Title:	**Outcomes Following Intraoperative Management in Patients Undergoing Esophagectomy**: *A Combined Report from the Multicenter Perioperative Outcomes Group and the Society of Thoracic Surgeons*
Principle Investigators:	Tara Semenkovich, MD MPHS, Varun Puri, MD MSCI **(Wash U Surgery)**
Co-Investigators:	**Wash U Anes** – Mark Willingham, MD, Michael Avidan, MBBCh **UVA Anes** – Randal Blank, MD, PhD, Jacob Raphael, MD **UVA Surgery** – Dustin Walters, MD **UM Anes** – Sachin Kheterpal, MD; Douglas Colquhoun, MB, ChB, MSc; Milo Engoren, MD; Michael Mathis, MD **UM Surgery** – Andrew Chang, MD **Yale Anes** – Robert Schonberger, MD, Wanda Popescu, MD **Yale Surgery** - Justin Blasberg, MD
Approved by Mentor:	Michael Mathis, MD
Type of Study:	Retrospective Observational
IRB Number / Status:	HUM00052066 / Accepted
Aims:	**<u>Primary Aim:</u>** 1. **Evaluate for differences in <u>anastomotic</u> complications in three contexts: [1] "bundles" of perioperative management identified in PCRC 0042 (Intraoperative Management Strategies in Patients Undergoing Esophagectomy) as well as individually with: [2] varying intraoperative vasopressor exposure, and [3] varying intraoperative fluid administration.** We hypothesize that decreases in anastomotic complications are independently associated with [1] an optimal perioperative management bundle; [2] decreased intraoperative vasopressor exposure; and [3] restrictive fluid administration. **<u>Secondary Aims:</u>** 2. **Evaluate for differences in the <u>overall</u> complication rate in the same three contexts.** We hypothesize that an optimal perioperative care bundle exists, associated with decreased overall complication rates. a. **Sub-aim: <u>Respiratory</u> complications.** We hypothesize that decreases in respiratory complications are independently associated with restrictive fluid administration. b. **Sub-aim: <u>Cardiac arrhythmia</u> complications.** We hypothesize that decreases in cardiac arrhythmia are independently associated with restrictive fluid administration.
Patients/Participants:	**Inclusion:** Patients undergoing esophagectomy at MPOG-STS participating institutions. **Exclusion:** Patients whose cases are emergent.
Power Analysis:	A convenience sampling of all patients in this database yields 1,172 patients for analysis. A power analysis showed this will give us a 79.8% power to detect a 5% difference in leak rate.
Proposed Statistical Test/Analysis:	Differences in characteristics between groups with and without complications will be reported as mean +/- SD, median [IQR], or number (%) and tested with chi-squared and t-tests as appropriate. Univariable analysis will be performed on the identified parameters of interest and covariates to test for association with primary and secondary outcomes. Two multivariable analyses will be used to explore associations with the outcomes, adjusting for significant ($p<0.05$) covariates: (1) with the anesthetic characteristics included as the summary "bundle" of care and (2) the individual anesthetic parameters (fluids, vasopressors, opioids, epidural usage, and sedatives) included individually.
Resources:	Perioperative records query from MPOG-STS participating institutions, performed via IT support. Financial support as per departmental funding at participating sites.

Introduction:

A primary concern in perioperative management of patients undergoing esophagectomy is optimizing perfusion of the gastric conduit used in reconstruction since anastomotic leaks can be a morbid complication of the procedure and affect approximately 9-13% of patients undergoing this operation.[1–3] Despite agreement about the importance of blood flow to the conduit, there is debate regarding optimal fluid management versus vasopressor use in patients who are undergoing esophagectomy. With regards to anastomotic complications in particular, some providers are concerned that diminishing blood flow to the conduit with vasopressor use may be detrimental and consequently advocate liberal use of fluids to maintain normotension and adequate conduit perfusion. Others are concerned that substantial tissue edema from excessive fluid administration may compromise healing of the anastomosis, and so prefer a more restrictive fluid administration strategy, favoring vasopressors for treatment of hypotension.[4]

Three studies examining complications in esophagectomy have been performed so far utilizing the Society of Thoracic Surgeons (STS) database, and have largely found that comorbidities that would be expected to compromise blood flow or affect wound healing were associated with increased morbidity and mortality.[1–3] While these studies explored useful predictive factors for morbidity following esophagectomy – including some intraoperative characteristics – limitations to the STS database have currently precluded a comprehensive evaluation of the full "bundle" of anesthetic exposures possibly predicting adverse outcomes: these include use of fluids, vasopressors, epidural anesthesia, opioids, and sedatives.

Several previous studies have examined fluid management with regards to pulmonary complications, and have shown an increased rate of problems such as pneumonia, prolonged intubation, or ARDS with increasing fluid use,[4,5] but there is comparatively little data on anastomotic complications. Small studies looking at singular aspects of fluid and vasopressor use in either animal models or utilizing intraoperative assessment of microperfusion have found mixed results regarding the effects of vasopressors, apparently dependent on the overall volume status.[4,5] No studies to date have examined the overall effect on outcomes of "bundles" of anesthetic care.

The MPOG-STS integration provides a unique opportunity to study this controversial area of intraoperative management for esophagectomies by combining highly granular intraoperative anesthetic exposure data from the MPOG database with corresponding preoperative patient characteristics and postoperative complication data from the STS database. The integrated dataset will allow us to examine the short term outcomes related to the conduit as well as overall morbidity in the context of various anesthetic management strategies, and expand on the previously performed studies in a meaningful way.

This proposal addresses the second stage of a two-part retrospective multicenter observational study, building on proposal **PCRC 042 (Intraoperative Management Strategies in Patients Undergoing Esophagectomy).** Following the descriptive analysis characterizing intraoperative care for esophagectomy patients and identifying common "bundles" of care in the first stage, we propose to assess the outcomes of patients that receive varied perioperative management, specifically focusing on anastomotic, respiratory, and overall complication rates in this second stage.

Our primary aims are:

1. **Evaluate for differences in anastomotic complications in three contexts: [1] "bundles" of perioperative management identified in PCRC 0042 (Intraoperative Management Strategies in Patients Undergoing Esophagectomy) as well as individually with: [2] varying intraoperative vasopressor exposure, and [3] varying intraoperative fluid administration.**
    - We hypothesize that decreases in anastomotic complications are independently associated with [1] an optimal perioperative management bundle; [2] decreased intraoperative vasopressor exposure; and [3] restrictive fluid administration.

Our secondary aims are:

2. **Evaluate for differences in the <u>overall</u> complication rate in the same three contexts.**
    - We hypothesize that an optimal perioperative care bundle exists, associated with decreased overall complication rates.

      Sub-aim: <u>Respiratory</u> complications.
        - o We hypothesize that decreases in respiratory complications are independently associated with restrictive fluid administration.

      Sub-aim: <u>Cardiac arrhythmia</u> complications.
        - o We hypothesize that decreases in cardiac arrhythmia are independently associated with restrictive fluid administration.

<u>Methods:</u>

Study Design: This will be a retrospective multicenter observational study examining outcomes including anastomotic leak, composite morbidity/mortality, pulmonary, and cardiac complications for adult patients undergoing non-emergent esophagectomy. Data will be obtained from all MPOG-STS participating institutions, and patients with deterministically-matched MPOG and STS data will be analyzed. Esophagectomy cases will be identified by esophagectomy surgical procedure codes as available within the STS database, excluding cases performed emergently.

Sources of Information: Relevant covariates can be derived from both the MPOG and STS datasets. Patient demographics, individual preoperative comorbidities, procedure indications, and surgical approach will be captured via STS variables. A composite Elixhauser Score, anesthetic exposure variables (Table 1), and additional operative characteristics including duration of the procedure and intraoperative hypotension will be captured via MPOG variables. Primary and secondary outcome data will be derived from STS-reported variables, and are defined below.

Data Handling: The three factors we would like to examine in the context of our primary and secondary outcomes are [1] the "bundle" type of anesthetic care provided, [2] vasopressor usage, and [3] fluid administered. "Bundles" of care will be defined through latent class analysis in the first part of this study: **PCRC 042 (Intraoperative Management Strategies in Patients Undergoing Esophagectomy)** by examining all MPOG patients undergoing esophagectomy. Patients who have MPOG and STS data available will then be classified into one of the identified "bundles" for analysis of outcomes in this second part of the study. Intraoperative medications will be converted to a composite equivalent dose, as defined in Table 1 of the **PCRC 042 proposal**, which is duplicated here for easy reference: vasopressors in norepinephrine equivalents, opioids in morphine equivalents, epidurals in both duration of local anesthetic administration and morphine equivalents, and sedatives/hypnotics in minimum alveolar concentration (MAC) equivalents. Each fluid type will be considered individually on univariate analysis, but a composite measure and total intraoperative fluid balance will also be calculated for use in our multivariable models as follows:

To obtain a total composite measure of intraoperative fluid balance, crystalloids/colloids/blood products as well as estimated blood loss will be additionally analyzed in a sensitivity analysis in this second part of the study:

> Total Blood Administered mL = [Packed red blood cells (units)]*350mL + [Fresh frozen plasma (units)]*250mL + [Platelets (5-packs)]*250mL + [Cryoprecipitate (5-packs)]*100 + [Packed red blood cells (mL)] + [Fresh frozen plasma (mL)] + [Platelets (mL)] + [Cryoprecipitate (mL)]

Fluids administered (including crystalloids, colloids, and blood products) will be summed using a conversion to a crystalloid/colloid ratio of 1.5 and crystalloid/blood product ratio of 3.0[6] and an intraoperative fluid balance will be calculated as follows:

Intraoperative fluid balance = [crystalloid mL] + 1.5*[colloid-equivalent mL] + 3.0*[total blood mL- estimated blood loss– Insensible loss – Surgery Loss

Insensible loss = (Hours NPO until incision + surgery hours) * Weight factor

Weight factor =

- 40 + weight if weight > 20kg

Hours NPO until incision will be approximated as hours from the midnight leading into the day of surgery until surgical incision.

Surgery loss = third space loss * weight * surgery hours

Third space loss =

- 3 mL/kg/hr for minimally invasive esophagectomies
- 5 mL/kg/hr for non-minimally invasive esophagectomies

Intraoperative fluid balance will be transformed to a categorical variable for use in the multivariable model, using either quartiles or thresholds identified in the descriptive portion **PCRC 042** of this study.

Table 1, duplicated from **PCRC 042 proposal (Part 1 of the proposed study)**:

Medication or Fluid Class	Measurement Base Unit	Reference Formula / Categorical Variable
Crystalloids	Crystalloid mL	Total of all isotonic crystalloids
Colloids	Colloid-equivalent mL	(Total of all low-concentration albumin) + (Total of all low molecular weight hydroxyethyl starch) + 3.3 * (Total of all high-concentration albumin) + 1.3 * (Total of all high molecular weight hydroxyethyl starch)[36]
Blood products	Blood product unit	[Packed red blood cells (units)] + [Fresh frozen plasma (units)] + [Platelets (5-packs)] + [Cryoprecipitate (5-packs)] + [Packed red blood cells (mL)] / 240 + [Fresh frozen plasma (mL)] / 200 + [Platelets (mL)] / 250 + [Cryoprecipitate (mL)] / 250
Vasopressors	Norepinephrine equivalent	[norepinephrine (µg/kg)] + [epinephrine (µg/kg)] + [dopamine (µg/kg)]/150 + [phenylephrine (µg/kg)]/10 + [ephedrine (mg)]*2 + [vasopressin (U)]/[0.4*weight (kg)]
Opioids	Morphine equivalent	[morphine (mg)] + [fentanyl (mcg)]*0.1 + [hydromorphone (mg)]*10/1.5 + [oxymorphone (mg)]*10 + [sufentanil (mcg)] + [remifentanil (mcg)]*0.1 + [methadone (mg)]*MethadoneEquivalenceFactor[#] + [alfentanil (mcg)]*.01 #: Methadone Equivalence Factor = 4 for total methadone dose 1 to 10 mg 8 for total methadone dose >10 to 20 mg 10 for total methadone dose >20 to 30 mg 12 for total methadone dose >30 to 40mg
Epidurally-administered local anesthetics	Intraoperative hours with administration	(i) Not placed (ii) Placed, not dosed prior to extubation (iii) Placed, dosed intraoperatively for <50% of intraoperative hours (iv) Placed, dosed intraoperatively for >50% of intraoperative hours
Epidurally-administered opioids	IV morphine equivalent	10*([morphine (mg)] + [fentanyl (mcg)]*0.1 + [sufentanil (mcg)] + [remifentanil (mcg)]*0.1 + [hydromorphone (mg)]*10/1.5)
Sedatives/Hypnotics	Minimum Alveolar Concentration (MAC) equivalent	[propofol rate (mcg/kg/min) / 150] + [*dexmedetomidine adjustment]* + [(expired sevoflurane) / 1.8 + (expired isoflurane) / 1.17 + (expired desflurane) / 6.6 + (expired nitrous oxide) / 104] x $10^{0.00269 \times (\text{age of patient} - 40)}$ *dexmedetomidine adjustment* = (0.35 * infusion rate) for infusion rates < 1 mcg/kg/hr (0.35 + (infusion rate – 1) * 0.12) for infusion rates 1-2 mcg/kg/hr 0.47 for infusion rates > 2 mcg/kg/hr

Outcome Definitions:

- **Definition of anastomotic leak:** A previous STS study documented a 10.6% anastomotic leak rate which, although not explicitly clear from the study, appeared to be defined by the STS variables of medically treated or surgically treated leaks, which the authors acknowledge was likely an underestimate of the true rate.[1] When we examined our own STS data for the years that MPOG data is available, we found a leak rate of 12% (31 unique patients out of 255) when defined by surgically treated leaks (19 documented cases) and medically treated leaks (6 cases with no overlap with surgical cases), as well as those patients who were discharged with a chest tube (11 cases, with 5 also charted as having a leak). Based on clinical experience and the observed overlap in how complications are charted in our own data, we feel the addition of the patients who were discharged with a chest tube to those defined as having a medically or surgically treated leak is important to achieve a better estimate of the true leak rate. To be comprehensive, we will include the STS variables of: Anastomosis Requiring Medical Treatment Only, Conduit Necrosis Requiring Surgery, Unexpected Return to the OR (when performed for Anastomotic Leak or Conduit Necrosis), and Discharge with Chest Tube in our definition of leak for this study.

- **Definition of mortality/major morbidity composite outcome:** We will examine 30-day mortality. For our composite outcome of major morbidity, we will include all variables that define anastomotic leak, pulmonary complications, and cardiac complications, as well as the following adverse outcomes: Unexpected Return to the OR (for Bleeding, Empyema, Chylothorax), Myocardial Infarct, Sepsis, New Central Neurological Event, Renal Failure, Unexpected Admission to ICU.

- **Definition of pulmonary complications:** We will define pulmonary complications using the STS variables of: Pneumonia, ARDS, Respiratory Failure, Initial Vent Support >48 Hours, Tracheostomy, Other Pulmonary Event. A sample of "Other Pulmonary Event" cases will be hand-reviewed to further characterize this outcome.

- **Definition of cardiac arrhythmia complications:** We will look specifically at arrhythmias using the variables of Atrial Arrhythmia Requiring Treatment and Ventricular Arrhythmia Requiring Treatment.

Selection of Covariates:

We will plan to evaluate previously identified predictors of anastomotic leak as well as overall complications following esophagectomy in our univariate analyses. These include significant predictive factors of complications previously identified in studies utilizing the STS database:

- A 2009 study by Wright et al examined an outcome of total major morbidity and mortality in esophagectomy, including reoperation for bleeding, anastomotic leak, pneumonia, reintubation, ventilation >48 hours, and death in the composite endpoint. In this analysis, they identified FEV1, age, race, heart failure, coronary disease, vascular disease, hypertension, diabetes, ASA rating, smoking status, and steroid use as significantly predictive on multivariable analysis.[2]
- A 2016 study by Raymond et al reexamined risk factors for major morbidity (adding renal failure and recurrent nerve paresis to the list above) and mortality and found that age, obesity, heart failure, Zubrod score, type of procedure, smoking status, and squamous histology were predictive.[3]
- A 2013 study by Kassis et al specifically explored risk factors for anastomotic complications within the STS database anastomotic complications, and identified heart failure, hypertension, renal failure, and procedure type as significantly predictive on multivariable analysis. They also found obesity, coronary disease, vascular disease, steroid use, diabetes, tobacco use, and procedure length >5 hours to be significant on univariable analysis.[1]

- We presented the study hypotheses to a group of Thoracic surgeons and based upon this expert group's opinion will also include year of diagnosis and operative approach (minimally invasive vs. open, and transthoracic vs. not) as covariates.
- Based on presentation of this proposal to the MPOG group, anonymized site ID will also be considered as a covariate.

We also will evaluate additional factors predictive of GI anastomotic leaks from other series that are available within our dataset on univariate analyses: weight loss, anemia, hypotension, inotrope usage, blood transfusion, neoadjuvant chemoradiation[7], total number of comorbidities (Elixhauser Index), cancer diagnosis, and higher tumor stage.[8]

- Of note, intraoperative hypotension will be considered as a covariate in our primary analysis. Since hypotension may essentially be an intermediate outcome (i.e. anesthetic management exposures variables such as fluid and vasopressor restriction may lead to hypotension, which then may lead to postoperative complications), a sensitivity analysis will be performed evaluating intraoperative hypotension as a mediator variable as well.

A summary of the potential covariates to be considered and the source of the data is listed in the following table. The number of covariates selected for inclusion into the multivariable models will be determined based on the final available sample size.

STS Covariates	**MPOG Covariates**
Age	Hypotension (Time-weighted area under 55 mmHg)
Race	Inotrope Usage
Gender* (not found to be significant in prior studies but will be included)	Blood Transfusion
Procedure Type	Procedure Length
Obesity	Elixhauser Score (Total Number of Comorbidities)
Weight Loss	Anonymized Site ID
Heart Failure	
Coronary Disease	**MPOG Exposure Variables**
Vascular Disease	Fluids Administered (Crystalloid Equivalents)
Hypertension	Vasopressors (Norepinephrine Equivalents)
Diabetes	Opioids (Morphine Equivalents)
ASA Rating	Epidural Usage (Local Anesthetics and Opioids)
Zubrod Score	Sedatives/hypnotics (MAC Equivalent)
Smoking Status	
Steroid Use	
FEV1	
Tumor Histology Type	
Tumor Stage	
Anemia	
Cancer Diagnosis	
Year of Diagnosis	

Statistical Analysis: Continuous variables will be evaluated for normality and reported as mean +/- SD or median [IQR]. Categorical variables will be reported as number (%). Differences in demographic characteristics, comorbidities, operative parameters, and anesthetic parameters between groups with and without complications will be tested with chi-squared and t-tests as appropriate. Univariable analysis will be performed on the identified parameters of interest and covariates to test for association with our three outcomes: anastomotic leak, pulmonary complications, and composite major morbidity or mortality. Two multivariable analyses will be used to explore associations with the outcomes, forcing in all exposure variables and adding in the preselected number of covariates found to be significant on univariable analysis (using a Bonferroni correction to determine the significance level, and assessing for collinearity): (1) with the anesthetic characteristics included as the summary "bundle" of care and (2) the individual anesthetic parameters (intraoperative fluid balance, vasopressors, opioids, epidural usage, and sedatives) included individually.

Missing Data: Missing data elements will be evaluated for imputation using multiple sequential imputation based on regression models or categorized into an unknown category.

Power and Sample Size: Convenience sampling will be used in this retrospective study. If the management strategy is dichotomized (ie: into a fluid restrictive vs liberal strategy) with roughly equal groups, a power analysis with an alpha of 0.05 shows that we will need: 1178 patients to have an 80% power to detect a 5% difference (absolute risk reduction, ie: 8 vs 13%), 2031 patients to detect a difference in the leak rate of 4% overall, or 2998 to detect a difference in the leak rate of 3% overall. Currently there are 1172 patients available, giving us a 79.8% power for a 5% difference. Relative numbers of cases by site currently include: University of Michigan (512), Washington University – St. Louis (245), University of Virginia (182), Oregon Health & Sciences University (182), Yale (51).

Results:

Proposed tables include:

1. A summary table reintroducing the "bundles" discovered in part one of this analysis, similar to the Hypothetical Table 4 that will result from the first part of this study **PCRC 042 proposal**. These "bundles" will be used as categories in our univariable and multivariable analyses. Example:

Bundle of Care	**Description**
1	Major Characteristics of Identified on Latent Class Analysis
2	
3	

2. Patient demographics and covariates in the total cohort, patients with a leak, patients with a pulmonary complication, and patients with our composite major morbidity and mortality outcome. Example:

Characteristic	Total Cohort	Patients with Anastomotic Complications	Patients with Any Major Morbidity or Mortality	Patients with Pulmonary Complications	Patients with Arrhythmias
	N=est 1,172	N= est 117 (10%)	N=	N=	N=
Demographics:					
Age					
Race					
Gender					
Comorbidities:					
Obesity					
Weight Loss					
Heart Failure					
Coronary Disease					
Vascular Disease					
Hypertension					
Diabetes					
Anemia					
Smoking Status					

Steroid Use					
FEV1					
Esophageal Cancer Diagnosis					
Composite Comorbidity Measures:					
ASA Rating					
Zubrod Score					
Elixhauser Score					
Tumor Factors:					
Tumor Histology Type					
Tumor Stage					
Operative Factors:					
Procedure Type					
Procedure Length					
Hypotension					
Inotrope Usage					
Blood Transfusion					
Fluids Administered					
Vasopressors					
Opioids					
Epidural Usage					
Sedatives/Hypnotics					
Bundle Class:					

3. Univariable and multivariable analysis of parameters associated with anastomotic leak, exploring patient "bundles" in one multivariable model and all the individual anesthetic parameters separately in another model. Example:

	Univariable Analysis		**Multivariable Analysis by Bundle of Care**		**Multivariable Analysis by Individual Anesthetic Parameters**	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Demographics:						
…						
Comorbidities:						
…						
Operative Factors:						
Procedure Type						
Procedure Length						
Hypotension						
Inotrope Usage						
Blood Transfusion						
Fluids Administered						
Vasopressors						
Opioids						
Epidural Usage						
Sedatives						

Bundle Class						

4. Univariable and multivariable analysis of parameters associated with the composite outcome of major morbidity or mortality, exploring patient “bundles” in one multivariable model and all the individual anesthetic parameters separately in another model.
5. Univariable and multivariable analysis of parameters associated with pulmonary complications, exploring patient “bundles” in one multivariable model and all the individual anesthetic parameters separately in another model.
6. Univariable and multivariable analysis of parameters associated with the cardiac arrhythmia outcomes of major morbidity or mortality, exploring patient “bundles” in one multivariable model and all the individual anesthetic parameters separately in another model.

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