Cancer of the oesophagus

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Summary

Oesophageal cancer is the fourth most common tumour in developing countries, comprising mainly squamous cell tumours, although the incidence of adenocarcinoma has increased enormously over the last decades. Surgical resection has long been acknowledged as the mainstay of treatment, and developments in surgical technique are reviewed. The roles of radiotherapy and chemotherapy in the management of oesophageal cancer remain unclear, especially as the majority of studies to date have been uncontrolled trials. We present an analysis of 601 patients who underwent resection for carcinoma of the oesophagus between 1970 and 1994 in the Department of Clinical Surgery, St James's Hospital, Dublin. The analysis shows clearly that, while peri-operative mortality continues to improve, conventional surgery offers little prospect of cure in the majority of cases. We have therefore embarked upon a prospective controlled trial of neoadjuvant chemoradiotherapy followed by surgery versus surgery alone in patients with adenocarcinoma or squamous cell tumours of the oesophagus. Preliminary results indicate that multi-modality treatment may have a valuable role to play in the treatment of carcinoma of the oesophagus.

Keywords: oesophageal cancer, surgery, radiotherapy, chemotherapy

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Incidence

Oesophageal cancer is the fourth most common tumour in developing countries and the 15th in developed countries.¹ Until comparatively recently, the vast majority of patients with oesophageal cancer presented with squamous cell tumours. Within the last few decades, however, the incidence of adenocarcinoma of the oesophagus has increased enormously. Evidence substantiating this increase has emerged independently from the US, Germany, the UK and Denmark. An analysis by Blot *et al*² showed that between 1976 and 1987 the incidence of oesophageal adenocarcinoma in nine areas in the US rose annually by 9.8% for black males and 9.4% for white males so that by 1987 adenocarcinoma accounted for 34% of oesophageal cancers in white males.

The only confirmed risk factor in adenocarcinoma of the oesophagus is Barrett's oesophagus and while there are no population-based statistics demonstrating an increase in the incidence of Barrett's oesophagus, this condition is the end result of gastro-oesophageal reflux, which appears to be increasing in incidence in the Western World. By contrast, there are several known risk factors associated with the development of squamous cell carcinoma of the oesophagus, the best known of which are tobacco, alcohol, nitrosamines and mineral (molybdenum) and nutritional (vitamins A and B) deficiencies (box 1). While the high-incidence areas of the Caspian littoral, the Transkei and Northern China continue to report figures in excess of 1/1000, elsewhere in the world the incidence of squamous cell carcinoma of the oesophagus has either fallen slightly or remained static.

In Europe and the US, the main epidemiological risk factors are the consumption of alcohol and tobacco. The most dramatic evidence of this is in Northern France where the incidence is around 40/100 000 in contrast to most other areas in Europe with incidences of less than 10/100 000.³

Surgical resection

The management of oesophageal cancer has undergone significant changes in the last few decades. Surgical resection has long been acknowledged as the mainstay of treatment despite a formidable mortality of circa 30% in the decades from 1940 to 1970. The meta-analysis carried out by Muller *et al*⁴ who reviewed published figures from 1980 to 1990 showed a significant fall in mortality to 13% associated with an improved resectability rate from 39 to 56% but little or no change in the five-year survival rate which rose insignificantly from 15 to 18% during that decade.

The improvement in the mortality rate owed less to better surgical techniques than to improvements in pre- and post-operative care, better anaesthesia, a better understanding of nutritional support and better prevention and control of sepsis. The failure to improve survival suggests that present surgical techniques are inadequate.

Conventional resection for oesophageal cancer has been standardised for several decades (box 2). Lesions around the cardia and in the lower oesophagus were approached via a left thoraco-abdominal incision and a variable amount of the upper half of the stomach was removed and the lower oesophagus to a level just below the arch of the aorta. For lesions in the middle third of the oesophagus the Lewis-Tanner approach was employed with resection of the lower and middle thirds of the oesophagus and anastomosis high in the chest. Upper third lesions were either not resected and referred for radiotherapy or were resected using the Lewis-Tanner approach with the anastomosis sited as near as possible to the thoracic inlet.

The extent of any associated lymphadenectomy was very variable and at most included lymph nodes around the coeliac axis, left gastric, hepatic and splenic

Carcinoma of the oesophagus: aetiological factors
<i>Squamous</i> <ul style="list-style-type: none">• genetic• chronic inflammation• vitamin deficiencies (A,B,C)• nitrosamines• molybdenum deficiency• alcohol• tobacco
<i>Adenocarcinoma</i> <ul style="list-style-type: none">• Barrett's oesophagus

Box 1

Surgical options
<i>Conventional</i> <ul style="list-style-type: none">• thoraco-abdominal approach• Lewis-Tanner oesophagectomy• three-phase oesophagectomy• transhiatal oesophagectomy
<i>Extended surgery</i> <ul style="list-style-type: none">• en-bloc oesophagectomy• three-field lymphadenectomy

Box 2

arteries and a dissection in the lower mediastinum including lymph nodes around the carina. Five-year survival using these techniques was less than 20%. One half of deaths could be attributed to metastatic disease but more importantly 50% of fatal recurrences were in the remaining oesophagus or in the mediastinum.⁶

A number of factors may account for these depressing facts. Because the oesophagus lacks a serosal layer, once the tumour invades the muscular layer, it can penetrate rapidly beyond the confines of the oesophageal wall to surrounding structures. An adequate lateral dissection can, therefore, be difficult or impossible. The propensity for tumour to spread proximally in the submucosal layer means that 8 to 10 cm of oesophagus proximal to the tumour must be resected to get adequate vertical clearance. This is not always possible using the left thoraco-abdominal approach for lower third tumours or the Lewis-Tanner approach for high middle third or upper third tumours. Lymph node resection may often be reasonably adequate in the abdomen but a thoracic dissection confined to the lower mediastinum is not adequate.

The introduction by McKeown⁷ of three-phase resection was one of the first attempts to tackle the problem of inadequate resection. While his technique received a lot of attention it was not widely adopted and this may have been due to the fact that, because the abdominal, thoracic and cervical dissections were carried out sequentially, the procedure was a rather lengthy one. A further problem was the not infrequent difficulty of delivering a bulky tumour into the neck. An additional technical problem was delivering the cardia into the cervical incision in order to divide and close it. However, three-phase oesophagectomy undoubtedly reduces the incidence of proximal tumour involvement when compared with conventional resection although, as Wong⁸ points out, the difference between a cervical anastomosis and one located at the thoracic inlet via the Lewis-Tanner approach is not more than 1-2 cm and unlikely to make much difference.⁹

Skinner's en-bloc resection¹⁰ is a radical approach to complete local clearance in which a block of tissue with 10-cm margins proximal and distal to the tumour includes the thoracic oesophagus, the thoracic duct, the azygos vein, the posterior pericardium and all the fibro-fatty tissue in the posterior mediastinum. Although evidence of excellent local control can be demonstrated, this is confined to the chest and recurrence in cervical lymph nodes is not uncommon. The benefits of en-bloc resection according to Skinner were restricted to a select group of patients in whom fewer than five regional nodes were involved in tumour and in whom complete penetration of the oesophageal wall by tumour had not occurred. The five-year survival in these patients was 29%.¹¹ An additional benefit, however, was the significant reduction in the incidence of local recurrence, either anastomotic or mediastinal, after en-bloc resection, which was only 5%.

Orringer's decision to develop transhiatal resection was based on his belief that most tumours at presentation had already disseminated widely as micro-metastases and that, therefore, extensive local resection did not eradicate the disease.¹² The advantage of transhiatal resection lies in removing the primary tumour with at least some of the adjacent lymph nodes with the least disturbance to respiratory function thus diminishing the incidence of one of the major complications of oesophagectomy. The disadvantages are unreliable staging of the disease and the possibility of leaving involved nodes behind in the mediastinum. A further disadvantage that we have recorded from our experience is an increased incidence of chylothorax. Orringer reported a 2.5% incidence of chylothorax after transhiatal oesophagectomy.¹² In our experience the incidence was 10.5% after transhiatal resection in contrast to an incidence of 0.2% for transthoracic resection.¹³ We now restrict transhiatal oesophagectomy to occasions when pharynx, larynx and oesophagus are resected for post-cricoid cancer.

Despite impressive survival figures reported from Japan, three-field lymphadenectomy remains controversial. The protagonists of this extensive procedure point to the studies of Tsurumaru *et al*¹⁴ demonstrating cervical lymph node involvement in 34% of patients with oesophageal cancer. Abdominal lymph node metastases were present in 50% of patients. In addition, Akiyama found that in 36% of patients with upper thoracic oesophageal tumours, 12% with mid-thoracic oesophageal tumours and 11% with lower thoracic oesophageal tumours, metastases were present in the superior mediastinal lymph nodes.¹⁵ As a general rule dissection of superior mediastinal lymph nodes is not included in conventional oesophageal resection.

The advantages of extensive abdominal, mediastinal and cervical lymphadenectomy are an improved five-year survival (reported by Kato *et al*¹⁶ to be 49%), a reduction in local recurrence and a more accurate staging of the

tumour. In the nationwide Japanese study which compared three-field and two-field dissections, the five-year survival for three-field dissection was more modest at 34%. However, this remained statistically better than the figures for two-field dissection which was 27%.¹⁷ The great disadvantage of three-field dissection is the high incidence of recurrent laryngeal nerve paralysis. In the multi-centre trial referred to above, the incidence of recurrent laryngeal nerve paralysis with standard lymph node dissection was 14%, in contrast to a 20% incidence with three-field dissection. The high incidence after standard lymphadenectomy suggests that such routine lymph node dissection includes the superior mediastinum where the left recurrent laryngeal nerve is at risk during the dissection on the left side of the trachea and the right nerve may be injured at the thoracic inlet. The mortality rate was 2.8% for the extended operation and 4.6% for the standard operation. Desai *et al*¹⁸ noted that postoperative recurrence of tumour after standard lymphadenectomy was predominantly in lymph nodes whereas after extended lymphadenectomy distant metastases were more common.

The advantages of three-field lymphadenectomy are closely related to better control of locoregional disease and patients are unlikely to benefit if distant micro-metastases are already present. The likelihood of such metastases is high if more than five nodes are involved. Multi-modality treatment appears an alternative approach to therapy which takes account of the possibility of occult distant metastases.

Radiotherapy and chemotherapy

Both radiotherapy and chemotherapy have been employed by numerous workers over the past few decades but rarely in the context of a controlled clinical trial. However, a number of facts have been established. Radiotherapy is less effective than surgery in terms of survival.¹⁹ Pre-operative radiotherapy does not enhance survival²⁰ and there is no evidence that postoperative radiotherapy improves survival.^{21,22}

Most studies on chemotherapy have been uncontrolled trials. In one of the few randomised trials carried out no advantage was found for pre-operative chemotherapy when compared with pre-operative radiotherapy.²³ Further studies have involved multiple chemotherapy, with and without irradiation and the following conclusions can be drawn. Combined or multiple chemotherapy is better than treatment with a single drug. A combination of multiple chemotherapy and radiotherapy further enhances the therapeutic value of the regimen. Cytotoxic drugs act as radiosensitizers as well as cytotoxic agents. For this effect to be achieved, the chemotherapy and radiotherapy must be given simultaneously. Finally, pre-operative chemoradiotherapy is of greater benefit than adjuvant treatment given postoperatively.

The most effective combination of chemotherapeutic agents is 5-fluorouracil and cisplatin. Total radiotherapy doses have been in the range 30–40 Gy. It is probable that the higher dose is more appropriate. Toxicity is relatively low with regimens such as that outlined above and in our experience there has been no increase in operative mortality. Not surprisingly, the best results in terms of survival correlate well with complete tumour response and control of locoregional disease is enhanced.

The majority of studies to date were uncontrolled trials and at least one used what would appear to be an inadequate dose of radiotherapy. Response rate is higher in squamous tumours than in adenocarcinomas but we have found a worthwhile 20% response rate in the latter. Our response rate for squamous cell carcinomas was 34%.

Response rate correlates well with survival. In the study reported by the Southwest Oncology Group, the overall survival at two years was 28% and at three years 16%. When complete responders only were included, the two-year survival rose to 67% and the three-year survival was 45%.²⁴

Summary of advances in management

The technical developments of the last few decades and changes in management philosophy have led to a number of improvements in treating carcinoma of the oesophagus. The importance of 8–10 cm margins is now recognised as essential for the prevention of anastomotic recurrence. This makes cervical or very high intrathoracic anastomosis mandatory for proximal tumours or total gastrectomy and intrathoracic oesophagojejunal anastomosis for tumours whose main bulk is below the cardia. Wide lateral clearance (or en-bloc resection) and at least full upper and lower mediastinal lymph node dissection is necessary to minimise local (mediastinal) recurrence and three-field dissection

should be considered for proximal tumours. In view of the serious morbidity and mortality associated with chylothorax, prophylactic ligation of the thoracic duct is an option which should be considered in all cases.

Transhiatal oesophagectomy, although it has the advantage of minimising pulmonary complications and the additional advantage of providing good proximal clearance, is unlikely to provide adequate lymph node clearance for most tumours and should be reserved for tumours around the cardia or for cases where pharyngolaryngoesophagectomy is being done for carcinoma of the pharynx. Chemoradiotherapy, if used as adjuvant therapy, should be done in the context of a controlled trial.

Retrospective data from Dublin

Our management of oesophageal cancer has undergone considerable changes over the past two or three decades. Between 1970 and 1994, 700 patients underwent surgery for carcinoma of the oesophagus and pharynx in our department, 73 of whom had a pharyngolaryngectomy for post-cricoid carcinoma, 15 had incomplete records, and 11 did not proceed to resection. We present an analysis of the remaining 601 patients who underwent resection for carcinoma of the oesophagus during that period.

PATIENT DETAILS

Males accounted for 60% of patients. The mean age for male patients was 63.7 years (range 27-84 years) and for women was 65.4 years (range 30-85 years). The resection rate represents 85% of patients seen and evaluated. Adenocarcinomas accounted for 51% of tumours and 48% had squamous cell carcinomas. A small number of patients had rare tumours, eg, lymphoma, melanoma. Lymph nodes were positive in 80% of patients with adenocarcinoma and in 52% of patients with squamous cell carcinoma. Full thickness wall penetration was present in 95% of adenocarcinomas and in 96% of patients with squamous cell carcinoma.

More than 90% of adenocarcinomas were located at the cardia and in the lower third of the oesophagus in contrast to squamous cell carcinomas of which 46% were located in the middle and upper thirds of the oesophagus. Upper third tumours (excluding pharyngeal lesions) are rare comprising <4% of squamous tumours.

COMPLICATIONS

Respiratory complications were relatively common, affecting 40% of patients undergoing resection. The diagnosis in 70% of those patients was pneumonia or pleural effusion and patients responded readily to treatment. Respiratory failure requiring ventilatory support occurred in 18% of patients with respiratory complications and 8% of patients with pulmonary complications died. Aspiration pneumonia occurred in 7% of patients with a cervical anastomosis but only in 1% of patients with an anastomosis in the chest.

Leakage from the anastomosis occurred in 7% of patients. The mortality associated with anastomosis leakage was 62%. There were fewer leaks (3%) after three-stage resection with cervical anastomosis than after any other procedure although the leak rate was 14% after transhiatal resection. However, this anomaly can probably be explained by the fact that transhiatal resection numbers were small ($n=22$) and two of the three leaks in that group were minor with one fatality.

Chylothorax was a serious complication and five of eight patients developing this complication died. The incidence following all forms of transthoracic resection was 1% but after transhiatal resection was 14%. In our view, chylothorax is best treated by early surgical intervention ligating the duct where it lies to the right of the aorta above the right hemidiaphragm.

Recurrent nerve paralysis occurred in 3.8% of patients, mostly following three-stage resections or transhiatal oesophagectomy.

MORTALITY

The overall mortality for the 25-year period of this review was 15%. The mortality has been calculated as the 90-day in-hospital mortality. There has been a gradual reduction in peri-operative mortality and in the last 100 cases it has been 11%. This is probably an acceptable mortality for a resection rate of 85%. In 50% of deaths the cause was non-technical and was attributable to co-existing disease, eg, cardiac or respiratory disease. Anastomotic leak, haemorrhage and sepsis were the most frequent causes of death from technical faults and accounted for 33% of the total mortality.

Age and procedure were the only two factors with a statistically significant

Table 1 Survival following oesophagectomy, including 90-day mortality

Survival	Adeno-carcinoma	Squamous carcinoma	p
1 year	93/250 (37%)	90/250 (36%)	ns
2 years	49/226 (22%)	55/226 (24%)	ns
3 years	29/207 (14%)	32/215 (15%)	ns
4 years	16/168 (8%)	19/195 (10%)	ns

Table 2 Survival correlated with wall penetration and lymph node involvement for adenocarcinoma

Penetration	-	+	-	+	p
	-	-	+	+	
Lymph nodes					
1 year	14/17 (82%)	29/40 (73%)	6/11 (55%)	58/158 (37%)	<0.0001
2 year	10/14 (71%)	17/37 (46%)	2/10 (20%)	28/140 (20%)	<0.0001
5 year	2/5 (40%)	4/24 (17%)	1/5 (20%)	6/92 (7%)	<0.014

Table 3 Survival correlated with wall penetration and lymph node involvement for squamous carcinoma

Penetration	-	+	-	+	p
	-	-	+	+	
Lymph nodes					
1 year	28/39 (72%)	57/119 (48%)	5/9 (56%)	33/100 (33%)	<0.0001
2 year	19/38 (50%)	41/113 (36%)	3/8 (38%)	10/97 (10%)	<0.0001
5 year	7/21 (33%)	14/81 (17%)	0/7 (0%)	3/75 (4%)	<0.0001

impact on mortality. The mortality for patients over 80 years was 40% (p<0.0002) and in patients undergoing transhiatal resection the mortality was 33% (p=0.02). The outcome in the very elderly is self-explanatory. The poor outcome for patients undergoing transhiatal resection can probably be explained by the fact that transhiatal resection was offered to patients with poor respiratory function or other co-existing disease which precluded thoracotomy or time-consuming dissection.

Overall survival was poor (table 1). However, there was a marked difference when patients were stratified according to the extent of the disease. The most significant parameters were wall penetration and nodal involvement (tables 2 and 3). It is evident from the tables that involvement of lymph nodes, even if wall penetration is not complete, is associated with poor prognosis.

Survival figures prior to the trial were worse than they were a decade ago²⁵ and this correlates with the rising incidence of Stage III and IV disease and also with the increased incidence of adenocarcinoma which has a higher percentage of nodal involvement than squamous (80% vs 52%).

Controlled trial of neoadjuvant chemoradiotherapy

Retrospective analysis of surgical treatment of carcinoma of the oesophagus shows clearly that, while peri-operative mortality continues to improve, conventional surgery offers little prospect of cure in the majority of cases. Improved long-term survival could only be anticipated either by adopting the extensive three-field lymphadenectomy or by adopting a multi-modality approach to treatment. The former offers better control of locoregional disease only but the Japanese experience has clearly demonstrated that this was associated with improved long-term survival. Chemoradiotherapy also offers improved control of locoregional disease with the additional possible benefit of controlling distant micrometastases, if present.

We decided to adopt the latter approach and have begun a prospective controlled trial of neoadjuvant chemoradiotherapy followed by surgery versus surgery alone. Chemotherapy is given in two courses during the first and sixth week of treatment and consists of 5-fluorouracil (15 mg/kg) for five days and cisplatin (75 mg/m² body surface area) on day seven preceded by hydration on day six (box 3). The radiotherapy course consists of 40 Gy administered in 15 fractions over three weeks. Surgery is carried out at the end of the eighth week.²⁶

There are four limbs in the trial, multi-modality treatment versus surgery alone for both squamous cell carcinoma and adenocarcinoma of the oesophagus. The trial is ongoing but a number of comments can be made at this time. The neoadjuvant regimen has a relatively low toxicity and does not make subsequent surgery more difficult. Complete histological responses have

Chemo/radiotherapy regi-
men

- radiotherapy: 40 Gy, days 1–5, 8–12, 15–19
- chemotherapy:
 - 5-fluorouracil, 15 mg/kg/day, days 1-5, 36-40; cisplatin, 75 mg/m², days 7, 42
- surgery: day 56
- chemotherapy or operation withheld if white cell count <3.5

Box 3

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been observed in both squamous cell and adenocarcinoma. Significant downstaging of tumours have occurred in both squamous cell carcinomas and adenocarcinomas, with a large increase in node-negative patients after neoadjuvant therapy. There is a trend emerging towards improved survival in both types of tumour.

These early results encourage us to believe that multi-modality treatment may have a valuable role to play in the treatment of carcinoma of the oesophagus.

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