Techniques for Managing Esophagectomy:
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Critical Learning Objectives
- What are the key challenges in managing patients presenting for esophagectomy?
- Identify specific strategies to reduce pulmonary morbidity
- Discuss how fluid management impacts anastomotic healing
- Describe utility of anesthesia led pain management for esophagectomy patients

Outline of Syllabus:
1. Introduction and Epidemiology
2. Development of Surgical Approach
   a. Evolution of the minimally invasive approach
3. Key perioperative issues leading to morbidity / mortality
   a. Anastomotic Healing
   b. Intraoperative fluid management
      i. Impact on pulmonary outcomes
      ii. Utility of Goal directed therapy
   c. Intraoperative ventilation management and pulmonary outcomes
   d. Postoperative management
      i. Impact of pain management approaches in open vs minimally invasive surgery

Introduction to the Clinical Problem:
Esophageal Carcinoma is a highly lethal disease that affects thousands of patients annually. 5-year survival rates have improved over 30 years from 5% up to 19% [1], along with improvements in operative mortality for esophagectomy, which now ranges from 8-11%[2,3]. Roughly 17,000 patients are diagnosed annually in the US and > 15000 patients die each year[4].

The majority of esophageal tumors are either squamous cell carcinoma (SCC) or adenocarcinoma, each of which has distinct treatment options. SCC is associated with tobacco or alcohol use; begins as epithelial dysplasia before evolving to carcinoma and finally becoming invasive. Perioperative mortality is higher for SCC, often due to the location of the tumor, which is typically above the tracheal bifurcation in the upper third of the esophagus [4] (Figure 1). Adenocarcinoma, in contrast, typically arises from sequelae of GERD and the development of Barrett’s esophagus. Because of the etiology adenocarcinoma lesions are typically located near the GE junction with a concomitant improvement in operative mortality [4].
Overall therapy remains debatable and depends on type and extent of cancer lesions emphasizing the importance of accurate tissue diagnosis and staging. Currently, multimodal therapy including chemotherapy, radiation and surgical resection exists as the best overall option for many patients. Trials focusing on tumors at the esophagogastric junction versus the upper esophagus are not well differentiated thus it is difficult to make a blanket statement about ideal therapy. There have been a number of meta-analysis publications attempting to answer this question and each has looked at surgery vs combined chemoradiotherapy plus surgery [5-8]. The largest of these analyses reported a survival benefit of 8.7% at two years time point, and appeared similar in both adenocarcinoma and SCC [7]. In addition, this benefit was not offset by the higher operative mortality associated with surgical resection. Finally, while surgical resection has historically been standard, and remains so today, there is increasing evidence that chemoradiotherapy can achieve survival rates at 5 years of up to 27% in select groups of patients, which calls into question which cases should have surgical management [4]. The remainder of this review will focus on surgical techniques assuming either primary resection or combined neoadjuvant chemoradiotherapy with surgery.

**Surgical Approach:**

Esophagectomy has been evolving for over 100 years, and has been performed with multiple approaches including right of left thoracotomy, cervical, abdominal, minimally invasive, or a combination of all of these. Early operations carried out in the late 1800’s up until 1912 did not attempt to restore continuity between the pharynx and the mouth. Progressive operations during the early 1900’s up to 1930’s utilized a staged approach to restore continuity, while the major progress of immediate reconstruction and restoration of continuity occurred in the mid 1930’s [1].

Dr. Billroth (also an accomplished pianist, violinist and composer) was one of the early pioneers who developed cervical techniques to mobilize the esophagus and along with Dr. Czerny who is credited with the first local excision of esophageal carcinoma (the patient survived one year). Billroth himself resected a more extensive lesion two years later but the patient died of associated mediastinitis.

Dr. Franz Torek is credited with the first resection of a mid esophageal carcinoma which was carried out in 1913 utilizing a left transpleural approach. The upper portion of the esophagus was brought out of a cervical incision; the lesion was excised, and tunneled under the skin to make an esophagostomy stump. The distal portion was managed through the transpleural approach and tied off as for an appendix stump. Following the 2 hr 43 minute procedure, during which the anesthetic consisted of 100 ml of ether delivered through a woven silk tube for intubation and spontaneous ventilation (the Meltzer-Auer method), the patient was given a coffee enema (to induce bowel mobility) and strychnine to elevate the blood pressure. One week later the stump was connected to the gastrostomy by a rubber tube. The patient refused any further reconstructive surgery for the conduit, and lived 13 years before dying of unrelated causes.
Additional major advances in the early 1900s include development of the transpleural resection, initially carried out by Dr. Ohasha in Japan. Dr. Ohasha is credited with the first thoracic resection of carcinoma and immediate reconstruction of the esophagus, and utilized free thoracotomy without positive pressure ventilation, (which did not become standard for a number of years). This was followed in the west in 1937 when Dr. Marshall, as well as a separate team Drs Adams and Phin reported on successful resections and reconstruction in the lower third of the esophagus. Interestingly, Dr. Seo, also from Japan, reported a review of the world literature up to 1932 and demonstrated a mortality of 144 / 155 patients (95.4%) [9]. Ivor Lewis described his work on resection of the middle third of the esophagus in 1946 using a right-sided two-phase approach that is a standard still today. Simultaneous development of the pull through technique from the cervical approach- initially by Denk, and subsequently developed by Dr. Grey-Turner, coupled with direct approaches allowed the further development and improvement noted in the 1940’s and 50’s. In fact, by 1954, Garlock and Sweet both reported surgical series on 75 patients with 33% mortality and 287 patients with 18% mortality respectively [1]. Japan, with its high incidence of carcinoma, allowed for great refinement in technique, with Dr. Nakayama (student of Ohasha) reporting on 953 resections with a 5-8 % operative mortality.

Current surgical approaches utilize various components of these early approaches based on tumor location and planned operation. The Ivor Lewis technique (transthoracic esophagectomy through right thoracotomy) (illustrated in Figure 4) is most successful in lesions involving the upper 2/3 of the esophagus, Barretts, or caustic ingestion complications of the lower esophagus [10]. A left sided thoracotomy approach may be more useful in cases involving the distal esophagus, GE junction and gastric cardia. The transhiatal esophagectomy without thoracotomy remains a useful technique for curative or palliative procedures, with the limitation of limited ability for full lymphadenectomy and lack of visualization of the thoracic esophagus. A tri-incisional technique is also employed by some surgeons which gives the advantage of the Ivor Lewis approach, along with a cervical esophagogastric anastomosis which is then outside the radiation field for multimodal therapy. Finally, since the 1990’s, laparoscopic techniques have allowed for development of esophagectomy by minimally invasive approach. Minimally invasive approaches exist for both the Ivor Lewis procedure, as well as the tri- incisional version combining thoracoscopic / laparoscopic mobilization with the cervical incision / anastomosis. Early results are promising, but there remain significant challenges to both the surgeon and anesthesia teams using minimally invasive approaches.

**Key perioperative issues leading to morbidity / mortality**

The remainder of this syllabus will focus on the specific issues that have direct impact on morbidity and mortality for esophagectomy patients. While the impact on mortality may be relatively limited in this regard, there is ample room to minimize the significant morbidity found...
in following esophagectomy, namely pulmonary complications, and anastomotic healing. Anesthetic management impacts these areas through ventilator management combined with pain management strategies, as well as overall fluid and hemodynamic management.

Anastomotic healing is clearly one of the major risk factors for overall reduced clinical outcomes, and the mechanism behind ideal wound healing is multifactorial. Anastomotic leak rates range from 10-37% looking at both cervical and thoracic sites, and those patients with anastomotic leaks accounted for over 35% of the reported mortality [2]. Morbidity following anastomotic leak depends on site of the leak, with thoracic lesions carrying a higher risk. Fortunately, new approaches to managing these complications include use of esophageal stents to treat the leak, which may prove to be greatly advantageous to future patients [11]. As the anastomotic site is typically quite distal to the blood supply, this injury site is predisposed to poor vascularity and healing. Wound – tissue oxygenation is therefore a fundamental concern, and multiple theories exist in terms of management. Using intestinal tonometry, previous investigators have measured Δ pCO2 levels which is reflects local tissue anaerobic metabolism. At the site of the anastomosis, ΔpCO2 peaked within 24 hours and returned to baseline on POD 4, suggesting that the greatest risk was within the first 24 hours [12], and that an oxygen debt or recovery period existed for up to 4 days. Two surgical techniques may improve blood flow: supercharging (adding additional vessel conduits to pedicle) and ischemic preconditioning (utilizing concept of temporary ischemia to tissue prior to actual disruption of blood flow). Anesthetic management can have an effect here by interacting with vasomotor tone (thoracic epidural) or through infusion of vasodilators such as nitroglycerine[2]. Thoracic epidural use has some evidence to support improvement in anastomotic healing via improved microvascular circulation[13,14]. It also plays a key role in pain management and pulmonary recruitment postoperatively and will be discussed in later sections.

Vasopressor use during surgery, along with techniques for hemodynamic and fluid management, plays an enormous role in anastomotic outcomes. There is both animal [15] and human data [16] indicating that significant reduction in anastomotic perfusion occurs with use of vasopressors such as norepinephrine in the setting of acute blood loss. However in the normovolemic model, it appears that use of norepinephrine does not impair anastomotic blood flow by laser speckle imaging [17], thus making overall conclusions on management here difficult. This study also demonstrated that artificially elevating blood pressure to augment flow does not provide any benefit in anastomotic blood flow in the esophagus; the converse however is not true as hypotension results in reduced anastomotic blood flow. Importantly for anesthesiologists, management of hypotension associated with anesthesia related decreases in SVR can be safely accomplished using short-term infusions of phenylephrine. A study in myocutaneous free flaps demonstrated no difference in flap blood flow with use of moderate doses of phenylephrine (1 ug/kg/min infusion) [18]. One key management detail that has been clearly demonstrated in the above studies is that significant reductions in anastomotic blood flow occurs in the setting of hypotension, so this state must be avoided.

Given that vasopressors in hypovolemia are detrimental, yet probably acceptable in a normovolemic state, this leads to the question of ideal fluid management. Esophagectomy is a challenge as the open surgical wound and extensive operative dissection generates evaporative losses requiring replacement; yet there is also the thoracic aspect using one lung ventilation and the associated potential concern for increased lung water / edema. General surgery fluid
management has classically involved aggressive fluid therapy to maintain circulating blood volume given the fasting fluid deficits, bowel preparation, and evaporative losses. Also of concern is third space loss, which is based on data using various blood volume tracers demonstrating a reduction / contraction in extracellular volume (ECV) not accounted for by blood loss [19]. This third space theory has long been held true and served as the basis for intraoperative fluid therapy; yet it may be based on entirely flawed data. Meta analysis data by Brandstrup et al in 2006 looked at 61 trials that measured ECV in various hemorrhagic models to determine the plausibility of the existence of the “third space” [20]. A direct quote from the overall conclusions of this paper describes the outcome very eloquently:

“In summary, the finding of a contraction of the ECV caused by operation or hemorrhagic hypotension is based on 5 experimental and 5 human studies. Common for these trials are the use of a SO4 tracer, and the calculation of the ECV from a single or very few blood samples obtained after 20 to 30 minutes of equilibration. These findings have not been reproduced by trials using multiple sampling, longer equilibration times, different tracers, or kinetic analysis. The general understanding that hemorrhage and operation causes a contraction of the extracellular space needing replacement probably is based on flawed methodology.” From: Brandstrup B, Svensen C, Engquist A Hemorrhage and operation cause a contraction of the extracellular space needing replacement--evidence and implications? A systematic review. Surgery 2006; 139: 419-32.

If in fact, the so-called “third space” does not exist, then it brings into question much of the classic fluid resuscitation practices taught in anesthesiology residency. There are now numerous trials in general surgery populations demonstrating the utility of a restrictive fluid management protocol. Of concern here, is the use of the terms liberal vs restrictive therapy, as there is significant variability from trial to trial. A 2009 review[21] summarized findings of seven randomized trials looking at liberal vs restrictive fluid therapy. Liberal management resulted in fluid administration ranging from 2750 – 5300, while restrictive management was 998 – 2240ml. Trials included general surgery and orthopedic surgery and looked at multiple outcomes including return of GI function, length of hospital stay, overall pulmonary function, postoperative hypoxemia, nausea, and pain. As all seven of these randomized trials used different definitions for liberal vs restrictive as well as focusing on various outcomes, no conclusion could be drawn from the standpoint of one uniform approach to fluid therapy. There have been two publications specifically on the fluid management in esophagectomy [22,23], however both are case series. Kita et al, compared one group managed by a relatively liberal fluid management to a second group started at a subsequent time point that was managed with a restrictive strategy. They demonstrated that the restricted group (which received 749 ml IV fluid compared to 2386 ml in the liberal group) showed reductions bronchoscopic suctioning post op, extubation failure, need for tracheostomy, as well as a reduced hospital LOS [22]. Neal and Wilcox reported on the use of a multimodal approach to managing esophagectomy patients, which included a “restrictive” fluid management approach, however this study was in only 56 patients without a comparison group so meaningful conclusions can not be drawn[23]. Confusing this issue of course it the debate on type of fluid used (colloid vs crystalloid). There is some evidence for improved anastomotic wound healing using colloids [2], however the evidence is not overwhelming and this topic is beyond the scope of this talk.
Where does this leave us in deciding how to manage the patient for esophageal surgery? Based on the above discussion, avoidance of gross fluid overload seems to be the most prudent approach. There has been continued interest and debate about individualized fluid management to optimize hemodynamics based on the concept of the Frank Starling curve. While use of pulmonary artery catheters was an improvement over central venous pressure, which does not assist in blood volume assessment, the PAC itself seems to confer risk in the general patient and thus is not encouraged. Current approaches to goal directed therapy includes using esophageal Doppler monitors, and arterial waveform analysis to generate stroke volume variation or pulse pressure variation. Multiple systems exist and evidence is mounting as to the utility of these monitors in complex surgical patients outside of the cardiac room. Esophageal Doppler is perhaps the most promising, however hardly an option for the esophagectomy patient. Options for measuring this include the Flo-trac, LiDCO and PiCCO systems. Each of these is based on algorithms that use the change in respiratory pattern induced alterations of the pulse wave contour to predict stroke volume and therefore fluid status. There is good evidence for improved perioperative outcomes in various surgical populations including septic shock, in patients treated with goal directed therapy [24]. Recently, Bisgaard et al published a report on utility of the LiDCO system in optimizing stroke volume and oxygen delivery in open abdominal aortic surgery. The authors did demonstrate an improvement in oxygen delivery indices, but failed to show any difference between the intervention groups. Interestingly, total fluid variations between the groups was minimal and only differed in the first 6 hours post op (by 600 ml)[25].

A final consideration for goal directed therapy and using stroke volume variation is the impact of one lung ventilation (OLV) on this measured parameter. Recently, Haas et al published a small study comparing the use of goal directed therapy between lung resection patients and esophagectomy patients. They collected fluid administration data, as well as complete metabolic and lung oxygenation indices (including extravascular lung water index). They did not find any difference in extravascular lung water index between these two groups, or between any of the measured parameters, suggesting that this approach may be valid in OLV despite the alterations in thoracic pressures[26].

**Pulmonary Outcomes and the Anesthesiologist:**

Pulmonary complications are reported to be the most frequent adverse event following esophageal surgery in multiple reports ([27-31]. Prevention of pulmonary morbidity following esophagectomy is potentially one of the largest areas that the anesthesiologist can impact patient outcomes and depends on ventilation management, fluid management and postoperative pain management.

Ferguson et al reported on predictive factors for development of pulmonary complications (defined as need for reintubation, prolonged ventilation, and pneumonia) in a retrospective study of cases from 1980 – 2009 (n=516); 38% of patients developed major pulmonary complications and these patients demonstrated an increase in operative mortality of 10fold. Independent risk factors by multiple logistic regression analysis for increased risk of pulmonary complications include: increased age, reduced lung function as measured by FEV1% or DLCO %, elevated serum creatinine, reduced physical performance status, current smoker and use of
thoracotomy. These parameters can serve as a useful guide for patients at increased risk for problems.

Clearly development of acute lung injury (ALI), or acute respiratory distress syndrome (ARDS) is associated with extremely high mortality. This is thought to occur in roughly 10% of esophagectomy patients and mortality exceeds 50% [29]. Clear evidence exists in ventilator management for ARDS is critical and should employ lower “lung protective” tidal volumes (4–6 cc/kg), along with use of PEEP and limitations to peak and plateau pressures [32]. The inflammatory response to ventilation mediated through interleukins, has been shown to be elevated with mechanical ventilation, OLV, as well as simply due to esophagectomy [31]; and is associated with lung injury. Michelet et al demonstrated a reduction in interleukin levels during OLV in 2006 by using a lung protective strategy. Interestingly pre-OLV tidal volumes for both groups were 9 cc/kg, while during OLC the protective group was ventilated with 5cc/kg plus 5 cmH20 PEEP.

While there are numerous reports in a variety of animal and human models on the inflammatory response to ventilation, it does remain unclear if reduction in interleukin production has a direct effect on patient outcomes [2]. With that in mind, current recommendations to reduce this response follows the concept of ARDS management and represents a departure from the classic ventilation management during OLV that has been presented in many anesthesiology textbooks over time. Key management details are:

- 4-6 cc/kg tidal volumes using pressure controlled ventilation
- Optimization of PEEP (remember that PEEP will increase the shunt fraction to some degree)
- Limit peak pressures to < 35 mmHg and plateau pressure < 25 mmHg

Pain Management:
Clearly intraoperative management is critical, but postoperative pain control is a key aspect in anesthetic planning. The use of thoracic epidural analgesia has been demonstrated in multiple trials involving abdominal and thoracic surgery and as such should be considered standard of care for esophagectomy [13,14,23,27,33-35]. Some of the potential advantages in epidural use include improved blood flow to the anastomotic site as discussed above[13,14], as well as earlier extubation times and reduced pneumonia rates[2]

Many institutions are now employing an anesthesiology based acute pain service, which manages patients with indwelling epidural catheters. Along with epidural catheter placement, use of multimodal therapy may well add to the efficacy in managing post operative pain, and potentially mediate the development of chronic post thoracotomy pain syndrome[36]. Based on experience in orthopedic joint replacement and thoracic procedures, various protocols have been developed to manage these patients. An example of the protocol developed by Dr. Matthew Fiegel for use at University of Colorado Hospital is as follows:
VATS

Preoperative Holding Area: Goal: Have adjuvant/neuromodulatory medications on board before pt leaves preop
1. Oxycodone extended release 20 mg PO if <70 y.o. and 10 mg PO if ≥70 y.o.
2. Celecoxib 400 mg PO if <70 y.o. and 200 mg PO if ≥70 y.o.
3. Pregabalin 150 mg PO if <70 y.o. and 75 mg PO if ≥70 y.o.

-Intraoperative: Goal: Early dosing of epidural for decreased signal propagation and systemic opiate usage
1. No intraoperative ketorolac
2. Intercostal blocks by surgeon
3. APAP 1000mg IV

Post Anesthesia Care Unit (PACU): Goal: Have functioning IVPCA or alternative plan before the patient leaves PACU
1. For pain score ≥4/10, preferred order for medication administration is:
   a. Ketonolac 15 mg IV x 1 PRN
   b. IVP analgesics as normally ordered on PACU post orders. Start IVPCA before discharge.

Nursing Unit: Goal: Durable pain relief for improved pulmonary mechanics and decreased incidence of post-thoracotomy syndrome
1. IVPCA
2. Acetaminophen 1000 mg PO (or IV if NPO) TID
3. Either
   a. Ketonolac 15mg IV Q6hrs PRN X 48hrs or
   b. Celecoxib 200 mg PO BID if <70 y.o. and 100 mg PO BID if ≥70 y.o.
4. Pregabalin 75mg PO daily until discharge

Thoracotomy

Preoperative Holding Area: Goal: Have adjuvant/neuromodulatory medications on board before pt leaves preop
1. Oxycodone extended release 20 mg PO if <70 y.o. and 10 mg PO if ≥70 y.o.
2. Celecoxib 400 mg PO if <70 y.o. and 200 mg PO if ≥70 y.o.
3. Pregabalin 150 mg PO if <70 y.o. and 75 mg PO if ≥70 y.o.

-Intraoperative: Goal: Early dosing of epidural for decreased signal propagation and systemic opiate usage
1. No intraoperative ketorolac
2. Dosing of epidural within 30min of incision
   a. Opiate per anesthesiologist discretion
   b. Local anesthetic per anesthesiologist discretion
3. Re-dosing of epidural at beginning of closing
   a. Local anesthetic per anesthesiologist discretion
4. APAP 1gm IV

Post Anesthesia Care Unit (PACU): Goal: Have functioning PCEA or alternative plan before the patient leaves PACU
1. Immediate dermatome assessment by PACU nurse
   a. Call APS #83324 if dermatome inadequate to cover incision
   b. Begin PCEA with as little delay as possible
      i. Dosing suggestions
         1. Rate 6mL/hr with range from 4-10mL/hr with 3mL bolus
            a. Bupivicaine 0.1%
            b. Hydromorphone 6mcg/mL (can adjust for chronic narcotic use)
   2. Ketonolac 15mg IV for shoulder/chest tube pain X 1
   3. If rescue IVP pain meds necessary, please notify APS before patient leaves PACU

Nursing Unit: Goal: Durable pain relief for improved pulmonary mechanics and decreased incidence of post-thoracotomy syndrome
1. Acetaminophen 1000 mg PO (IV if NPO) TID
2. Ketonolac 15mg IV Q6hrs X 48hrs
3. Then Celecoxib 200 mg PO BID if <70 y.o. and 100 mg PO BID if ≥70 y.o.
4. Pregabalin 75mg PO daily until discharge
5. APS to manage PCEA

Coordination:
To maintain consistency and clarity all thoracic patients with an epidural will be managed by the Acute Pain Service (APS) even if they do not adhere strictly to the above protocol. After the epidural is removed, the APS will coordinate with the Thoracic teams the time frame for APS sign off service and turn over of pain management.
Minimally Invasive Esophagectomy (MIE):
Some of the most exciting surgical innovations in esophageal cancer surgery exist in the development of improved laparoscopic and robotic techniques. This approach allows for completion of the classic Ivor Lewis operation through the use of multiple port sites (can be as many as 9-10) in the thoracic and abdominal region. Advantages include reducing the thoracotomy/abdominal incision size, reducing blood loss, reducing inflammatory response, and improving postoperative outcomes. Sihag et al recently published surgical results comparing outcomes in open vs minimally invasive Ivor Lewis procedures[37]. They demonstrated no difference in operative time, adequacy of oncologic resection or 60-day mortality. They did find reductions in blood loss, ICU LOS, hospital LOS, and intraoperative IV fluid requirements in the MIE group compared to the open group. Using multiple logistic regression, they identified MIE to be the only independent variable associated with improvement in pulmonary morbidity. Postoperative pain management consisted of epidural catheters in the open group, and IV PCA pain control in the MIE group.

There is a relative paucity of data regarding MIE so making conclusive recommendations on ideal management is challenging. We do understand from experience in video assisted thoracoscopic surgery, that development of chronic neuropathic pain still exists despite avoidance of the classic thoracotomy[36], and so presumably this same phenomena may occur with MIE. Based on this, it is reasonable to recommend using a similar multi-modal approach to postoperative pain control as demonstrated above. Also, keep in mind that various surgeons have wide ranges of experience with minimally invasive techniques and so this may change the conversion to open rate significantly from institution to institution, making use of thoracic epidural more critical.

Conclusions:
Esophagectomy is a surgical and anesthetic challenge that has undergone significant changes early attempts over 100 years ago. Our understanding of the inflammatory mediation during this procedure has grown along with improvements in surgical technique and adjuvant therapy, leading to better overall mortality for patients. The main perioperative concerns including considerations for anastomotic healing, fluid management, pain management and pulmonary management have been discussed in detail. One area that was not addressed was cardiovascular morbidity, which includes arrhythmias in a high number of patients. Exact causes for this is unclear, but may be related to surgical dissection and pathology of the lesions. Overall recommendations however remain to follow the standard cardiac evaluation guidelines as for any non-cardiac case [38].
References:
