

## Oesophageal cancer surgery in 20 years: will robotics and augmented reality lead the way?

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How would you describe cancer? Perhaps you would scientifically suggest that it is a disease process with errors in our genetic code resulting in our cells malfunctioning. But perhaps, as Christopher Hitchens suggested, instead the most common response would be to personify it with a 'malice' towards which we can allocate a personal hatred.<sup>(1)</sup> Every incidence of cancer will result in a personal battle, from which any victory is the champion of human endeavour. This endeavour includes the individual's fight, their family's support, the specialist nurses' endless hours and the work behind the expertise of modern medicine and surgery. Unfortunately, as the surgeon Atul Gawande elegantly describes, "the paradox at the heart of medical care is that it works, so well, and yet never well enough".<sup>(2)</sup> Despite this, or maybe in spite of this, progress continues to be made in the treatment of cancer. This work seeks to briefly explore what cancer of the oesophagus is, how we currently approach treatment and then to discuss the future of surgery. This includes robotics and the use of virtual and augmented reality to improve surgical and survival outcomes.

8,784 new cases of oesophageal cancer were diagnosed in the UK in 2013, representing 2% of all UK cancer cases.<sup>(3)</sup> However, 5% of all cancer deaths in the UK were attributed to oesophageal origin with only 12% of patients living 10 years from diagnosis.<sup>(3)</sup> Due to the late diagnosis of patients, often the cancer is too advanced for treatment to help. Nevertheless 30-40% of oesophageal cancer patients are currently treated with an aim to cure them.<sup>(4)</sup> Depending on the type of cancer of the oesophagus we can use endoscopic resection, chemotherapeutic drugs, radiotherapy, surgery or a combination of these. Minimally invasive surgery has developed and involves the use of cameras (laparoscope/thoracoscope depending on site of the camera port) through little incisions to explore within body cavities without having to perform large 'open' surgery. This is routine for many gastrointestinal operations frequently performed, for example the removal of a gallbladder or an appendix. Such are the advancements in modern surgery that it is now possible to operate using robotics.<sup>(5)</sup> This is an extension of minimally invasive surgery for there are only small incisions for the 'arms' of the robot to enable access and allow the surgeon the ability to see and explore the anatomy without having an openly dissected patient on the table. In the case of oesophageal surgery the use of robotics is still in its infancy but given its success in other areas perhaps there is a future for its application.

### The Oesophagus – Anatomy and Function

The oesophagus is the "gullet" or "food pipe" that connects the throat to the stomach serving as a conduit for food. Approximately 18-25cm long, it originates at the level of the cricoid cartilage that can be felt as the circular ring beneath the prominent thyroid cartilage that forms the Adam's apple. Food is swallowed via wave-like contractions of circular muscle in the wall of the oesophagus. The oesophagus runs behind the windpipe into the chest, through the diaphragm and into the stomach at the gastro-oesophageal junction (GOJ).

When the ability to prevent reflux of stomach content upwards is lost then symptoms of heartburn and acid reflux are experienced. If experienced over a long period of time it is referred to as Gastro-Oesophageal Reflux Disease (GORD). The acid of the stomach is an irritant, especially to areas of tissue neither protected nor expecting to come into contact with it. As such, the thin flat cells of the oesophagus can become inflamed and disorganised. The region affected is then referred to as Barrett's oesophagus (BO). Hence this disorganised (or dysplastic) region is associated with chronic reflux.<sup>(6)</sup>

### What is cancer?

Cancer is when the cells of our body grow in an uncontrolled and non-required manner. When this occurs the cells may lack the resemblance of the type of cell in which they originated. The

number of these cells grows and can pass through local boundaries between normal tissues thus 'invading' locally or a few cancerous cells can break off and spread elsewhere in the body producing secondary sites of cancer (metastases). The effects of cancer fundamentally are due to the loss or disruption of the normal function of the body. For example a tumour or collection of these inappropriately growing cells can prevent an organ from performing its action, can compress blood vessels or impinge upon nerves etc. Hence in the oesophagus they can cause difficulty swallowing or indigestion in the upper abdomen (dyspepsia).

Cancerous cells provide themselves with their own growth signals; have the ability to replicate and produce more cells indefinitely; and to avoid mechanisms that would otherwise cause cell death or inhibition of their growth.<sup>(7)</sup> How exactly do cells acquire such properties? Our DNA forms the genes that are the instruction manuals from which proteins can be built. These proteins have functions within the cells. Errors in the specific code of the DNA sequence are called mutations and these usually occur when the genome is copied inaccurately. Hence a mutation will cause a part of the cell to be missing or not function correctly. If we were for example wiring a plug, an error in our instruction manual may cause the appliance to not work or perhaps enable the plug to short circuit and cause some incorrect activity and damage. Similarly in cells these mutations can either cause the cell to not work or to function incorrectly causing damage. We have repair mechanisms that should prevent such errors occurring and, if severe enough, can initiate a programmed cell death (apoptosis). Thus, it follows that when we have a mutation in repair mechanisms themselves we can accumulate lots of further errors.

### Oesophageal adenocarcinoma (OAC) vs. squamous cell carcinoma (SCC)

Cancer of the oesophagus predominantly takes two forms defined by their microscopic appearance and cells of origin. Oesophageal adenocarcinoma (OAC) is associated with gastric reflux and Barrett's Oesophagus. It is thought that there is a migration of the gastric 'cardia' cells that exist in the upper portion of the stomach to the region of the GOJ and the lower oesophagus.<sup>(8)</sup> These cells then take on the appearance of cells of the intestine and can become cancerous.<sup>(8)</sup> It has long been thought that OAC may be the result of a progression of the disorganisation seen in BO resulting in changes in appearance and function eventually becoming substantive enough to constitute cancer. However the chances of a person with BO developing OAC are very low. A meta-analysis looking at the data from 57 individual studies, including 11,434 patients, demonstrated that 1 in 300 patients per year with BO would progress to higher-grade dysplasia (more disorganisation) and eventual adenocarcinoma.<sup>(9)</sup> In a study that examined patients with BO where some progressed to OAC and others did not they established that a stable genome with a lower likelihood to mutate is associated with lack of progression to OAC with the reverse true in those that did progress.<sup>(10)</sup>

Overall there appears to be a progression from BO to OAC but this may not be a linear fashion. There are predominantly mutations in the CDKN2A and TP53 genes but, rather than one population of cells outcompeting the others through an accumulation of mutations, there may be competition between different clonal populations with differing likelihood of mutation (i.e. differing genomic stability).<sup>(11-15)</sup>

Due to the association between reflux and OAC there is an increased risk of developing OAC if you are obese.<sup>(3)</sup> Metabolic Syndrome is a collection of central abdominal obesity, insulin insensitivity (resulting in increased blood sugar), and high fats in your blood. Most likely as a consequence of the central abdominal obesity, sufferers of metabolic syndrome are at increased risk of developing OAC. Other conditions causing reflux, for example a hiatus hernia, may also act as risk factors.<sup>(3)</sup> However there are some protective factors such as the presence of the bacteria *H. pylori* in the stomach for they reduce the amount of acid present thus ensuring that any refluxed stomach content is less irritable.<sup>(3,16,17)</sup>

The other type of oesophageal cancer is that called Squamous Cell Carcinoma (SCC). It is a cancer of the thin flat cells that usually line the oesophagus. It is the most common cancer of the oesophagus in the world and is more prevalent in the developing world. It has strong

associations with alcohol and smoking with some suggestion that together they may have an even greater effect on increasing your risk.<sup>(17)</sup> As with any cancer, increasing age is associated with a greater risk of developing either OAC or SCC, with nearly 57% of new cases in the UK diagnosed in patients over the age of 70.<sup>(3)</sup> Additionally there is a greater risk of these cancers occurring in men, perhaps in the past this is due to the proportion of men that were more likely to drink and smoke, however as these activities have become more balanced across the genders over time the discrepancy in the incidence of oesophageal cancer in men remains.<sup>(3)</sup> A healthy diet with high fruit and vegetable content is also protective and could perhaps explain why there is an increased risk of oesophageal cancer in lower socioeconomic regions.<sup>(3)</sup>

### Initial management decisions: staging and grading of cancer

Due to the insidious onset of oesophageal cancer and the accumulation of symptoms prior to accessing medical care nearly 50% of patients will have metastases at diagnosis.<sup>(16)</sup> This means that the cancer will have spread from the initial 'primary' tumour and will have cells elsewhere in the body producing 'secondary' sites. These occur once the cells of the initial tumour have invaded the local tissue and found entry into the blood or the lymphatic systems in which the various vessels distribute the cancerous material elsewhere. Needless to say it is much worse to present with these multiple lesions around the body for simple surgery to remove the primary tumour becomes minimal in benefit as the cancer is elsewhere. In such scenarios systemic therapy such as that of chemotherapy may be employed.

Following diagnosis treatment decisions depend on many factors. The tumour itself, as part of the diagnostic process, will be given a stage and a grade as shall be explained below. In addition the type of cancer (SCC or OAC), location (upper oesophagus – more likely SCC, or middle/lower oesophagus – more likely OAC), age, and overall health of the patient is considered. The local hospital policies, national guidelines and multidisciplinary team (MDT) will all influence the decision.

As part of the diagnostic procedure it is likely that the patient will have undergone an endoscopy procedure and had biopsies taken. An endoscope is the camera put down the throat to examine the oesophagus from the inside with some needle attachments to enable samples of the tissue to be taken (i.e. a biopsy). Removal of shallow regions of the oesophagus whilst using a camera (endoscopic mucosal resection; EMR) is often performed in early staging procedures to enable the suspect lesion to be removed and examined under a microscope.<sup>(16)</sup>

Staging of a tumour refers to the measure of the extent of spread of a cancer. The universally adopted approach is that of Tumour, Node and Metastasis (TNM) for which each part is given a score and together summarises the tumour's spread (table 1).

- 'Tumour' refers to the depth of involvement of the layers of the oesophagus. For example T1 describes a tumour that involves only the surface-most layer and as such it is more easily treated. In contrast T4 describes a tumour that has spread through the full thickness of the oesophagus and possibly into adjacent structures.
- 'Node' refers to the involvement of nearby lymph nodes. The lymphatic system helps to drain fluid from around cells and return it to the blood. It also acts as a vital component of our immune system containing these nodes in which our white blood cells identify and react to foreign harmful organisms. Due to the lymphatic system draining a region in a similar way that our veins do so, it provides cancerous cells with a motorway to spread elsewhere in the body. As part of the staging the number of these nodes involved is counted for it provides us with a proxy for the extent that the cancer may have spread.
- 'Metastasis' refers to the presence or absence of 'secondary' sites of tumour spread and would be an indicator of a poorer outlook for the patient. To assess these criteria a combination of CT-scans, PET-CT scans and endoscopic ultrasound scans are

used to provide the most comprehensive and accurate assessment from which treatment planning can develop.

Stage	Tumour	Node	Metastasis	Therapeutic options
0	Tis	N0	M0	Local ablative therapy
I	T1	N0	M0	Surgery
IIA	T2	N0	M0	Surgery
	T3	N0	M0	
IIB	T1	N1	M0	Neoadjuvant therapy with or without surgery
	T2	N1	M0	
III	T3	N1	M0	Neoadjuvant therapy with or without surgery
	T4	Any N	M0	
IVA	Any T	Any N	M1a	Chemotherapy or radiation therapy with or without surgery
IVB	Any T	Any N	M1b	Palliative Treatment

Table 1. The TNM staging system for oesophageal cancer and how it is treated.<sup>(17)</sup>

Tumour grading is also taken into consideration. This refers to the degree of differentiation of the cancer. This depicts the extent to which the now cancerous cells appear like the cells from which they originated. If they appear similar but with some difference it is deemed a low grade and therefore less aggressive. However more disorganised cells with less resemblance to their original appearance are deemed a higher grade. These are more likely to be invasive and spread to involve other layers of the oesophagus. Barrett’s Oesophagus, the pre-cancerous state often seen before OAC, frequently demonstrates a ‘high grade dysplasia’.<sup>(16)</sup> This means the cells appear disorganised with little resemblance of the normal cells and are deemed to be likely to progress to becoming cancerous. As such there is much interest in the use of endoscopic mucosal resection/submucosal dissection to remove such lesions prior to them becoming cancerous.<sup>(18)</sup>

### Therapeutic options

There are four main categories of treatment for oesophageal cancer:

- (1) *Endoscopic therapy* – removing small shallow regions of suspicious or cancerous tissue;
- (2) *Chemoradiotherapy* – consisting of chemotherapeutic drugs toxic to cancerous cells and/or radiotherapy which describes the use of X-rays to damage cancerous cells;
- (3) *Surgery* – the aim is to completely remove a tumour leaving no cancerous cells behind with minimal impact on functionality and quality of life;
- (4) *Palliative care* – when it is unlikely to cure a cancer due to the advanced nature upon diagnosis or age/frailty of the patient such that they may not be able to withstand other treatment options.

This piece lacks the breadth to sufficiently cover all these treatment modalities and focuses on the surgical techniques and future developments.

#### 1. Endoscopic therapy

As mentioned above, the opportunity to remove the cancerous tissue whilst guided by a camera that is passed down the throat is only viable for those with early and shallow tumours. It is offered when there are no nodes involved or metastases. This approach is preferred to surgery for it is less invasive and has fewer risks associated with it. Comparable outcomes in regards to survival are seen with endoscopic mucosal resection/submucosal dissection to those in surgery and are possible in the elderly or frailer population.<sup>(16,18)</sup> In addition there are newer technologies that can be used in conjunction with these approaches such as photodynamic therapy<sup>(19,20)</sup> and thermal ablation therapy including: laser, argon plasma coagulation (APC)<sup>(21)</sup>, cryotherapy and radiofrequency ablation.<sup>(16)</sup> These aim to destroy any cancerous cells and possibly any cells that may become cancerous in future such as those in Barrett’s Oesophagus. The main complications involving endoscopic therapy are the formation of strictures in the oesophagus and possibly perforation, especially when using ablation therapy.<sup>(16)</sup> For further details regarding the diagnosis and management of Barrett’s

Oesophagus and early high-grade dysplasia please see the British Gastroenterology Society's guidelines.<sup>(22)</sup>

## 2. Chemoradiotherapy in conjunction with surgery

Chemotherapeutic drugs are those that target cancerous cells. They are used to treat metastatic disease that has spread around the body for they are distributed around the body and affect all cells. The reason that cancerous cells are killed and not the majority of our non-cancerous cells lies within the action of the drugs: the majority of chemotherapeutic drugs inhibit or cause damage during the stages of replication when cells copy their DNA. The consequential damage is so great that these cells can no longer survive thus undergoing programmed cell death. Cancerous cells, by their very nature, are rapidly replicating cells that have escaped the control of the body. Thus as these cells are copying their own DNA at a rate much quicker than the majority of our body's cells they die whilst leaving our remaining cells intact. It is for this reason that people on chemotherapy lose their hair or experience extreme nausea and vomiting because the hair follicles and cells lining the gut are naturally highly replicating cells and thus are affected as much by the treatment as the cancerous cells. As with any treatment it remains a balance between the benefits and harms experienced by individual patients.

Radiotherapy refers to the use of X-rays targeted onto the cancerous lesions to cause damage and cell death. Frequently used is external beam radiotherapy in which X-rays from outside the body are targeted at the tumour. Once again damage accumulates in the targeted cells and not all of the body's cells in the path of the X-ray beam. This is managed by manoeuvring the position of the X-ray emitter such that the beam stays focused on the cancerous cells themselves. A good analogy would be that of a spotlight providing light to an actor on stage: the actor will remain in the light even if the spotlight moves as long as the operator changes the direction of the light gradually to maintain focus. Radiotherapy does cause some damage to the surrounding structures and can cause skin damage and even burning pain but once again it is dependent on individual tolerability and a balance of the benefits achieved.

Chemotherapy or radiotherapy can be applied alone or in conjunction with surgery. If given prior to surgery it is termed neoadjuvant and the aim is to shrink the tumour as much as possible to enable a simpler surgery and removal of the whole tumour. If given after surgery it is termed 'adjuvant' chemoradiotherapy. Here the aim is to target any microscopic cells that may have remained after the surgery has been completed and thus prevent these from growing and replacing the tumour that has been removed. In the most recent audit of the UK 78% of those undergoing curative surgery to remove the oesophagus also received some form of chemotherapy or chemoradiotherapy.<sup>(4)</sup>

In oesophageal SCC significant meta-analyses looking at multiple trials totalling over 1000 patients each demonstrated no benefit in radiotherapy<sup>(23)</sup> or chemotherapy<sup>(24)</sup> provision prior to surgery. However studies do exist that suggest there may be benefit to pre-op chemotherapy, especially in stage I or II oesophageal SCC.<sup>(25-27)</sup> Similarly there are studies that both support<sup>(25,26)</sup> and refute<sup>(28,29)</sup> the use of cisplatin and 5-fluorouracil based chemotherapy prior to surgery for OAC. A large meta-analysis with nearly 3000 patients demonstrated the benefits of chemoradiotherapy provision prior to surgery in both oesophageal SCC and OAC but only in OAC was pre-op chemotherapy alone beneficial.<sup>(30)</sup> In the recent CROSS trial the provision of chemotherapeutics carboplatin and paclitaxel with radiotherapy prior to surgery was compared to surgery alone in 366 patients with either oesophageal SCC or OAC.<sup>(31)</sup> They demonstrated a significant benefit in overall survival in patients receiving the chemoradiotherapy prior to surgery, consistent in both oesophageal SCC and OAC.<sup>(32)</sup> Pre-op radiotherapy alone appears to have no benefit although pre-op chemotherapy offers survival benefit in oesophageal adenocarcinoma only. Overall, it appears that the combined provision of chemotherapy and radiotherapy before surgery is beneficial in oesophageal carcinoma of any type.

Adjuvant chemoradiotherapy, i.e. that given after surgery, has been demonstrated to provide a survival advantage in adenocarcinoma of the stomach and gastro-oesophageal junction

with the benefit persisting over 10 years.<sup>(33,34)</sup> Additionally the MAGIC trial looking at epirubicin, cisplatin and 5-fluorouracil given before and after surgery for adenocarcinoma of the lower oesophagus, GOJ and stomach demonstrated that the chemotherapy group had a greater likelihood of overall survival and progression free survival.<sup>(35)</sup> It must be noted that only 42% of patients completed the chemotherapy regimen with 36% not undertaking the post-op chemotherapy. This is significant for it highlights that the extent of the insult suffered by the body following extensive surgery means that not all patients can recover in time to receive useful chemotherapy. Further, the toxicities associated may cause many patients to stop their regimes early for such is the reduction in quality of life experienced.

### 3. Surgery

If a patient has a cancer confined to the oesophagus then the most sensible approach is to remove the portion of the oesophagus affected and hence cure the patient. Such an operation is called an oesophagectomy. If the gastro-oesophageal junction is affected or the upper stomach then a partial or total removal of the stomach may also be performed. For simplicity this work focuses on the removal of the oesophagus rather than the removal of the stomach. There are two main approaches to removing the oesophagus and they differ in how access to the chest cavity is achieved: one can either enter via the chest wall (transthoracic) or from the abdominal cavity by travelling up through the hole (hiatus) in the diaphragm where the oesophagus travels so that it may connect with the stomach (transhiatal).

The most common approach is the transthoracic route but there are variations in how this is performed. The Ivor Lewis technique involves an abdominal incision and a right thoracotomy (incision through the chest wall) with the reconnection of the stomach and remaining oesophagus occurring in the upper chest. Less frequently a left thor-abdominal approach can be made, differing to the above by side of the chest incision. A 3 phase approach can also be taken: in the Mckeown technique entry into the chest is first achieved, followed by an abdominal incision, and finally an incision in the neck through which the connection between the stomach and remaining oesophagus is made. Advantages of the Mckeown technique include easier access to this connection if a leak were to occur after the operation. The choice of technique depends upon the clinical Siewert tumour type<sup>(36)</sup> reflecting its location. There are separate abdominal, chest and neck regions of lymph nodes that may be potential sites of spread of oesophageal cancer and debate continues regarding the need to remove just the abdominal and chest regions or whether or not to include the nodes of the neck.

The current death rate following oesophageal surgery is 4.3% at 90 days after the operation.<sup>(4)</sup> This, alongside 30-day mortality, has fallen from the previous audit performed 5 years previously. Nearly 4 in 10 patients (36.9%) undergoing an operation on their oesophagus will suffer a complication, with the most common being respiratory complications (1 in 5; 19.1%).<sup>(4,37)</sup> Other complications include leakage from the connection between the remaining oesophagus and the stomach, leakage from a large lymphatic vessel in the chest, wound infection or heart related problems. When using a neck incision to enable reconnection other complications, such as vocal cord paralysis due to recurrent laryngeal nerve damage, can occur.<sup>(5)</sup> Evidently such large open operations put a significant amount of stress on the body and the likelihood of complication will restrict the number of patients that are medically fit for this operation. As a consequence minimally invasive procedures have been developed.

#### 3.1 Minimally invasive surgery

Minimally invasive procedures ('keyhole' surgery) involve the use of small incisions for a camera and tools to be inserted, enabling a surgeon to operate within the body cavity. In 1992 Cuschieri *et al.*<sup>(38)</sup> described the first 5 patient series to use such an approach through the chest wall to operate on the oesophagus. This was followed in 1996 by the first removal of the oesophagus alongside the associated lymph nodes within the chest cavity using a 'thoracoscopic' or keyhole approach.<sup>(39)</sup> Soon after the first total endoscopic Ivor Lewis technique was used<sup>(40)</sup> and an approach using cameras in the chest and abdomen was described.<sup>(41)</sup> The rationale behind the interest in such techniques was the hope to minimise surgical injury and blood loss thus potentially reducing time required in intensive care and in

hospital. The main obstacle in the demonstration and acceptance of such techniques is the proof that it is at least equally likely to cure a patient of their cancer.

In the UK the use of minimally invasive approaches for oesophagectomies is increasing with 43.1% of those performed between 2012 and 2014 being minimally invasive or a hybrid combination with open surgery.<sup>(4)</sup> Evidence shows this to be an increasingly popular choice amongst surgeons reflecting the growth of supportive literature. However it must be considered that there is a possibility for a selection bias when comparing studies using the newer minimally invasive approaches; simpler cases may be selected to undergo such procedures and hence could suggest a false benefit if there were one present.

As hypothesised, a reduction in respiratory complications, blood loss, length of hospital stay and morbidity is seen in minimally invasive oesophagectomies in comparison to open surgery, as demonstrated by multiple meta-analyses that collate the data of multiple individual trials.<sup>(42-47)</sup> Despite there not being a substantial number of studies comparing long term cancer survival between minimally invasive and open oesophagectomy the 3-year<sup>(43,48,49)</sup>, 5-year<sup>(48)</sup> and average (median) survival<sup>(48)</sup> appears to be equivocal. Additionally the number of lymph nodes cleared does not differ<sup>(43,46)</sup> but there is a widely reported increase in length of the procedure.<sup>(48)</sup> One review also demonstrated an increased likelihood of narrowing (strictures) occurring at the connection between the oesophagus and stomach in the minimally invasive approach.<sup>(43)</sup>

The technicalities of such approaches have also been studied and it appears that the patient lying on their front (prone positioning) on the operating table is beneficial through allowing better oxygen supply, less compromise of lung function, a better view of the anatomy for the surgeon, less blood loss and enables more lymph nodes to be removed.<sup>(50-57)</sup> Comparisons of the 2-phase Ivor Lewis approach and the 3-phase Mckeown minimally invasive approaches have been made. In a review of over 1,000 patients there was no difference in mortality or retrieval of lymph nodes between the approaches but the Mckeown method had an increased risk of recurrent laryngeal nerve damage and leakage from the new oesophagus-stomach junction.<sup>(58)</sup> A more recent individual study also suggested there may be an increased risk of respiratory complications and morbidity.<sup>(59)</sup> Overall minimally invasive techniques are beneficial: they reduce the length of hospital stay and size of surgical injury with at least comparable cancer survival outcomes.<sup>(60,61)</sup> Perhaps an Ivor-Lewis approach is favourable but only upon considering the frequency of recurrent laryngeal nerve injuries.

Inherent drawbacks persist in minimally invasive surgery: the surgeon's view on a camera screen is 2D and not 3D thus impacting upon depth perception; the visual field may be limited due to positioning of the scope; the sense of touch is lost with no tactile feedback to aid exploration of anatomy; and there is disconnection between hand-eye co-ordination.<sup>(62)</sup> Nevertheless with training and practise these challenges can be overcome. Specialised surgery of the oesophagus should be performed at high volume tertiary referral hospitals with specialised multi-disciplinary teams and skilled surgeons who perform such operations at least 20 times per year for this minimises the rate of complications and maximises the efficiency of resource usage.<sup>(16,37,63)</sup> This extends further to the use of robotics where the 'centralisation' of resources and skills enables greater efficiency of time and resources alongside improved patient outcomes.<sup>(64)</sup>

### 3.2 Robotic Surgery

The development of the widely publicised Da Vinci robot (figure 1; Intuitive surgical, Inc., Sunnyvale, CA, USA) has opened a range of possibilities to surgeons. The use of a robot is an extension of the principle of minimally invasive techniques with initial application to oesophageal surgery occurring in the early 2000s.<sup>(65-67)</sup> The surgeon operates the 'arms' to perform the surgery observing the anatomy via an inserted camera. The benefits of such an approach include improved ergonomics of the instrumentation enabling more adequate positioning and reduced surgeon fatigue.<sup>(61)</sup> High magnification can allow close visualisation of structures within the chest that may be of particular benefit when the structures are moving during breathing. New technologies involve the use of binocular cameras to enable depth perception and improved instrument movement to better mimic the action of a surgeon's

hands.<sup>(5,61)</sup> In addition, new techniques such as tremor suppression can enable precise surgery with exact motions.<sup>(5,61)</sup> With adaptations such as these, perhaps there is a role for the use of robotics within oesophageal surgery.

Very few trials comparing the use of robotic assisted oesophageal surgery have been conducted so far and with small numbers of patients involved it is hard to draw any significant definitive conclusions. This reflects the infancy of robotic use in this field making it at the forefront of surgical development. Nevertheless there are many single centre case reports of individual experiences and initial comparisons in oncological outcomes such as resection margins and post-operative complications. Robot assisted minimally invasive (o)esophagectomy (RAMIE) has been applied using a trans-hiatal<sup>(68)</sup>, 3-phase Mckeown<sup>(69,70)</sup> and 2-phase Ivor-Lewis<sup>(64,71-74)</sup> approach with some combined laparoscopic and robotic (hybrid) approaches.<sup>(75)</sup> There appears a similar tendency for preferential use of the Ivor-Lewis 2-phase (abdominal and chest) approach with robot assistance matching the tendency for Ivor Lewis preference in minimally invasive techniques.<sup>(4)</sup>

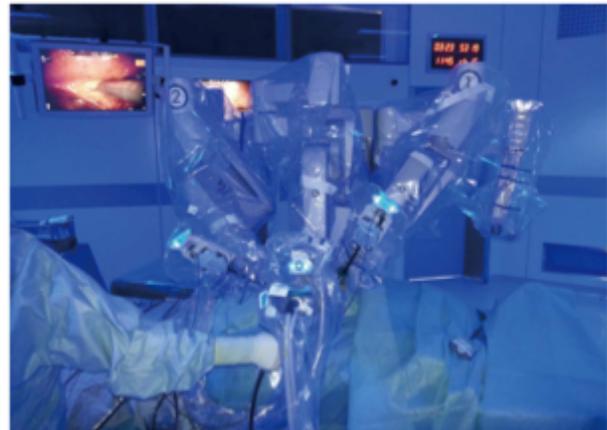


Figure 1. The Da Vinci robot docking during the removal of an oesophagus.<sup>(77)</sup>

Robotic use in transhiatal oesophageal surgery over a 3-year period involving 40 patients demonstrated that clear resection margins (i.e. complete tumour removal) could be achieved in 94.7%.<sup>(68)</sup> However 25% experienced leakage at the connection of the stomach to the remaining oesophagus and 35% suffered recurrent laryngeal nerve paresis.<sup>(68)</sup> Despite patients regaining vocal cord function and healing of the leakage these complications were at a rate greater than those in the literature regarding minimally invasive transhiatal surgery. The authors concluded that robotic use remained a viable approach that should be considered but refinement of technique and increased experience may be required. A recent review considering such an approach included 5 papers (including that mentioned above) with a total of 118 patients demonstrated that a reduced duration of operation could be achieved vs. approaches via the chest with blood loss limited to 100ml or less.<sup>(5)</sup> Complication rates were similar in minimally invasive and robot assisted abdominal entry only operations, although a greater number of post-operative hiatal hernias were demonstrated in one study. Further, the success of the removal of cancer and associated lymph nodes was only reported in 3 of the papers although in these there appears at least comparability to existing procedures.<sup>(5)</sup> Long-term survival was not recorded in any of the studies due to limited length of follow-up thus there remains a need for properly organised randomised controlled trials with suitable follow-up.

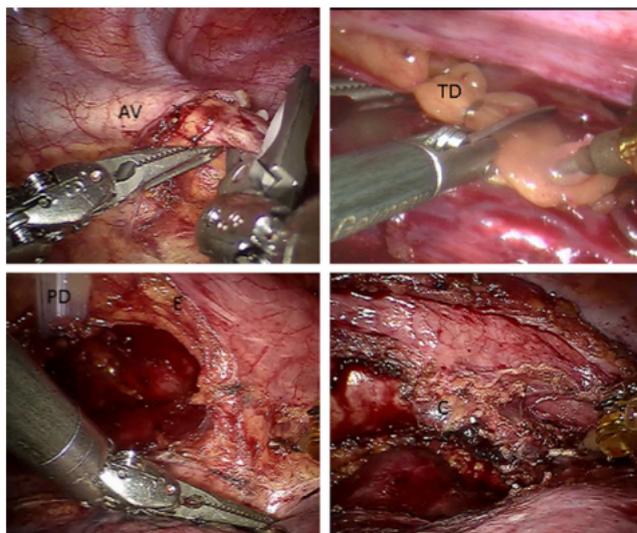
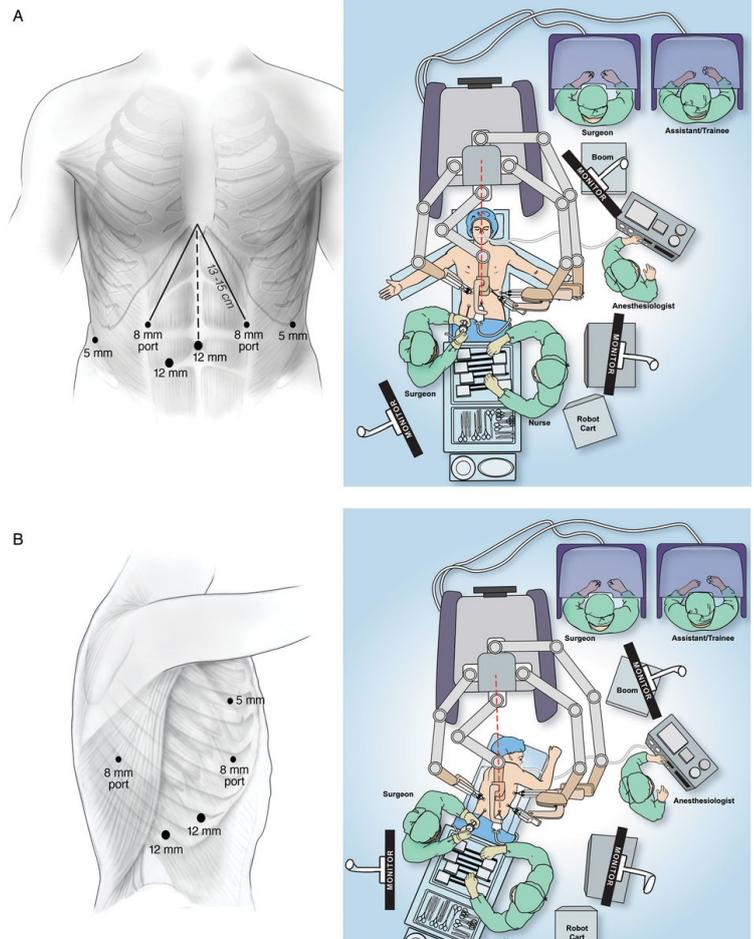


Figure 2. The chest stage of a Robot Assisted Minimally Invasive Oesophagectomy (RAMIE). The azygos vein (AV), thoracic duct (TD) - a large lymphatic vessel, a Penrose drain (PD), the oesophagus (E) and the carina (C) are labeled.<sup>(5)</sup>

RAMIE via a 3-phase Mckeown approach in 47 patients resulted in lung complications in 21 (44%) of patients and a post-operative mortality of 6% that is comparable with outcomes in open surgery.<sup>(69)</sup> Again despite short-term equivalence in completeness of tumour removal there is a deficiency in long-term follow-up.

The evidence available suggests there is equivalence between minimally invasive techniques and robot assisted Ivor-Lewis oesophagectomies regarding complication rates, length of hospital stay and successful excision of cancer.<sup>(70-74,76)</sup> There is a significantly longer duration of operations using robotic assistance, which was demonstrated to reduce over time as the surgeon's experience with robotic surgery increased.<sup>(74)</sup> This suggests that perhaps equivalence in procedures at present with lesser experience using robotics could enable improvements in the future if robotic surgery were to be as widely used and accepted as that of endoscopic surgery. The most common complications were related to respiratory illness, anastomotic leak/stricture, heart related (mostly atrial fibrillation) and the presence of lymphatic fluid in the chest (chylothorax)<sup>(5,61,74,77)</sup> although these remained equivalent to those experienced in open operations. However the length of hospital stay and time required in intensive care remained within the expected ranges.<sup>(5)</sup> For a schematic of theatre set-up see figure 3.



**Figure 3. The positioning of a 4-arm robot, the attending surgeons and theatre staff during (a) the abdominal phase and (b) the chest phase of the removal of an oesophagus<sup>(70)</sup>**

Overall there appears to be equivalence but no demonstrable benefit in the use of robot assistance in minimally invasive oesophagectomy regarding removal of the cancer and lymph nodes, complication rates and duration of hospital stay. At present it cannot be commented upon whether or not robotics offers any advantage in long-term survival for there remains a lack of long-term, multicentre randomised controlled studies. Recently a large single-centre trial has been initiated with a minimum 5-year follow-up to attempt to bridge this gap.<sup>(64)</sup>

The combination of robotic Ivor-Lewis oesophagectomy with neoadjuvant chemoradiotherapy (NCR) demonstrated no difference in operative outcomes such as frequency of complication, completeness of resection or duration of hospital stay but long-term survival differences have not been reported as yet.<sup>(78)</sup> One would hypothesise that there is some survival advantage in providing neoadjuvant chemoradiotherapy given that patients who demonstrate response to NCR have improved overall survival and disease free survival.<sup>(79,80)</sup>

It is suggested that there may be a reduced learning curve required to become proficient at robotic surgery as opposed to minimally invasive endoscopic approaches for oesophagectomy<sup>(73,77)</sup> with the use of dual operating consoles enabling structured learning during robotic surgery.<sup>(71)</sup> This would increase the number of surgeons with proficiency which one can only assume to be beneficial. The cost of the robot and associated equipment is considerable and likely a limiting factor regarding its implementation.<sup>(73)</sup> Additionally the increased duration of theatre time required increases the expenses associated. There remains a monopoly in the market with Intuitive Surgical<sup>(5)</sup> but perhaps once patents expire there will be increased competition and supply to thus meet the demand.

### 3.3 Virtual and Augmented Reality in surgery

In our exceedingly computerised world it is now possible to use pre-operative CT and MRI scans to construct a virtual 3D model of individual patients using virtual reality software (figure 4). This allows the anatomy to be virtually explored by surgical teams enabling them to plan their approach suitably and identify any anatomical variations that may otherwise complicate the picture during surgery.<sup>(62,81,82)</sup> The synthetic image produced can be superimposed upon real-time images from surgery.<sup>(62)</sup> This Augmented Reality (AR) has been applied to brain<sup>(83)</sup> and maxillofacial surgery<sup>(84)</sup> where fixed bone and surrounding soft tissues enable accurate navigation for surgeons. Complications arise when applying this to oesophageal surgery for the margins depicted by the scans are between similarly dense soft tissues rather than between bone and say fat which appear very different in the resultant images. To further complicate matters, movement of soft tissues is experienced during surgery in the chest as a consequence of the effort to breathe and actions of the surgery itself deform the anatomy from its original structure thus limiting the use of pre-operative imaging.

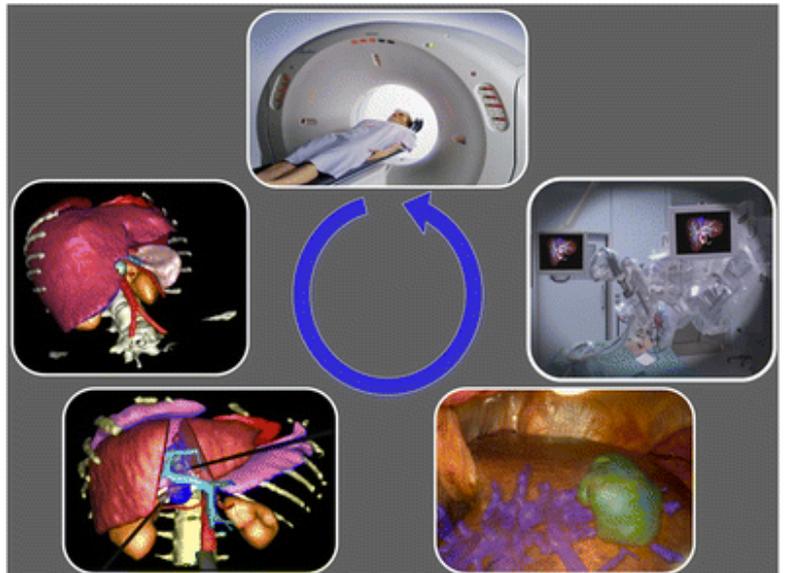


Figure 4. A depiction of the involvement of computer-assisted surgery. Initial CT/MRI scans enable a virtual 3D model to be produced which can be explored pre-operatively and superimposed upon the anatomy during surgery.<sup>(86)</sup>

Different technical approaches exist that can be used to map visual input and produce visualisation of structures. Rendering refers to the generation of a 2D or 3D image from a data file involving specifics of the scene to be depicted such as the geometry or visual characteristics. Direct volume rendering is an approach that allocates an optical property e.g. colour to data but its use is limited to when there is a significant difference in the contrast of tissues such as in some tumours or blood vessel anomalies.<sup>(62)</sup> By contrast, surface rendering creates a 'structure' that encompasses an organ's surfaces and thus enables 3D visualisation.<sup>(62)</sup> The difficulty arises when trying to demonstrate the synthetic picture on the live anatomy in such a manner that it reflects the surgeon's point of view but not impeding their 'true' vision. Projectors can be used but struggle to demonstrate a true 'surgeon's eye' view. Currently real-time video images from an endoscopy camera or head-mounted camera can allow superimposition of the virtual image. This is especially applicable in robotic surgery

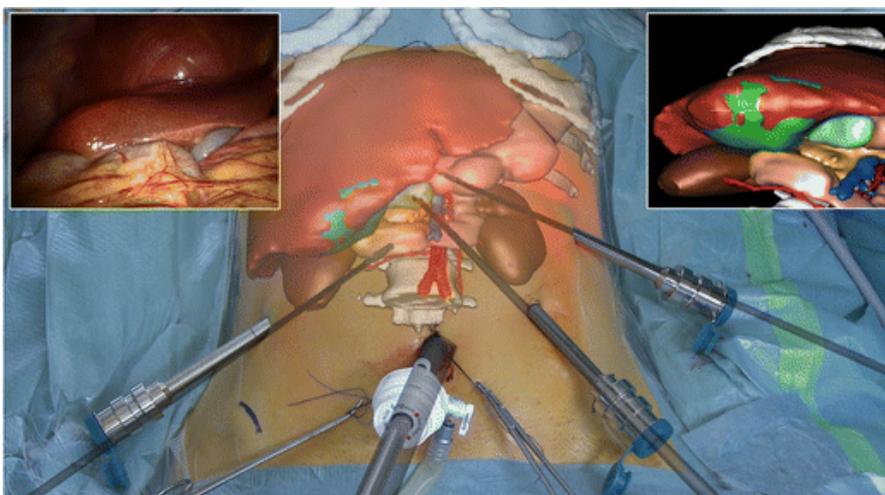


Figure 5. Projection of a virtual reproduction of the anatomy of the patient is projected onto their skin to enable optimal positioning of instruments.<sup>(86)</sup>

where camera operation provides the surgeon's view and as such the real and synthetic views can be combined to enable a better-informed view. Additionally the projection of the virtual image onto the patient's surface may enable more accurate placement of the robotic arms (figure 5). Such approaches have been performed successfully in robotic liver surgery<sup>(85,86)</sup> and could have future applications in RAMIE.

## Conclusion

Oesophageal cancer of any form is an unforgiving illness that is associated with late identification and consequential poor survival.<sup>(3)</sup> Surgery is the main curative approach for locally advanced cancer that has not yet spread to other sites but it is still a developing field and far from perfect. Nevertheless the widely accepted and practised concepts of minimally invasive surgery appear to reduce the number of complications and length of hospital stay whilst maintaining effective removal of the tumour. The exciting future with robotics is becoming a reality that will hopefully improve with experience and opportunity. At present there is a deficiency of studies large enough to truly compare the effectiveness to that of minimally invasive surgery although some studies are currently underway.<sup>(64)</sup> Case series and initial data suggest that it may be at least equivocal in outcomes with a potentially smaller learning curve than in minimally invasive surgery. Additionally the use of augmented reality, which would have been a video game concept not long ago, is now very much a reality with an astounding range of potential applications both before and during surgery. The largest caveat is cost effectiveness due to the significant investment in training and technology required for robotics and computerised input. In our era of austerity the juxtaposition of what we intellectually/surgically can achieve and the reality of economics will evoke passion and debate. The technology is exciting and promising but full realisation lies just beyond the horizon; lets hope medicine crosses that horizon.

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