinoma is static. In Scotland, lower third oesophageal cancers are increasing at an annual rate of 2%. Opening the conference, Professors Alan Cameron and Olof Nyren, from the US and Sweden respectively, described epidemiological studies demonstrating these trends and showing that although squamous carcinomas are related to poor socio-economic circumstances, to smoking and to alcohol ingestion, adenocarcinomas have little or no relationship to these factors; they are most likely to occur in overweight men with a history of severe gastro-oesophageal reflux (GOR). A possible molecular explanation for the association with reflux may relate to a down-regulation of cell-cell adhesions in the presence of inflammatory mediators, as described by Janusz Jankowski in his presentation. Carlos Caldas described the genetic differences between both oesophageal squamous and adenocarcinomas and the normal oesophageal mucosa. Unfortunately, the mutations identified so far seem to occur at a late stage in the malignant transformation process and, to date, have not been useful in the early identification of individuals at risk of developing malignancy. Perhaps the identification of families with a predisposition to oesophageal carcinoma may help to demonstrate early mutations. Some 1-2% of patients with oesophageal cancer in Scotland have a first-degree relative with an oesophageal malignant tumour, and given that the overall incidence of oesophageal cancer is 8/100,000, there is evidently a much increased familial incidence of the disease. This may be a worthwhile avenue for research based on the SAGOC population data.

For many years, Barrett's metaplasia of the lower oesophagus has been considered a causal predisposition to adenocarcinoma. However, Olof Nyren's case-control studies in Sweden show that severe GOR is the single most important association, irrespective of the presence or absence of Barrettt's oesophagus. Perhaps Barrett's oesophagus and oesophageal carcinoma both result from GOR, and it is the reflux that predisposes to malignancy. This is a subject of both theoretical and practical importance that clearly requires further investigation.

The question of endoscopic surveillance in known cases of Barrett's oesophagus remains controversial. Barrett's metaplasia certainly indicates a risk of adenocarcinoma, but there is still uncertainty about its clinical management. Before an answer to this question can be offered, it is necessary to agree how Barrett's oesophagus should be defined. Should it be defined by an identifiable minimal length of columnar-lined mucosa above the gastro-oesophageal junction, or is its essential feature the presence of intestinal metaplasia on biopsy, irrespective of the length of columnar-lined segment? (Incidentally, as Stuart Spechler pointed out, neither of these definitions would have been recognised by Norman Barret in his original description of the condition!) Agreement on a definition of Barrett's oesophagus is important because appropriate endoscopic surveillance of the patients will vary depending upon the definition used. Dawn Provenzale demonstrated that the cost-effectiveness, and therefore optimal design, of such surveillance programs is critically dependent upon the frequency of adenocarcinoma in the population being surveyed. If, for example, the annual incidence of carcinoma in Barrett's oesophagus is approximately 0.5%, endoscopic surveillance at five-year intervals is optimal; whereas, if the incidence of carcinoma is 1%, surveillance at two yearly intervals produces the maximum benefit but is expensive. Intervals of three to five years bring the enhancement of quality-adjusted life expectancy into the cost range of other interventions accepted in current clinical practice. Quite obviously, economic data such as these are ingredients of today's health policy-making, and clinicians interested in oesophageal cancer do well to understand these issues.

Rather than follow-up all patients with Barrett's oesophagus, it has been suggested that because patients with epithelial dysplasia are at highest risk of developing carcinoma, they should be the prime focus of attention. There are, however, significant problems with the identification of dysplasia within a Barrett's oesophagus – a

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task thought by many of us rather naively to be fairly clear-cut. Professor Mike Dixon illustrated the subjectivity of identifying dysplasia histologically, which may explain the variations in frequency of progression and regression of dysplasia reported in different studies. The input of specialist pathologists with expertise in the field might improve diagnostic consistency, but manpower difficulties create a major barrier to the provision of such a service in the UK. Other diagnostic problems arise from variations between centres in biopsy techniques and protocols. In this context an analogy that has been drawn is that the size of a standard endoscopic biopsy taken from a 3-4 cm length of Barrett's oesophagus corresponds to the size of the penalty spot on a soccer pitch. The scope for sampling error is therefore large. Newer technologies may help to overcome this problem: for example, elastic scatter spectroscopy as described by Dr Irving Bigio could provide a new 'smart' biopsy technique.

Even the best possible surveillance and treatment of patients with established Barrett's oesophagus may have only a modest effect on oesophageal carcinoma overall. Alan Cameron's work in Olmsted County, Minnesota, suggests that no more than one in five cases of Barrett's oesophagus are detected in life. The SAGOC data indicates that only about 10% of adenocarcinomas in Scotland occur in patients already known to have Barrett's oesophagus. The implications of these figures are that for the population as a whole, surveillance of patients currently known to have Barrett's oesophagus cannot have a major impact on either the incidence of oesophageal adenocarcinoma or its outcome in most patients.

The selection of optimal treatment for established oesophageal malignancy was reviewed by Professor Rudiger Siewart, who emphasised that risk analysis should be undertaken for each individual patient. The many factors that must be considered in such appraisal can be summarised as:

1. Stage of the disease.
2. Premorbid general condition and state of health of the patient.
3. Clinician- and institution-related factors.

At the end of this appraisal, a decision is made as to the goal of treatment (i.e. cure or palliation) and how best it may be achieved. Traditionally, this has translated into a surgical (cure) or a non-surgical (palliation) approach, but alternative methods of treatment are now available and must be considered, especially combinations of treatment. Increasingly, it is also becoming important to consider whether effective treatment can be provided in the patient's local hospital or whether transfer to a specialist unit is preferable.

Endoscopic ultrasound (EUS) examination of the oesophagus is now acknowledged to be the most accurate pre-operative means of determining respectability of oesophageal cancers, largely because of its accuracy in determining the T-stage of oesophageal tumours. Nevertheless, Paul Fockens pointed out that one area where EUS is not useful is in distinguishing mucosal from submucosal disease. However, it may be that in this situation, the concept of 'diagnostic mucosal resection' means that such staging differentiation is not important. In other words, if the area of abnormal mucosa is resected endoscopically and subsequent histopathology of the endoscopically resected tissue shows submucosal involvement, there is an enhanced probability of nodal disease and more extensive treatment (usually surgery) is indicated. In contrast, endoscopic mucosal resection can be accepted as definitive and sufficient tumour resection for patients in whom a small tumour is shown to be confined to the mucosa, although consideration in such instances should probably be given to ablation of surrounding abnormal mucosa, using treatment such as photodynamic therapy (PDT) as described by Professor Thierry Patrice. Indeed, PDT alone may be adequate treatment for Tis and T1 cancers. At present, uncertainty regarding the accuracy of pre-treatment staging when PDT is used probably limits its wider application.

Unfortunately, most patients with oesophageal cancer present with advanced tumours and for them the crucial question is whether treatment based on surgical resection is possible. EUS demonstration of adjacent organ involvement (T4 disease) often contra-indicates surgery as primary treatment. Nodal disease in the mediastinum is not reliably determinable with any of the modalities currently available (EUS, CT, MRI, PET), but interestingly, despite its prognostic significance, mediastinal node involvement is not regarded at present to be an important determinant of resectability. The presence of enlarged coeliac axis nodes is a different matter, however, and should be regarded as equivalent to distant metastatic spread. Although surgeons differ in their views regarding the advisability of resection of more advanced tumours, most would agree that the aim of surgery should be a complete resection of macroscopic and microscopic disease (R_0 resection). Palliative oesophageal resections have little place nowadays.

The differing surgical strategies described by Professors Siewart, Lerut and Lundell illustrated the controversy that reigns about the optimal surgical approach to resectable tumours, and the extent of lymphatic clearance recommended, even after the decision has been made that surgery is advisable. Additional controversy relates to the role of adjuvant and neo-adjuvant therapy in resectable oesophageal cancers. Two large multi-centred trials have recently been reported using similar regimens of pre-operative 5FU and cisplatin in patients with resectable oesophageal cancers (squamous and adenocarcinomas). In the USGI intergroup trial, treatment was continued post-operatively but no survival benefit was seen in the chemotherapy arm when compared with surgery alone. In contrast, the recent MRC trial demonstrated a 10% survival benefit at two years and improved median survival of four months in the neo-adjuvant group. Much interest has been shown in the newer chemotherapeutic agents and in the future, genetic profiles of tumours may allow particular drugs to be targeted specifically at particular tumours, as discussed by Professor Gordon McVie. The encouraging results of the MRC trial do emphasise the value of properly conducted clinical studies and in this connection it is disappointing that only 9% of eligible patients surveyed in SAGOC were enrolled in ongoing clinical trials.

Chemo-radiotherapy in patients with oesophageal cancer is still of considerable interest. Early studies by Herskovic *et al*. showed the effectiveness of a combination of chemo-radiotherapy over radiotherapy alone for locally advanced tumours. The precise role of this treatment in combination with surgery for resectable tumours is less clear. The randomised trials that have been conducted report similar

response rates (complete responses vary between 25-28%); long-term survivals were similar for patients treated with chemo-radiotherapy followed by surgery (32-26% three-year survival.) Two trials report benefit from combination treatment compared with surgery alone, whereas one trial has reported no difference, this being conducted on patients with stage I and II tumours where the surgery alone cohort showed 36% survival at three years. Chemo-radiotherapy may therefore have a more useful role to play in the treatment of more advanced tumours, perhaps to allow down-staging of the cancer pre-operatively so that R_0 becomes possible when it would not have been possible otherwise. The regimen described by Professor Arlene Forestiere clearly had such an effect and, as she emphasised in her presentation, careful pre-operative staging was essential to permit a selection of patients likely to achieve maximum benefit from this modality of treatment. Once again, the importance of EUS was emphasised and it is cause for concern that this 20-year-old technology is still not widely available in the UK. In Scotland, only 2% of patients with oesophageal tumours underwent EUS during 1997-99.

During the period covered by SAGOC audit, two-thirds of patients were deemed to be unsuitable for curative treatment at the time of presentation. Palliative treatment is often directed at improving swallowing and many techniques are available to re-establish an oesophageal lumen in a cancer-occluded oesophagus. These include laser (NdYAG and semi-conductor diode), photodynamic therapy, argon beam coagulation, intubation techniques, radiotherapy (external and brachytherapy) and alcohol injection. Professor Neville Krasner emphasised that palliative treatment must not lose sight of the aim of relieving the patients' symptoms and that it is essential patients are comprehensively assessed and treatment selected for their individual needs. Interestingly, the SAGOC data indicated that distressing dysphagia was not a major symptom in most patients with advanced oesophageal cancers and perhaps it may be that overmuch emphasis has being given to re-establishment of an oesophageal lumen (which does not necessarily equate with relief of dysphagia) and not enough to relief of symptoms such as nausea, tiredness, anxiety and depression.

In a compelling contribution which held the total attention of the conference, David Kirby, Chairman of the Oesophageal Patients' Association, described his conviction that advances in biological science, diagnostic technology and application of new surgical and non-surgical treatments will help to improve patient outcomes. In addition, however, there are aspects of treating oesophageal cancer that are seldom validated by the rigour of the controlled clinical trial or health technology assessment, but are nevertheless greatly appreciated by the patients themselves. The contribution of specialist upper GI cancer nurses, involved in supporting patients while in hospital and thereafter, is a prime example of a component of care greatly valued by patients and their families.

Clinical trials do contribute to knowledge, but more fundamentally, the organisation of cancer care needs to be modernised. The service must respond to the anxieties, opinions and experiences of the patients themselves if there is to be real commitment to the principle that the patient is an individual and must always be treated as such.