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Oesophageal Cancer and the Anaesthetist

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Key points.

- Oesophageal carcinoma is becoming more common and its pathology and patient demographics are changing.
- Careful pre-operative assessment is needed to select appropriate patients and optimise them before surgery.
- Exquisite attention to analgesia, fluids and ventilation intra-operatively is needed for the best post-operative outcome.
- Oesophagectomy surgery can be associated with a number of complications, which include organ failure and critical illness.
- Anaesthetists may also be involved in palliative therapy for oesophageal carcinoma.

A: Introduction

Oesophageal cancer is the eighth most common malignancy worldwide, with a rapidly increasing incidence. 20-30% of patients have metastases at initial presentation.[1] Curative therapy for many patients involves surgery, often with preoperative chemotherapy.[2] Despite ongoing improvements, oesophageal surgery remains high risk with substantial associated morbidity and mortality.

B: Changing pathology of oesophageal cancer

In Western developed countries, around 80% of oesophageal tumours are adenocarcinomas and 20% squamous cell carcinomas. Other tumour types are rare. In developing nations and the Far East (including China and Japan), squamous cell histology continues to predominate.[1] Risk factors for the two types are shown in Table 1.

Outcome for patients with oesophageal cancer remains poor, with survival rates of around 20-25% at two years for advanced disease.[3] This dismal outcome is related to a propensity for metastasis to arise even from superficial tumours and for patients to present late, already having developed invasive tumours, often with nodal and/or metastatic disease.[2]

A: Pre-operative assessment, neoadjuvant chemotherapy and pre-habilitation

Surgery alone may be used for localised disease. Neoadjuvant chemoradiotherapy, received by most patients, is typically used in T3 (tumour invading oesophageal adventitia but not distant structures) or N1 (regional lymph node metastasis) disease.[1] Staging will normally include a laparoscopy for biopsy and peritoneal

washings. Drug combinations include cisplatin/5-flurouracil, paclitaxel/carboplatin, cisplatin/fluoropyrimidine and oxaliplatin/fluorouracil.[1] In the USA, chemotherapy is usually combined with radiotherapy.[2]

Both cisplatin and 5-fluroruracil are cardio- and hepatotoxic, with cisplatin also exhibiting nephrotoxicity. Although a washout period of several weeks between chemotherapy and surgery usually allows normalisation of haemopoiesis, leukopenia, infection risk and thrombocytopenia, an increased risk of haemorrhage may persist in some patients. In patients with complications from chemotherapy, complex multidisciplinary planning may be needed to decide on the delaying surgery further to allow adequate recovery, or early cessation of chemotherapy to allow better patient fitness for surgery.

Risk factors for peri-operative morbidity and mortality are:[4 5]

- Poor cardiac and/or pulmonary function
- Advanced age
- Tumour Stage
- Diabetes mellitus
- Impaired general health
- Hepatic dysfunction
- Peripheral Vascular Disease
- Smoker
- Steroids

Evaluation of cardiopulmonary exercise testing in oesophagectomy candidates by controlled trials is not extensive, but the inability to deliver 800ml$min^{-1}m^{-2}$ oxygen and a lower anaerobic threshold (AT) correlates with increasing peri-operative risk.[4] A decline in peak oxygen delivery and AT is observed following chemotherapy, although these values normally improve with time prior to surgery.

Pre-optimisation of comorbid disease management is necessary, especially as medical comorbidities are common. Smoking cessation should be encouraged, as smoking is associated with potentially severe complications. Appropriate management should be instigated for pre-operative anaemia, as even mildly reduced haemoglobin levels are associated with adverse outcomes.

Nutrition is very important in these patients. Various changes, including earlier detection and rising incidence of reflux-related adenocarcinomas, mean obesity is increasingly common compared to cachexia, at least in those fit enough to be considered for surgery. It presents major challenges peri-operatively for regional anaesthesia, positioning, surgical access, duration of surgery and management of perioperative ventilation. Despite being obese, patients can still be malnourished or hypermetabolic, and careful nutritional support with the involvement of a dietician is necessary.

In the underweight, cancer cachexia and dysphagia contribute to a poor nutritional state, as does psychological fear and inability to eat certain foods. Progressive dysphagia limits the consumption of energy dense foods like bread and meat and patients may subsist on thin soups, pureed meals and drinks. Chemotherapy and radiotherapy can also contribute to malnutrition.

Nutritional support, with fortified drinks and/or nasogastric or jejunostomy feeding (which may be inserted at the time of laparoscopic assessment and staging of the tumour), are important in optimising patients for surgery.[1] Supplementation pre-operatively is indicated where patients fail to take 75% of their goal calories and tube feeding is indicated for patients with deficiencies of 50% or more.[6]

Pre-habilitation, that is, physiotherapy and exercise training pre-operatively to improve physical fitness, has yet to be evaluated for patients undergoing oesophagectomy. However, this is an area of substantial interest and is likely to become increasingly important in the future.

A: Perioperative Management for Oesophagectomy

B: Surgical approaches and anaesthetic considerations

Surgery involves excision of the oesophagus and relocating the stomach in the mediastinum to form the so-called gastric conduit connecting the pharynx to the remaining gastrointestinal tract (figure 1), with the abdominal stage performed first. The anastomosis is formed at extreme end of the foregut's blood supply. This renders it vulnerable to ischaemia unless there is careful management of haemodynamic parameters and fluid to ensure its perfusion is maintained. In revision oesophagectomy, a colonic interposition is performed, using a section of colon on a pedicle. This is a high risk procedure in a potentially surgically hostile field, with multiple vulnerable anastomoses.

There are a number of surgical approaches and many surgeons will use variations on the conventional descriptions. The Ivor Lewis approach involves a laparotomy to

assess tumour extent and mobilise the stomach, followed by a right thoracotomy for the resection and anastomosis. Laparotomy incisions may be conventional midline (figure 2A) or “roof-top” (figure 2B), the latter meaning that the incision is closer to the thoracotomy and therefore better-covered by an epidural catheter compared to a vertical incision. The tri-incisional or McKeown technique uses a cervical incision for the upper anastomosis (figure 2C). This means that the incision is performed in an area which has not been subject to previous radiotherapy (if used) and, in the event of a leak, a cervical drain is technically easier to insert.[7] The transdiaphragmatic (or thoracolaparotomy) approach involves an incision from the thoracotomy site to the umbilicus, dividing the diaphragm surgically (figure 2D).

Transhiatal oesophagectomy classically involves laparotomy and dissection of the lower oesophagus through an enlarged diaphragmatic hiatus, followed by removal of the oesophagus and re-anastomosis via a left cervical incision, thereby avoiding thoracotomy altogether (figure 2E). This may be useful in patients with malignancies of the lower third of the oesophagus where thoracotomy is undesirable, such as those who have previously undergone thoracic surgery. Dissection around the mediastinum is frequently associated with arrhythmias and ventricular compression causing hypotension (although this frequently occurs in transhiatal surgery, it is not uncommonly encountered during the thoracic phase of other approaches, especially with thoracotomy).

Minimally Invasive Oesophagectomy (MIO) involves using thoracoscopic and laparoscopic surgical techniques in place of open incisions. Many surgeons will perform hybrid techniques, for example laparoscopic abdominal followed by open thoracic surgery. Amongst the most common is a variation of the Ivor Lewis with multiple ports (typically around 10) for the thoracic and abdominal components. In

some centres the thoracoscopy is partly performed prone to aid surgical access. Robotic techniques have also been described.[7]

B: Analgesia

Analgesia is a significant challenge following oesophagectomy surgery, given the multiple incisions and their distribution. Good pain relief is important for post-operative respiratory function, compliance with physiotherapy, mobilisation and prevention of complications. Chronic pain is also a significant problem following thoracotomy in particular and this can be reduced by good pain relief in the early post-operative period.

Pre-emptive thoracic epidural analgesia has been shown to reduce chronic post-operative pain following thoracotomy.[4] Thoracic epidural is widely considered the gold standard and it is our practice to place them for all patients, including MIOs, and use them for the first three to five days.[8] Patients without an epidural have been shown to have longer time ventilated post-operatively, a longer ICU stay and a higher opioid requirement. A retrospective analysis indicates a lower risk of anastomotic leak when epidural analgesia is used.[4] The level of insertion and consequent effectiveness will be determined partly by the surgical incision used (as discussed above). To ensure adequate cover of both lower end of a long laparotomy incision and thoracotomy, some centres will site two epidurals simultaneously.

Paravertebral blocks and catheters have been reviewed in CEACCP.[9] A recent meta-analysis of analgesia for thoracotomy versus epidural suggested they were equally efficacious, with fewer side effects, fewer pulmonary complications (a changed finding from previous meta-analyses) and lower failure rates.[10] However, this may not be wholly applicable to oesophagectomy patients, who also have

abdominal wounds. They may be useful where an epidural is strongly contra-indicated (but a paravertebral catheter is acceptable) or technically difficult to place.

Patient controlled analgesia is largely reserved for step-down analgesia or in the event of failed regional anaesthesia in most centres. Intravenous bolus ketamine has been shown to reduce pain scores and morphine consumption following thoracotomy compared to use of PCA alone, and may be used as adjunctive or rescue analgesia.[11] Ketamine can have significant side effects, requiring careful dosing.

A morphine PCA combined with a plain epidural may be useful for very large incisions not adequately covered by the epidural alone, or where there are incisions or other sources of pain in areas not covered by the epidural catheter (for example, cervical incision or shoulder pain from lateral positioning).

Adjunctive analgesics, such as gabapentin, pregabalin or low-dose tricyclic antidepressants may be useful for prevention of chronic pain post-operatively, but their early administration is limited as they are not available in parenteral form.

B: One Lung Ventilation.

The most important factor for safe lung isolation and one lung ventilation (OLV) is the anaesthetist's familiarity with the techniques. Lung isolation is necessary for the open thoracic or thoracoscopic phase of surgery. Most frequently this is achieved with a left-sided double lumen tube (DLT), the left being preferred as a right thoracotomy is used most often for surgical access and it is good practice to intubate the ventilated lung. Lung isolation with bronchial blockers has been described.[12] There are multiple variations of surgical technique (including prone thoracoscopy

with partial deflation of both lungs) and close liaison with the surgeon to plan optimal anaesthetic technique is mandatory.

Particular care should be exercised to prevent, detect and correct DLT migration, especially if the prone position is used. Some surgeons insufflate carbon dioxide into the pleural cavity to aid surgical access for thoracoscopy; this will cause the arterial CO_2 tension to rise, which may be difficult to compensate for during OLV.

B: Fluid management

Oesophagectomy presents great challenges for fluid management both intra- and post-operatively. Excess fluid administration risks not only pulmonary oedema but also venous congestion of the anastomosis. Insufficient fluid is associated with excess vasopressor use, increased myocardial strain and vasoconstriction, risking the anastomosis becoming ischaemic, and systemic effects including acute kidney injury. Sub-optimal anastomotic perfusion risks the development of a leak. This is further complicated if there is significant blood loss.

Preventing fluid overload appears to be crucial in obtaining good outcomes.[8] Extrapolation of indirect evidence from both GI and thoracic surgery also favours the avoidance of the administration of excess fluid,[4] although “excess” is challenging to define and the risks of inadequate fluid administration should not be underestimated.

One group have reported improved outcomes using a regime involving the avoidance of large volumes of fluid intra-operatively (a mean 4000ml of was administered intra-operatively in their case series), in combination with extubation in theatre, regional analgesia, early mobilisation and early initiation of feed. This, in combination with repeated clinical assessment and arterial blood gas analyses, is our unit’s practice.[13]

Cardiac output monitoring is challenging with Oesophageal Doppler and transoesophageal echocardiography self-evidently impossible for this surgery. The use of minimally invasive techniques have been advocated for the optimisation of stroke volume before the thoracic phase and for 12 hours post-operatively, with avoidance of aggressive fluid loading during the thoracic phase (where minimally invasive monitors cannot provide validated readings).[4]

B: Protective lung ventilation

The role of lung protective ventilation is well-established in Acute Respiratory Distress Syndrome (ARDS) and increasingly in both the critically unwell without ARDS and perioperative patients.[14] One-lung ventilation is usually necessary for adequate surgical access, with the deflated lung vulnerable to atelectotrauma and ischaemia-reperfusion injury; whilst the ventilated lung is exposed to the risks of ventilator-induced volu- and barotrauma, high FiO_2 as well as cardiovascular challenge from the shunt and raised pulmonary artery pressures. Previously, high tidal volumes and low/no PEEP were advocated to prevent atelectasis and minimise shunt, whilst over the last 15 years, low tidal volume, lung-protective strategies have become the norm for OLV.[4]

A: Perioperative pharmacological therapies

Perioperative pharmacological therapies to modulate the immune response are not used routinely in the UK, Europe or North America. However, in Japan and South Korea this practice is more widespread and briefly discussed here. It complicates comparison between Far Eastern and European/North American trial and outcome data and also may be of interest for future investigation.

Methylprednisolone given at the induction of anaesthesia has been shown to reduce pulmonary inflammation. A meta-analysis identified seven trials,[15] all from Japan. Only one had good methodology and all had modest numbers of participants. There was no difference in death rates, but improvement was demonstrated for organ dysfunction and respiratory complications, sepsis, liver dysfunction, cardiovascular dysfunction and anastomotic leak. Countering this, chronic steroid use has been identified as a risk factor for adverse outcome,[5] although the effect of one dose versus a long-term course and whether long-term steroids are merely a marker for chronic illness is, as yet, unknown. The evidence is very weak and a large, robust randomised trial is warranted before recommending the widespread use of perioperative corticosteroids.

Sivelestat is a neutrophil elastase inhibitor available in Japan and South Korea for the prevention and treatment of ARDS. A number of Japanese studies have investigated its role intra- and postoperatively in oesophagectomy surgery, although none so far have been reported from elsewhere. A meta-analysis[16] showed reduced duration of mechanical ventilation by day five and ARDS but no change in length of stay in ICU or hospital, nor the incidence of pneumonia, systemic inflammatory response syndrome, sepsis, anastomotic leak or wound infection. The trials used in the meta-analysis were mostly small, unblinded and non-randomised. Its role in oesophageal surgery requires larger clinical trials to be better defined.

A: Post-operative complications

B: Respiratory

This is the most common source of post-operative complications. Quoted rates vary (17-51%), although there is evidence of falling incidence overall, suggested to be related to better case selection, pre-operative optimisation and perioperative care.[17] Nevertheless, acquisition of pulmonary complications substantially increases the risk of mortality.[17] The risk of developing respiratory complications can be minimised by adequate analgesia, reversal of muscular blockade, normothermia and haemodynamic stability.[7] Extubation at the end of surgery has been shown to be safe for most patients.[13]

Pneumonia is a common and potentially serious complication, which is associated with a higher risk of death both peri-operatively and at five years follow-up.[18]

Chest physiotherapy following oesophagectomy has been shown to reduce postoperative respiratory complications, including atelectasis and pneumonia, to allow earlier removal of chest drains and has a lower risk of return to mechanical ventilation.[19] Early mobilisation will also improve respiratory function.

ARDS is an extremely serious complication of oesophagectomy,[4] which may be minimised with intra-operative lung protective ventilation and exquisite fluid balance as discussed above. If it occurs, ARDS should prompt consideration of an occult pathology, such as an unrecognised anastomotic leak or sepsis. If reintubation is needed, care should be taken to avoid oesophageal intubation as this may directly traumatise the already vulnerable anastomosis.

Recurrent laryngeal nerve palsy is associated with reflux and aspiration and has been described in anywhere between 4 and 67% of patients.[17] The nerve is vulnerable to injury, and requires meticulous surgical technique to protect it. Palsies are most often partial and transient but can be permanent. Paradoxically,

presentation may be delayed as vocal fold oedema in the immediate post-operative period may narrow the glottis to allow the folds to adduct adequately, with hoarseness occurring as the swelling settles. Laryngeal palsy predisposes to inadequate cough and increased risk of aspiration.[5]

Conventionally, non-invasive ventilation (NIV) has been considered contra-indicated in patients with recent upper gastrointestinal surgery, with concerns that high airway pressure transmitted to the conduit may reduce blood flow or lead to venous engorgement and compromise the anastomosis. Gastric/conduit distention may also play a role. There is a paucity of data to indicate whether NIV is safe.

B: Surgical

Nasogastric decompression of the conduit is routine to protect the anastomosis, allow identification of gastrointestinal bleeding and monitor gastric secretion volume.[4] The NG tube is inserted intra-operatively and is positioned with surgical guidance during conduit formation.

Anastomotic leak is amongst the most serious of surgical complications following oesophagectomy. Rates vary from 10-37% and may account for as much as 35% of perioperative mortality. As described above, the anastomosis is distant from the origin of its blood supply, leaving it at risk of ischaemia and therefore inadequate healing or even breakdown. Avoiding both tissue oedema and excessive vasoconstriction are important.[7] Major leaks present in the first 5 days with severe sepsis, although initially this may appear occult and a high index of suspicion is needed. Smaller leaks tend to manifest at around one week post-operatively with local neck wound infection, collections and pleural effusions. Small leaks are managed by keeping the patient nil by mouth, giving high protein enteral feed or total

parenteral nutrition, antibiotics, radiologically guided drainage collection, chest physiotherapy and performing serial contrast studies. Major leaks require surgical exploration and revision surgery.[17]

B: Cardiac

Supraventricular arrhythmias, particularly atrial fibrillation, are reported frequently following oesophagectomy and are associated with increased mortality risk (whether this is causal or merely associative is not known). Atrial arrhythmia may be related to direct contact from thoracic dissection or pericardial irritation, or associated with sepsis, anastomotic leak, pre-existing cardiac disease and age, or raised right atrial pressure following OLV.[4]

A: Palliation in oesophageal malignancy

A detailed discussion of all aspects of palliative care and the role of the anaesthetist, pain specialist and critical care physician are beyond the scope of this article. 75-85% of patients with oesophageal cancer are never treated with curative intent and thorough multidisciplinary management is the cornerstone of providing these patients with good care. The specific complications pertinent to oesophageal malignancy include: [20]

- Dysphagia management
- External Beam Radiotherapy and Brachytherapy
- Chemotherapy
- Nutritional support
- Analgesia

- Prevention of gastrointestinal bleeding.

Endoscopic stenting is the treatment of choice to alleviate dysphagia, although other options include chemo- or radiotherapy, endoscopic laser therapy, endoscopic chemical injections (e.g. ethanol), dynamic phototherapy, cryoablation and dilatations. They are usually placed under sedation, although general anaesthesia may be requested for some patients.[20] Bypass surgery is used much less frequently as stents are effective and endoscopic procedures less invasive and avoid the associated high perioperative morbidity and mortality. It is more often performed when curative surgery is abandoned intra-operatively due to intra-operative findings.

Analgesia may be challenging with limited or no access to the oral route and so sublingual, transdermal and other routes may need to be utilised. Stenting to regain access to the gastro-intestinal tract is often a key component of allowing easier analgesia and nutrition. Chronic pain therapies, such as gabapentinoids, may be valuable adjuncts.

General anaesthesia for open or laparoscopic surgery is sometimes required for palliative nutritional support access (via gastrostomy or jejunostomy).[6] These patients are frequently cachectic, anaemic, functionally immunosuppressed, suffering from ongoing gastrointestinal reflux and may have an obstructed oesophagus with food residue, requiring careful tailoring of the anaesthetic technique. This may also make analgesia dosing unpredictable, especially with regard to opioids, and so careful dose adjustment is required.

A: Summary

Oesophageal carcinoma is a serious disease burden worldwide, with anaesthetists, critical care and pain physicians involved in both curative attempts and palliation. Optimising anaesthetic management is an important part of improving perioperative outcomes.

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