Comparative effectiveness of emerging technology in surgery

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A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2017

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Program Authorized to Offer Degree:

Department of Global Health, School of Public Health

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Abstract

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Introduction: New surgical technology plays a major part in healthcare in the developed world but also must be considered as infrastructure grows for surgical care in low- and middle-income countries. Reliable epidemiologic and statistical methods for comparative effectiveness must be applied when choosing whether or not to adopt a new surgical approach or technology.

Methods: For Part I of this thesis, we performed a comparative effectiveness study of conventional and minimally invasive approaches to major and challenging hepatectomies using logistic regression and a non-inferiority approach. For Part II of this thesis, we use temporal trend analyses to examine outcomes and utilization among patients treated by either conventional surgical repair or endoluminal stenting for benign esophageal perforation.

Results: For patients undergoing major hepatectomy, minimally invasive approaches were non-inferior to conventional open surgery. In an assessment of patients with benign esophageal perforation, we observed a four-fold increase in the rate of treatment by stenting. While there was no difference in trends of adverse outcomes, stented patients had higher rates of death and healthcare utilization across.

Conclusions: Studies of comparative effectiveness should apply appropriate methods to match the clinical problem and data source. In this study, neither assessment suggests that the new technology was more effective than existing approaches. Reporting on comparative effectiveness of new surgical technology will be critical to policy makers and clinicians in the US and the developing world.

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Introduction to Thesis:

New technology plays an important role in healthcare and healthcare development around the globe. As new medical procedures and techniques are developed, enthusiasm for their application in patients can outpace evidence of their safety, efficacy and value compared with existing care standards. Furthermore, in resource-limited settings seen in low- and middle-income settings, adoption of effective therapies will continue to be a priority while costly or ineffective technology may be a hindrance to successful development of healthcare infrastructure. In the field of surgery, randomized trials comparing new approaches or devices with current ones are typically impractical and/or costly. Instead, surgeons and their patients rely upon data from observational studies to guide the choice of which new technologies are adopted for use and which are abandoned as costly, ineffective, or even unsafe. In this study we propose the following two aims:

1. To determine whether minimally invasive approaches to major liver resection are associated with equivalent rates of serious adverse events compared with standard open approaches to liver surgery.

2. To determine whether the trend in increasing use of endoluminal stents to treat esophageal perforations is associated with improved survival, healthcare utilization, or costs of care.

In many fields of surgery, minimally invasive approaches have been used to minimize perioperative pain, diminish intraoperative fluid losses, and avoid large incisions and their associated complications. While they are accepted as standard of care in many types of operations, minimally invasive surgery for major liver resection is still considered innovative, without clearly defined risks.[1] Despite this, it is known that nearly half of surgeons worldwide apply minimally invasive approaches for a selection of major hepatectomies.[2] In Part I of this thesis, we hypothesize that among surgeons with advanced training in liver surgery, minimally invasive approaches will be non-inferior to conventional open approaches. The findings of this study may help guide surgeons who in choosing whether or not to apply this newer approach to their practice for patients who require a major or challenging resection of the liver.

Esophageal perforation, though rare, carries a significant risk of morbidity and mortality. While standard treatment for esophageal perforation has remained open surgical drainage and repair of the esophagus, there has been a growing interest in the off-label use of endoluminal stents to treat these

perforations.[3,4] Several small studies demonstrate favorable outcomes in patients treated with esophageal stents, these investigations examine a limited number of patients, often under protocol at single institutions.[5–8] In Part II of this thesis, we hypothesized that, given the enthusiasm for stent use to treat esophageal perforation, there is a national trend of increasing use of this new technology. By measuring the outcomes and healthcare utilization of patients who undergo stenting or surgical repair after esophageal perforation, this study can provide evidence either for the continued use, abandonment or further study of this emerging technique.

Identifying non-inferiority and comparative effectiveness for these two procedures provides a model for new technology assessment. I plan to use these techniques in my academic career and apply them to future practice settings.

Part I: The Comparative Effectiveness of Minimally Invasive Surgery and Conventional Approaches to Major or Challenging Hepatectomy

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The following work has been published with the *Journal of the American College of Surgeons* under the following citation and has been reproduced under a retained right for use in a thesis:

Thornblade LW, Shi X, Ruiz A, Flum DR, Park JO. Comparative Effectiveness of Minimally Invasive Surgery and Conventional Approaches to Major or Challenging Hepatectomy. *J Am Coll Surg*. February 2017. doi:10.1016/j.jamcollsurg.2017.01.051.

Introduction: Laparoscopy has well-established benefits over the conventional, open approach to abdominal surgery including reduced pain, fewer wound complications, and shorter hospital stays.[9–11] As surgical resection for benign and malignant tumors of the liver has become safer and more common, so has the use of minimally invasive surgery (MIS) in liver resection.[12,13] Numerous studies support the use of MIS in liver resection, reporting less intraoperative blood loss, lower rates of bile leak, as well as fewer complications.[14–20] Data to support MIS hepatectomy, however, are derived predominantly from studies of patients undergoing non-anatomic or minor resections of the liver (two or fewer contiguous Couinaud segments) and most studies of MIS have not included high-risk resections.[21–24] According to the recent 2nd International Consensus on Laparoscopic Liver Resection, MIS minor liver resection is now considered standard of care but major hepatectomy (MH) (3 or more Couinaud segments) performed via MIS remains an innovative procedure.[1,25] As surgeons gain more experience with MIS techniques, there is growing interest in applying MIS in major liver resections.[26–29] The comparative effectiveness, including oncologic, safety and cost outcomes of MIS major hepatectomy, however, has not been established.

Prevention and control of significant hemorrhage remains the most important intra-operative goal during MH, which can sometimes be challenging in MIS.[26] A primary reason for choice of open approach over MIS is the perceived difficulty of resection.[30,31] A number of known technical, anatomic, and patient factors contribute to the difficulty of resection including tumor location (particularly right-posterior lesions), large tumor size and extent of resection, proximity to major vessels, underlying liver function and parenchymal texture.[32,33] The fibrosis and resulting portal hypertension of cirrhosis increases the risk of

hemorrhage during parenchymal transection and there is a paucity of data on the safety of MIS hepatectomy in patients with cirrhosis.[34,35] Similarly, the friable and steatotic liver parenchyma which results from chemotherapy or obesity may makes hemostasis more difficult and be associated with adverse outcomes.[36–39] Patient habitus may also add to the difficulty of liver resection although this has not been extensively studied. Liver resection in patients with morbid obesity require significantly longer operative times which may be due to difficulty of exposure and fatty infiltration of the liver parenchyma.[40] Although these patient factors influence the choice of surgical approach in liver resection, it is unknown whether MIS resection under challenging conditions is associated with worse outcomes. In this study, we aimed to measure the comparative effectiveness of MIS approaches to hepatectomy among the less well-studied groups of MH and patients with features of a challenging resection.

The National Surgical Quality Improvement Program (NSQIP) was developed by the American College of Surgeons for the purposes of measuring surgical outcomes, improving quality and safety of surgical care, and providing validated calculations of surgical risk.[41,42] Procedure-targeted modules within NSQIP allow hospitals to collect organ specific data on over 30 high-risk procedures within nine subspecialty areas.[43] Beginning in 2014, NSQIP formed the Hepatopancreatobiliary (HPB) collaborative and began collecting data on patient comorbidities, surgical factors and 30-day adverse events specifically related to liver resection. This data source presents an opportunity to perform large-scale evaluation of outcomes after major or challenging hepatectomy. By leveraging the NSQIP HPB collaborative procedure-targeted data, we aimed to measure serious morbidity and mortality as well as liver-related outcomes after MIS and open surgery among patients undergoing liver resection. We hypothesized that the MIS approach to both major and challenging hepatectomies among trained surgeons is as safe as the standard open approach.

Methods: ***Cohort selection*****:** We performed a retrospective analysis of all adult patients undergoing elective hepatectomy at 65 high-volume medical centers participating in the NSQIP HPB Collaborative in 2014. All patients included in the HPB collaborative dataset were linked to the NSQIP Public Use File, which includes preoperative laboratory, comorbidity, and demographic data as well as 30-day in-hospital and post-discharge adverse events. In order to exclusively capture liver resection cases, we excluded

patients who required biliary reconstruction, which involves bowel anastomosis. We identified and reported all cases that had a concomitant colon resection because these cases may have a higher risk of early post-operative complications. Demographic and historical data were obtained on patients prior to surgery including laboratory values (e.g. hepatic panel, etc.), medical comorbidities (e.g. diabetes, etc.) and other conditions existing at the time of surgery including infection or sepsis. Following surgery, patients were followed for 30 days for complications, reoperation or intervention, readmission, and death. Due to the de-identified nature of the data, this research was not considered human subjects research and did not require approval by the University of Washington's Human Subjects Division Institutional Review Board.

Comparison groups: We report outcomes from all hepatectomies, major hepatectomies (resection of ≥3 consecutive Couinaud segments, Current Procedural Terminology (CPT) numbers 47122: trisegmentectomy, 47125: left lobectomy, 47130: right lobectomy), and five subgroups indicating a challenging resection among all (major and minor) hepatectomies: large tumors, cirrhosis, ≥3 concurrent resections, patients with a prior history of neoadjuvant chemotherapy, and morbid obesity. Large tumors were defined as >5cm (for benign tumors) or tumor stages III and IV (for malignant tumors) (American Joint Committee on Cancer 7th edition, Cancer Staging System). Cirrhosis was identified either on preoperative imaging or by the surgeon at the time of operation based upon liver texture. Cases were identified in which the surgeon performed at least two concurrent resections (e.g. wedge, subsegmental, or segmental resections) in addition to the primary resection (either major or minor hepatectomy). NSQIP abstractors recorded any history of neoadjuvant chemotherapy from the patients' preoperative charts. Finally, morbid obesity was defined as a preoperative body mass index (BMI) ≥40 kg/cm^2.

Case definition: Cases were defined as MIS if it was documented that the resection was performed by laparoscopy or robotic assistance including any cases with open assistance. Surgical approach was defined as MIS by intention to treat, and therefore, any case that began by a minimally invasive approach but required open conversion was included in the MIS group. We excluded any cases described as hybrid approach (laparoscopic mobilization of the liver followed by open parenchymal transection, which is typically used in hepatectomy for living liver donation).

Outcomes: The primary outcome in this study was serious morbidity or mortality (SMM). NSQIP defines serious morbidity as any of the following events occurring during the 30-day period following surgery: organ space surgical site infection, surgical wound dehiscence, stroke, myocardial infarction, cardiac arrest requiring cardiopulmonary resuscitation, pulmonary embolism, respiratory failure requiring mechanical ventilation >48 hours after surgery, postoperative acute renal failure, sepsis, or septic shock.[42] Bleeding and subsequent transfusion is a component of SMM, however, as a common event after liver surgery that may not represent serious morbidity, we report transfusions separately as a secondary outcome.

There were five secondary outcomes including three liver-specific outcomes. First, we measured all patients who required transfusion of red blood cells. Second, we recorded any post-operative bile leak which is classified as persistent drainage of bilious fluid with three times the serum concentration of bilirubin. Third, we reported any patients who developed grade A, B, or C post-hepatectomy liver failure as defined by the International Study Group of Liver Surgery.[44,45] Fourth, we reported any patients requiring reoperation or invasive intervention including drainage or aspiration of a fluid collection, biliary stent placement, or angiography or embolization for bleeding. Finally, we reported all patients requiring hospital readmission within 30 days.

Analysis: We performed univariate analysis of relevant clinical variables using chi-squared and Fischer's exact tests (categorical variables) and two-tailed unpaired Student's t-tests (continuous variables). In order to control for known differences between patients undergoing MIS and open hepatectomy, we performed an adjusted analysis of patients in each group. Using logistic regression, we controlled for clinically relevant covariates including American Society of Anesthesia (ASA) Class, history of viral hepatitis, primary tumor pathology, presence of challenging resection types (including cirrhosis), presence of major hepatectomy, and operation-specific variables, including use of Pringle maneuver and use of concurrent tumor ablation. An additional factor included in the regression model was the NSQIP morbidity probability which is a value derived from a validated prediction model based upon 19 comorbidities including patient age, wound classification, preoperative albumin, and tests of coagulation factors.[41,42] Regression models reported in this study included only those covariates that were significantly different

between groups by univariate analysis with an alpha-level of ≤20%. Comparative assessment of outcomes between MIS and open surgery were performed for all hepatectomies, major hepatectomies, and each of the five challenging subgroups.

Because this study compares an established procedure (open MH) with an innovative procedure (MIS MH), we performed a *post-hoc* non-inferiority analysis for primary outcomes (i.e. SMM). We selected a non-inferiority margin of 5%, which represents the tolerated increase in adverse event rates for the novel procedure. We calculated the odds ratio (OR) corresponding to a 5% increase in rates of SMM in the open group. Using the regression model, we calculated one-sided 95% confidence intervals.

All statistical analyses were performed using commercially available software (Stata, version 14; StataCorp, College Station, TX; R-software, version 3.1.3). All statistical tests were considered significant if $p < 0.05$.

Results: ***All hepatectomies:*** Between January 1 and December 31, 2014, 2,819 patients (mean age 58 +/- 14 years, 53% female) underwent liver resection (36% major hepatectomy) at 65 medical centers. Including both laparoscopy and robotic approaches, 706 cases (25%) were performed via MIS, and 109 of these required conversion to open (15.4%). The rate of SMM was 6% among MIS cases and 13% among open cases ($p<0.001$). Unadjusted rates of transfusion (9% vs. 19%), bile leak (3% vs. 7%), post-operative liver failure (1% vs. 5%), and reoperation or intervention (5% vs. 10%), were also significantly lower in the MIS group compared with the open group, respectively (all $p<0.001$). The 30-day readmission rate was similar (8% vs. 10%, $p=0.09$) (Table 1). After adjusting for clinically relevant covariates listed in Table 1, MIS among all hepatectomies was associated with significantly lower odds of SMM compared with open resection (OR 0.57, 95% CI: 0.34-0.96, $p=0.03$). MIS was also associated with significantly lower odds of transfusion (OR: 0.60, 95% CI: 0.40-0.92, $p=0.02$), and postoperative reoperation or invasive intervention (OR 0.52, 95% CI: 0.29-93, $p=0.03$) (Table 2). Among all hepatectomies, MIS reached non-inferiority for SMM when compared with open resection.

Major hepatectomies: A total of 1,015 patients underwent major hepatectomy (MH) (mean age 57.0±14 years, 52% female, 13% MIS). Right hemi-hepatectomy was a greater proportion of the open MH group (55%) versus the MIS MH group (42%, $p=0.002$). Among MH, MIS patients had lower unadjusted rates of

serious morbidity and mortality than open resection (6% vs. 16%, p=0.004), as well as lower rates of post-operative liver failure (2% vs. 8%, p=0.03). There were no significant differences in rates of transfusion, bile leak, reoperation or intervention, or readmission (Table 3). After adjusted analysis, there was no significant difference in odds of SMM after MIS MH vs. open (OR: 0.37, 95% CI: 0.13-1.11, p=0.08), however MIS for MH did reach non-inferiority when compared with open resection (one-sided 95% CI: <0.93). There were no significant differences in odds of transfusion, bile leak, liver failure, reoperation or intervention, or readmission (Table 4). Because we anticipated that there are differences in difficulty even among major resections, we also measured outcomes for right hemi-hepatectomies (n=544, 10% MIS) and observed lower rates of SMM after MIS (5%) than after open (16%). After adjusted analysis, odds of SMM were significantly lower for MIS right hemi-hepatectomies (OR: 0.25, 95% CI: 0.07-0.87, p=0.03).

Challenging hepatectomy subgroups: From the entire cohort, 693 patients had large tumors (23% MIS), 285 patients had documented cirrhosis (33% MIS), 720 patients required ≥3 concurrent resections (20% MIS), 138 patients were morbidly obese (36% MIS), and 880 patients had a history of neoadjuvant chemotherapy (19% MIS). For patients undergoing ≥3 concurrent resections, median number of resections was two among both patients undergoing open (Interquartile Range (IQR): 2-4) and MIS resection (IQR: 2-3, p=0.052). Mean BMI among morbidly obese patients was similar among open (45.2 kg/m^2) and MIS resections (45.4 kg/m^2, p=0.86). Unadjusted rates of SMM were lower after MIS in patients with large tumors (6% vs. 14%, p=0.005), and patients with a history of neoadjuvant chemotherapy (5% vs. 16%, p<0.001). Patients with large tumors also had lower unadjusted rates of post-operative liver failure after MIS (1%) compared with open resection (6%, p=0.008). The distribution of outcomes by challenging subgroup is listed in Table 2.

After adjusted analysis, including adjustment for major resection, MIS resection for patients with history of neoadjuvant chemotherapy was associated with 67% lower odds of SMM compared with open resection(OR: 0.33, 95% CI: 0.15-0.70, p=0.004). There was no significant difference in odds of adverse outcomes between MIS and open resection among patients with large tumors, cirrhosis, those requiring ≥3 concurrent resections, or patients with morbid obesity. MIS hepatectomy reached non-inferiority compared with open hepatectomy for patients with large tumors (one-sided 95% CI<1.02) or with a

history of neoadjuvant chemotherapy (one-sided 95% CI<0.62). There was insufficient evidence, however, to indicate that MIS was non-inferior to open hepatectomies for patients with cirrhosis, those requiring ≥3 concurrent resections and for patients with morbid obesity.

Discussion: In this study, minimally invasive (MIS) hepatectomy was associated with a significant reduction in the risk of serious morbidity or mortality (SMM) including organ-space infection and organ failure. MIS was also associated with a significant reduction in odds of transfusion and post-operative reoperation or invasive intervention compared with open resection. For major hepatectomy (MH), resection of large tumors, or for patients with a history of neoadjuvant chemotherapy, MIS was found to be "non-inferior" to open resection. While the preponderance of major and challenging hepatectomies are performed via an open approach, reflecting the preference of many practicing surgeons, our findings suggest that short-term outcomes after MIS major hepatectomy are at least equivalent to and for some challenging subgroups may be superior to open resection.

By leveraging the newly formed NSQIP HPB collaborative, we are reporting the largest-to-date multi-institutional comparison of outcomes after major hepatectomy. There are a number of previously published studies on short-term outcomes after MIS hepatectomy, but most do not include any major hepatectomies.[46–48] Other studies have reported both major and minor hepatectomies but did not compare to open controls.[49–54] Five recent studies report both single and multi-institutional comparisons of MIS and open hepatectomies, but each reports fewer than 15 MIS major hepatectomies.[21,55–58] In 2013, Lin *et al.* reviewed four studies which report MIS major hepatectomy matched with open cases.[59] These data indicate that for major hepatectomies, MIS was significantly associated with less blood loss (3 of 4 studies), fewer transfusions (1 of 4 studies), fewer complications (2 of 4 studies) and shorter length of stay (3 of 4 studies).[60–63] Case-matched studies provide important data on outcomes of two different interventions; however, matching methods may not completely account for confounding by indication. By utilizing the standardized perioperative data collected through the NSQIP HPB collaborative, we were able to control for important differences between patients who undergo MIS or open resections in each of the comparisons. Logistic regression modeling was used to minimize the impact of confounding by indication on our estimates of outcome.

Our findings build upon those in recent analysis of the NSQIP HPB data by Bagante *et al.,* which reported lower postoperative morbidity and shorter length of stay after MIS hepatectomy.[19] In our study we aimed primarily to address the knowledge gap for major hepatectomies, a procedure that is considered by consensus opinion to be innovative and which has not been described previously from the nationwide NSQIP HPB collaborative.[1] Bagante *et al*. found that MIS was favored in eight of 24 separate outcomes. Our study adds to this evidence by reporting a single primary outcome allowing direct comparison of composite adverse events. Lastly, while Bagante *et al*. showed that if a hepatectomy is completed laparoscopically, then the outcomes may be favorable to open by including cases converted to open in the MIS group (intention-to-treat), our analysis adds evidence on the safety of this procedure.[19]

Research to date demonstrates agreement for MIS as the standard of care for minor hepatectomies, especially in liver segments with easy exposure and those not proximate to hilar structures, e.g. left lateral sectionectomy[1]. Standardized approaches to MIS major hepatectomy have not been widely adopted.[64] and for malignant disease, resection with negative margins remains a concern in MIS approaches. Despite this, there is a growing interest in use of MIS for larger resections. Across North America, Europe and East Asia, no more than half of surveyed surgeons employ MIS approach to major hepatectomies.[2] The 2nd International Consensus Conference on Laparoscopic Liver Resection reported an analysis of the current literature on minimally invasive major hepatectomy and concluded that this procedure remains innovative. The consensus jury made a call for larger scale studies of outcomes after this high-risk surgery.[1] Our study provides important data that addresses this knowledge gap.

While safety of innovative approaches is principally important, equivalent oncologic outcomes must also be demonstrated for MIS approaches to become standard of care. Oncologic outcomes after MIS hepatectomy are still questioned and while there are several studies reporting long-term outcomes,[21,65,66] to date no randomized studies have been completed in this area. There are two ongoing randomized trials of MIS for liver disease which, once published, may help inform the choice of approach in MIS liver resections. The Oslo-CoMet trial (Clinicaltrials.gov identifier NCT01516710) is currently enrolling patients with colorectal liver metastases for randomization to open or laparoscopic resection.[67] This study includes some major hepatectomies, however these findings will need to be applied with

caution to patients with primary tumors of the liver, which are, by design, not included in the trial. The ORANGE II trial (Clinicaltrials.gov identifier: NCT00874224) is randomizing patients for left lateral sectionectomy within a framework of Enhanced Recovery After Surgery to either laparoscopic or open resection.[68] This study is limited to minor resections but will provide data generalizable to both primary and secondary liver tumors. The addition of the upcoming ORANGE II PLUS trial (Clinicaltrials.gov identifier: NCT01441856) from the same European research collaborative will add needed information on outcomes after major hepatectomy and may complement the findings of our study.

Central to the choice of surgical approach is the anticipated difficulty of resection. While extent of resection is an important factor in this decision (e.g. major versus minor), tumor features, location, proximity to vasculature, quality of the parenchyma, and ease of access to the targeted segment(s) are likely as important as volume of liver resected. Ban *et al.* highlight the difficulty of standardizing measurement of the difficulty of liver resection.[30] The interplay of patient and tumor factors against surgeon experience renders perceived difficulty of resection less suitable to measurement. There is agreement that billing codes (e.g. CPT) do not adequately capture the differences among types of liver resections, and CPT codes are used in the NSQIP HPB module. Nevertheless, these data allow us to examine the challenging features of liver resection in a novel way. Similar to major hepatectomy, our data suggest that safety of MIS in resection of large tumors, patients with cirrhosis, and after neoadjuvant chemotherapy is at least equivalent to open resection. One explanation for this finding is that in patients with compromised parenchyma (cirrhosis or after chemotherapy), MIS approaches may be superior because of more limited parenchymal transection and preservation of collateral circulation.[21] For patients with morbid obesity or those requiring ≥3 concurrent resections, however, there is not sufficient data in this analysis to support MIS liver resection.

This study does have several limitations. Studies that compare effectiveness of two surgical interventions are subject to confounding by indication, meaning there are important differences between treatment groups that may be associated with both the choice of treatment and outcomes. By controlling for known patient- and surgery-related variables in a logistic regression model, we attempt to minimize any confounding. While propensity score matching is often applied in comparing two different

interventions, the NSQIP database does not provide surgeon or hospital identifiers that would be important for estimating the propensity of patients to undergo either open or MIS resection. An important factor in the choice of surgical approach is the anatomic location of the tumor. Superior-posterior resections are notoriously challenging; however, the NSQIP dataset does not identify these more difficult areas of the liver, and we therefore were unable to assess outcomes based upon this critical feature. Another important measure of quality in surgery for cancer is attaining negative margins however the NSQIP does not capture this pathological data. There are also limitations to the precision of some NSQIP variables. For example, cirrhosis was reported by either preoperative imaging or intraoperative examination, both of which likely have lower sensitivity for this diagnosis than a standard liver biopsy. Nonetheless, the macroscopic cirrhosis identified in this study is likely a subset of more advanced cases and therefore findings for these patients are conservative.

This study assesses only short-term postoperative outcomes and does not take into account the potentially favorable outcomes of MIS including shorter length of stay, reduced narcotic use, improved cosmesis, and rates of wound complications such as hernia. Quality of life may also play an important role in choice of surgery but at this stage in assessment, data do not exist to study these outcomes in liver resection. Finally, although we were unable to control for clustering of effects by surgeon or institution, the data for this study comes from specialty centers that employ surgeons with advanced training in laparoscopic liver resection. There is agreement that mastering MIS liver resection requires high case volume,[69,70] and therefore the results of this study should be applied strictly to the practice of surgeons with a similar level of training as those in the NSQIP HPB Collaborative.

Conclusions: This study finds that a minimally invasive approach to hepatectomy, including major hepatectomy, is associated with short-term outcomes that are equal or even superior to open surgery. While data is lacking to support its use in patients with cirrhosis, those requiring multiple (≥ 3) concurrent resections or in patients with morbid obesity, minimally invasive surgery appears to be non-inferior to open surgery in several challenging resections including patients with large tumors and after neoadjuvant chemotherapy.

Acknowledgements: We would like to thank the surgeons, patients and institutions that contribute data to the NSQIP HPB Collaborative. Dr. Thornblade was supported by a training grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK070555. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Table 1: Patient demographics, treatment characteristics, and outcomes among patients undergoing minimally invasive or open hepatectomy.

	MIS (n=706)	Open (n=2113)	All (n=2819)	p value
Major, n (%)	132 (19)	883 (42)	1015 (36)	**<0.001**
Demographics				
Age, mean (SD)	59 (15)	58 (13)	58 (14)	0.65
Female, n (%)	414 (59)	1073 (51)	1487 (53)	**<0.001**
Non-white race, n (%)	107 (18)	276 (16)	383 (17)	0.43
BMI, mean (SD)	28.8 (7)	28.3 (6)	28.4 (6)	**0.04**
Concomitant colon resection, n (%)	31(4)	93 (4)	124 (4)	0.99
ASA Class, n (%)				**0.002**
I	7 (1)	68 (3)	75 (3)	
II	215 (30)	537 (25)	752 (27)	
III	445 (63)	1361 (64)	1806 (64)	
≥IV	39 (6)	144 (7)	183 (6)	
NSQIP Morbidity Probability, mean (SD)	0.16 (0.07)	0.19 (0.08)	0.18 (0.08)	**<0.001**
Challenging subgroups, n (%)				
Large Tumor	157 (22)	536 (25)	693 (25)	0.11
Cirrhosis	93 (13)	192 (9)	285 (10)	**0.005**
≥ 3 concurrent resections	147 (21)	573 (27)	720 (26)	**<0.001**
Neoadjuvant	171 (24)	708 (34)	880 (31)	**<0.001**
Morbid Obesity	49 (7)	89 (4)	138 (5)	**0.005**
Pathology, n (%)				**<0.001**
Primary hepatobiliary	161 (23)	551 (26)	712 (25)	
Secondary (metastatic)	308 (44)	1092 (52)	1401 (50)	
Benign	217 (31)	349 (17)	566 (20)	
Liver specific features, n (%)				
Pringle maneuver	101 (14)	618 (29)	719 (25)	**<0.001**
Viral hepatitis	88 (14)	212 (11)	300 (12)	0.13
Concurrent ablation	82 (12)	320 (15)	402 (14)	**0.02**
Outcomes, n (%)				
Serious Morbidity or Mortality	42 (6)	267 (13)	309 (11)	**<0.001**
Transfusion	67 (9)	398 (19)	465 (17)	**<0.001**
Bile Leak	23 (3)	158 (7)	181 (6)	**<0.001**
Liver Failure	8 (1)	100 (5)	108 (4)	**<0.001**
Postop Reoperation or Intervention	38 (5)	209 (10)	247 (9)	**<0.001**
30-Day Readmission	56 (8)	215 (10)	271 (10)	0.09

MIS: minimally invasive surgery; n: number; SD: standard deviation; NSQIP: National Surgical Quality Improvement Program; ASA: American Society of Anesthesiologists

Table 2: Outcomes among patients undergoing both minimally invasive and open hepatectomy among five challenging subgroups including both major and minor hepatectomies.

	MIS	Open	All	p value
Large Tumor, n (%)	157 (23)	536 (77)	693 (100)	-
Major hepatectomy	36 (23)	280 (52)	316 (46)	**<0.001**
Serious Morbidity or Mortality	27 (17)	190 (36)	217 (31)	**<0.001**
Transfusion	9 (6)	76 (14)	85 (12)	**0.003**
Bile Leak	9 (6)	55 (10)	64 (9)	0.08
Post-Operative Liver Failure	1 (1)	30 (6)	31 (5)	**0.008**
Postop Reoperation or Intervention	11 (7)	62 (12)	73 (11)	0.10
30-Day Readmission	12 (8)	58 (11)	70 (10)	0.24
Cirrhosis	93 (33)	192 (67)	285 (100)	-
Major hepatectomy	16 (17)	68 (35)	84 (30)	**0.002**
Serious Morbidity or Mortality	7 (8)	19 (10)	26 (9)	0.66
Transfusion	8 (9)	32 (17)	40 (14)	**0.07**
Bile Leak	2 (2)	12 (6)	14 (5)	0.14
Post-Operative Liver Failure	5 (5)	17 (9)	22 (8)	0.30
Postop Reoperation or Intervention	5 (5)	21 (11)	26 (9)	0.12
30-Day Readmission	8 (9)	18 (9)	26 (9)	0.77
≥3 Concurrent Resections	147 (20)	573 (80)	720 (100)	-
Major hepatectomy	30 (20)	196 (34)	226 (31)	**0.001**
Serious Morbidity or Mortality	16 (11)	72 (13)	88 (12)	0.58
Transfusion	15 (10)	78 (14)	93 (13)	0.27
Bile Leak	9 (6)	40 (7)	49 (7)	0.69
Post-Operative Liver Failure	3 (2)	22 (4)	25 (4)	0.29
Postop Reoperation or Intervention	12 (8)	48 (8)	60 (8)	0.92
30-Day Readmission	15 (10)	47 (8)	62 (9)	0.74
Neoadjuvant Chemotherapy	171 (21)	708 (81)	879 (100)	-
Major hepatectomy	44 (26)	352 (50)	396 (45)	**<0.001**
Serious Morbidity or Mortality	9 (5)	110 (16)	119 (14)	**<0.001**
Transfusion	29 (17)	140 (20)	169 (19)	0.40
Bile Leak	8 (5)	57 (8)	65 (8)	0.12
Post-Operative Liver Failure	4 (2)	38 (5)	42 (5)	0.10
Postop Reoperation or Intervention	10 (6)	69 (10)	79 (9)	0.11
30-Day Readmission	13 (8)	83 (12)	96 (11)	0.29
Morbid Obesity	49 (36)	89 (65)	138 (100)	-
Major hepatectomy	8 (16)	19 (21)	27 (20)	0.48
Serious Morbidity or Mortality	4 (8)	11 (12)	15 (11)	0.84
Transfusion	11 (22)	16 (18)	27 (20)	0.53
Bile Leak	0 (0)	4 (5)	4 (3)	0.13
Post-Operative Liver Failure	0 (0)	2 (2)	2 (2)	0.29
Postop Reoperation or Intervention	5 (10)	8 (9)	13 (9)	0.82
30-Day Readmission	5 (10)	7 (8)	12 (9)	0.64

MIS: minimally invasive surgery
n: number

Table 3: Patient demographics, treatment characteristics, and outcomes among patients undergoing minimally invasive or open major hepatectomy

	MIS (n=132)	Open (n=883)	All (n=1015)	p value
Demographics				
Age, mean (SD)	57 (14)	57 (14)	57 (14)	0.95
Female, n (%)	73 (53)	451 (51)	524 (52)	0.37
Non-white race, n (%)	23 (20)	121 (18)	144 (18)	0.53
BMI, mean (SD)	28.2 (7)	27.6 (6)	27.7 (6)	0.23
Concomitant colon resection, n (%)	3 (2)	27 (3)	30 (3)	0.62
ASA Class, n (%)				0.47
I	2 (2)	43 (5)	45 (4)	
II	33 (25)	231 (26)	264 (26)	
III	87 (66)	551 (62)	638 (63)	
≥IV	10 (8)	57 (7)	67 (7)	
NSQIP Morbidity Probability, mean (SD)	0.23 (0.08)	0.24 (0.08)	0.24 (0.08)	0.31
Challenging subgroups, n (%)				
Large Tumor	36 (27)	280 (32)	316 (31)	0.35
Cirrhosis	16 (12)	68 (8)	84 (8)	0.08
≥ 3 concurrent resections	30 (23)	196 (22)	226 (22)	1
Neoadjuvant	44 (33)	352 (40)	396 (39)	0.21
Morbid Obesity	8 (6)	19 (2)	27 (2)	**0.02**
Pathology, n (%)				0.06
Primary hepatobiliary	34 (26)	242 (27)	276 (27)	
Secondary (metastatic)	65 (49)	454 (51)	519 (51)	
Benign	31 (23)	127 (14)	158 (16)	
Liver specific features, n (%)				
Pringle maneuver	29 (22)	209 (30)	298 (29)	0.06
Viral hepatitis	16 (14)	87 (11)	103 (11)	0.44
Concurrent ablation	16 (12)	83 (9)	99 (10)	0.41
Outcomes, n (%)				
Serious Morbidity or Mortality	8 (6)	136 (16)	145 (14)	**0.003**
Transfusion	23 (17)	216 (24)	239 (24)	0.08
Bile Leak	9 (7)	94 (11)	103 (10)	0.22
Post-Operative Liver Failure	3 (2)	72 (8)	75 (7)	**0.03**
Postop Reoperation or Intervention	12 (9)	111 (13)	123 (12)	0.34
30-Day Readmission	15 (11)	100 (11)	115 (11)	1

MIS: minimally invasive surgery
n: number
SD: standard deviation
NSQIP: National Surgical Quality Improvement Program
ASA: American Society of Anesthesiologists

Table 4: Odds ratios of primary and secondary outcomes associated with minimally invasive hepatectomy after adjustment.

	Outcome	OR (95% CI)	p value
All patients	Serious Morbidity or Mortality	0.57 (0.34-0.96)	**0.03**
n=2819 (706 MIS)	Transfusion	0.60 (0.40-0.92)	**0.02**
	Bile Leak	0.77 (0.40-1.50)	0.44
	Post-Hepatectomy Liver Failure	0.51 (0.22-1.18)	0.12
	Postop Reoperation or Intervention	0.52 (0.29-0.93)	**0.03**
	30-day Readmission	0.71 (0.41-1.22)	0.21
Major Hepatectomy	Serious Morbidity or Mortality	0.37 (0.13-1.11)	0.08
n=1015 (132 MIS)	Transfusion	0.53 (0.24-1.18)	0.12
	Bile Leak	0.57 (0.19-1.67)	0.30
	Post-Hepatectomy Liver Failure	0.33 (0.07-1.45)	0.14
	Postop Reoperation or Intervention	0.80 (0.34-1.92)	0.62
	30-Day Readmission	0.94 (0.37-2.41)	0.90
Large Tumor	Serious Morbidity or Mortality	0.54 (0.26-1.15)	0.11
n=693 (157 MIS)	Transfusion	0.57 (0.34-0.97)	**0.04**
	Bile Leak	0.65 (0.29-1.45)	0.29
	Post-Hepatectomy Liver Failure	0.19 (0.03-1.49)	0.12
	Postop Reoperation or Intervention	0.60 (0.29-1.24)	0.17
	30-Day Readmission	0.79 (0.40-1.58)	0.51
Cirrhosis	Serious Morbidity or Mortality	0.97 (0.36-2.61)	0.96
n=285 (93 MIS)	Transfusion	0.48 (0.20-1.14)	0.10
	Bile Leak	0.59 (0.12-3.00)	0.53
	Post-Hepatectomy Liver Failure	0.66 (0.22-1.99)	0.47
	Postop Reoperation or Intervention	0.66 (0.22-1.94)	0.45
	30-Day Readmission	1.25 (0.48-3.24)	0.65
≥ 3 concurrent	Serious Morbidity or Mortality	1.04 (0.56-1.92)	0.90
resections	Transfusion	0.79 (0.42-1.47)	0.45
n=720 (147 MIS)	Bile Leak	0.96 (0.43-2.14)	0.92
	Post-Hepatectomy Liver Failure	0.92 (0.26-3.46)	0.90
	Postop Reoperation or Intervention	1.04 (0.51-2.1)	0.92
	30-Day Readmission	1.49 (0.79-2.82)	0.22
Neoadjuvant	Serious Morbidity or Mortality	0.33 (0.15-0.70)	**0.004**
chemotherapy	Transfusion	1.07 (0.66-1.72)	0.78
n=879 (171 MIS)	Bile Leak	0.78 (0.35-1.72)	0.53
	Post-Hepatectomy Liver Failure	0.71 (0.24-2.13)	0.54
	Postop Reoperation or Intervention	0.72 (0.35-1.47)	0.36
	30-Day Readmission	0.61 (0.32-1.18)	0.14
Morbid Obesity	Serious Morbidity or Mortality	0.68 (0.17-2.63)	0.57
n=138 (49 MIS)	Transfusion	1.66 (0.57-4.89)	0.78
	Bile Leak	-*	-
	Post-Hepatectomy Liver Failure	-*	-
	Postop Reoperation or Intervention	1.09 (0.28-4.24)	0.90
	30-Day Readmission	1.48 (0.36-6.14)	0.59

*model failed to converge due to low event rates
MIS: minimally invasive surgery
n: number
OR: odds ratio
CI: confidence interval

Part II: A Nationwide Rise in the Use of Stents for Benign Esophageal Perforation

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Introduction: Benign perforation of the esophagus is a rare but highly morbid disease with a mortality of approximately 10-20%.[71] Untreated contamination of the mediastinum and pleural spaces leads to sepsis, multi-organ failure, and death. Definitive surgical treatment includes primary repair of the esophageal defect and debridement, decortication and drainage of the mediastinum and pleural spaces. Some patients are ineligible for operative management because of severe underlying comorbid conditions, poor functional status, complications of perforation (e.g. septic shock, respiratory failure, etc.), or delay in presentation. In such cases, the goals of treatment are to control the esophageal leak, drain contaminated thoracic cavities, and administer antibiotic and nutritional support. Drainage alone is often appropriate for isolated cervical perforation and creation of a controlled esophagocutaneous fistula (e.g. via T-tube drainage) combined with wide drainage has been used to control an esophageal leak when primary repair is not possible.

In the mid-2000's, the Food and Drug Administration (FDA) approved the use of esophageal stents for the management of malignant stricture and/or fistula. The use of stents for the management of benign esophageal perforation is a logical extension of the original FDA approved indication, and yet its use for this indication remains "off-label." A growing number of observational studies suggest that stents may be as effective as primary surgical therapy with lower associated risks, length-of-stay (LOS), and costs.[7,72,73] We hypothesize that off-label use of stents for management of benign esophageal perforation has increased during the past decade. A secondary goal of this study was to describe trends in overall outcomes and costs over time, and their association with varying approaches to treatment.

Methods: We performed a retrospective cohort study of adults diagnosed and treated for esophageal perforation between January 15, 2007 and June 30, 2014 with six months of follow-up using the Thomson Reuters MarketScan® Research Databases. This database includes information from employer- and health plan-sourced enrollment and claims data with person-level healthcare utilization across inpatient and outpatient settings. These data are available for workers and their dependents covered by employer-sponsored private health insurance. Diagnoses are codified using the International Classification of Diseases, 9th Revision (ICD-9), and procedures and services are codified using the Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes (see Appendix A). Patients were required to have continuous health plan enrollment two weeks prior to and six months after esophageal perforation (unless disenrollment was due to death within six months) to ensure complete capture of claims. The MarketScan® database only includes claims data for the supplemental insurance of those patients enrolled in Medicare. As such, patients enrolled in Medicare would have incomplete healthcare utilization data and so patients over age 64 were excluded. Other exclusions were a diagnosis of esophageal cancer in the year prior to and six months after perforation, and patients who underwent esophageal stenting for any reason in the year prior to perforation. This study was approved by the University of Washington Institutional Review Board.

Subjects were divided into three groups—those treated with surgical repair, esophageal stent without repair, or surgical drainage alone—based upon treatment codes during the first seven days of index hospitalization for esophageal perforation. If patients were stented and subsequently surgically drained, they were counted in the stenting group. Information was also collected on measured potential confounders. Age at the time of diagnosis, sex, and health plan type were obtained through enrollment data. The Charlson comorbidity index (CCI) was determined based on claims from inpatient and outpatient claims during the 30 days following diagnosis using methods by Quan.[74] Because endoscopy can lead to esophageal perforation, we also measured use of both diagnostic and therapeutic endoscopy during the 14 days prior to perforation as a surrogate for iatrogenic perforation. If patients had no documented endoscopy during the 14 days prior, we considered the perforation to be spontaneous (i.e. Boerhaave's).

Outcomes included discharges to home after index hospitalization and death during the index or readmissions within six months of diagnosis (MarketScan® does not ascertain outpatient deaths). Claims in the six months after diagnosis of esophageal perforation were used to describe healthcare utilization as measured by the LOS of the index hospitalization and readmissions. Total direct medical expenditures were measured in the six month period after perforation. Out-of-pocket costs (copayments, deductibles, and coinsurance) were also measured. This analysis takes the perspective of the insurer and the patient as total direct costs include both reimbursements to the insurer and out-of-pocket expenses for the patient. Costs were adjusted for inflation using the Consumer Price Index for Medical Care Services to 2014 United States (US) dollars.[75]

Differences between treatment groups were assessed by Analysis of Variance and Kruskal Wallis tests for normally and non-normally distributed continuous variables, respectively and by Chi-squared tests for categorical data. Unadjusted trends over the period of this study were assessed using a non-parametric test of trend (continuous variables) or a Mantel Haenszel test of trend (binary variables).[76,77] Patients who are treated with esophageal stents and surgical drainage are often sicker than those who are treated by conventional surgical repair. Because claims data do not provide sufficiently granular information about the patient's physiologic status, severity of comorbid conditions, and functional status, we did not perform comparative analyses of outcomes, utilization, or costs between management approaches. In order to estimate trends in treatments over time, however, we did adjust for potential changes in patient characteristics over time. Adjustment covariates included age, sex, Charlson comorbidity index, health plan type, and when applicable, presence of prior endoscopy. We assumed that stent use would occur in at least 10% of perforations. Accordingly, we used Poisson regression to estimate trends in the use of stents over time relative to surgical treatments because we assumed stent use to not be rare.[78] To measure temporal trends in outcomes, we modeled differences in in-hospital death (logistic regression), hospital LOS, total six-month costs (generalized linear model [GLM] with an identity link and gamma distribution), risk of discharge to home (Poisson, among those who survived the index hospitalization), and hospital readmission (logistic, for those who survived the index hospitalization) over time. Each adjusted analysis was performed among the total population of patients as well as a planned subgroup analysis for patients with presumed Boerhaave's perforation (i.e. excluding patients

who underwent endoscopy two weeks prior to hospitalization for perforation). Covariate data was missing for only health plan type and in only 4% of cases. There were no differences in treatment type between those with and without missing covariate data ($p>0.05$), and the proportion of patients with missing covariate data did not change over time ($p>0.05$). All analyses were case complete, and all adjusted analyses used robust standard errors. Statistical significance was defined by $p<0.05$. Analyses were performed using commercially available software packages (Stata v. 14.2 IC, StataCorp LP College Station, TX).

Results: Over this eight year study, 659 patients were hospitalized and treated for esophageal perforation (Table). Patients were predominantly middle-aged men. A majority had at least one comorbid condition and were enrolled in a low-deductible health plan. Just over a third underwent endoscopy two weeks prior to hospitalization for perforation, and a majority of these endoscopic procedures were therapeutic. Most patients were treated by surgical repair (69%) with the remainder of patients treated with either surgical drainage (17%) or via esophageal stenting (15%). Overall, typical index LOS was 13 days. While a majority of patients discharged home (77%), the rate of readmission was high (39%). Over the six month follow-up period, 6% of patients died during a hospitalization, and most deaths occurred during the index hospitalization. The median six month total cost of care after benign esophageal perforation for a given patient was $145,942, and the median six month out-of-pocket cost was $5,034. The total costs of care for the 659 patients in this study was $151.6M.

Figure 1 shows that the use of esophageal stents increased over four-fold from 7% in 2007 to 30% in 2014 (p-trend<0.001). The unadjusted rate of increase in stent use was 28% per year (incidence rate ratio [IRR] 1.28, 95% confidence interval [CI] 1.18-1.40). Over the same period, the frequency of surgical repair decreased by one quarter from 71% in 2007 to 53% in 2014 (p-trend=0.001). The unadjusted rate of decrease in surgical repair was 4% per year (IRR 0.96, 95% CI 0.93-0.98). Surgical drainage procedures did not change in frequency over the study period (p-trend=0.24). We explored whether any measured covariates changed significantly over time and found that enrollment in low-deductible insurance plans increased significantly (p=0.01) while enrollment in high-deductible plans decreased significantly (p<0.001) over the study period. Patient age, sex, comorbidity score, and

frequency of prior EGDs did not change over the course of eight years (all p>0.05). Adjusting for changing patient characteristics over time revealed the same trends (i.e. rates) in treatment type.

Figure 2 shows that the frequency of discharges home and six-month inpatient death rates did not change over time. Over the same period, the rate of readmission did not change significantly, nor did the median LOS or costs (all p>0.05). Adjusted analyses did not reveal any change in outcomes or costs over time (all p>0.05). While risk-adjusted LOS trended downward during the course of this study (p=0.04), this appeared consistent across treatment types.

Patient characteristics and unadjusted outcomes, utilization, and costs varied by treatment (Table). As expected, patients treated with a stent or surgical drainage tended to have more comorbid conditions relative to those who underwent surgical repair. Therapeutic endoscopy prior to perforation was associated with esophageal stenting (p=0.02). Surgical repair was associated with the lowest unadjusted hospital mortality and readmission rate, shortest LOS, and least costs. Patterns of utilization were notably different between stenting and surgical drainage. LOS of was highest for surgical drainage (16 days) with comparable readmission rates relative to surgical repair. In contrast, compared with surgical repair, stenting was associated with a similar LOS but with the highest rate of readmission occurring in over half of patients. Six-month mortality rates were similar and high for patients treated with either esophageal stenting (12%) or surgical drainage (11%). However, among the surgical drainage group a majority of these deaths occurred during the index hospitalization (9%), whereas a majority of these deaths occurred during subsequent hospitalizations among those treated with esophageal stenting (8%). Esophageal stenting was associated with the highest unadjusted six-month costs of care relative to surgical interventions. A *post-hoc* exploratory analysis (controlling for number of subsequent hospitalizations) revealed that the greater costs seen among patients treated by esophageal stenting may be explained by the higher rate of readmission in this group.

A planned subgroup analysis was conducted among patients who had not undergone endoscopy in the two week period prior to hospitalization for perforation. Temporal trends and patterns of outcomes, utilization, and costs across varying management strategies were similar in this subgroup with presumed

spontaneous (Boerhaave's) esophageal perforation compared to the overall population of patients with esophageal perforation (Appendix B).

Discussion: This study is the first to describe trends in the management of benign esophageal perforation in the US, as well as associated patient outcomes, healthcare utilization, and costs in the community-at-large. The key finding from this study is that the use of esophageal stents has increased by four-fold over eight years coincident with a proportional decrease in surgical repair and no evidence of a change in outcomes, utilization, or costs among the overall population.

The most likely explanation for the treatment trends observed in this study is that providers *believe* that esophageal stenting is frequently a reasonable alternative to surgical repair, and in some settings may be superior. It is logical to consider esophageal stenting for perforation management as a means to achieving source control. When coupled with adequate drainage of the mediastinum and pleural spaces, lung expansion, antibiotics, and nutrition, esophageal stenting as part of a comprehensive treatment plan might reasonably be expected to lead to similar outcomes as repair.[8] Supporting this logic are several retrospective single-institution or single health-system observational studies that have reported excellent outcomes associated with esophageal stenting among both patients who were and were not candidates for surgical repair.[3,7,8,72]

The alternative explanation for the treatment trends in our study is that patients have become "sicker" over time. However, we found no evidence of a trend in comorbidity index over time. Additionally, there is no reason to believe that patients have more severe manifestations of esophageal perforation and/or delayed presentations over time. Symptoms of esophageal perforation are typically severe leading patients to seek care. Access to care has likely not changed dramatically in the US over the study period for a population of individuals with employer-provided health insurance.

Despite significant changes in the management of esophageal perforation over time, there were no trends in outcomes, utilization, or costs. One explanation for this finding is that esophageal stenting and surgical repair have equivalent outcomes when applied selectively. It is likely that there are patients better served by surgical repair, and others who have equivalent or even superior outcomes with stenting. In our study, however, we are not able to parse out the indications providers used for selecting one

modality over the other. Another possibility is that esophageal stenting is inferior to surgical repair. If surgical outcomes are improving over time, then rapid adoption of esophageal stenting could "counter-balance" the improving surgical outcomes resulting in no overall change in this population's outcomes over time. It is somewhat discouraging that the adoption of a new treatment option for patients with esophageal perforation would not be associated with improved outcomes over time, but perhaps this is due to uneven application of stenting for patients most likely to benefit from stenting when no guidelines exist to help providers apply alternative treatment algorithms optimally.

For several reasons, our findings lead us to hypothesize that esophageal stenting is inferior to surgical repair in the community-at-large. Our analysis of outcomes after treatment reveal that surgical repair is associated with the best outcomes and surgical drainage is associated with the worst outcomes. This finding is expected given that some patients are "too sick" to undergo surgical repair and their outcomes are driven (i.e. confounded) by their underlying comorbid conditions or the severity or timing of the perforation. For this reason, we would also expect the outcomes of the esophageal stenting to be similar to surgical drainage, if stenting was used to treat the sickest patients. However, esophageal stenting appears to be "replacing" surgical repair rather than surgical drainage, and patterns of outcomes between stenting and surgical drainage were dissimilar. Patients treated with esophageal stenting had higher readmission rates. Our post-hoc analysis suggests that these readmissions appear to explain the higher six-month total costs of care associated with esophageal stenting. Finally, patients were more likely to die in a subsequent hospitalization compared to surgical drainage. This finding suggests that stented patients may experience delayed morbidity and mortality which could be explained by incomplete or absent source control (drainage of mediastinum and pleural spaces), suboptimal antibiotic administration, or failure to provide optimal nutrition.

Our study has several important limitations. The most important limitation is confounding from unmeasured variables that describe the severity of underlying comorbid conditions and functional status, complications of esophageal perforation, and time-to-presentation, degree of contamination, and physiologic impact on the patient. This limitation precludes knowing the indications for treatment. As a consequence, we cannot know for certain the reasons underlying temporal trends in management or

compare outcomes across management strategies. Risk-adjustment strategies such as regression and propensity score analyses cannot overcome the problem of unmeasured confounding.[79] Unfortunately, there are currently no clinical registries that ascertain variables relevant to the management of esophageal perforation, and all prior studies suffer from similar limitations as ours.[80] In addition, by specifying a minimum of two weeks enrollment prior to perforation, we may miss diagnoses of esophageal cancer or stenting procedures. A sensitivity analysis of patients with one full year of pre-enrollment (n=421), however, revealed the same trends in choice of treatment and outcomes. Another limitation is generalizability. Through MarketScan® we cannot describe the specialty training or location of care received, both of which may impact patient outcomes. It is also likely that associated outcomes among all treatment strategies are better in our population compared to the uninsured, unemployed, and individuals older than 65 years of age. Finally, the MarketScan® database does not ascertain deaths that occur outside the inpatient setting. As a consequence, it is possible that we may have underestimated short-term mortality.

The lack of high level evidence about the efficacy and safety of stents for benign esophageal perforations, and the increase in off-label use of stents for this indication reported for the first time in this study, reveal an opportunity—creation of a national clinical registry for benign esophageal perforation. Although a randomized trial comparing treatment outcomes is preferred, it is unlikely to be feasible because benign esophageal perforations are rare,[81] and a non-inferiority design typically requires a large sample size. In the absence of a trial, a clinical registry with prospectively defined data elements that ascertain relevant variables of interest (including indication, severity of underlying comorbid conditions and functional status, and severity and timing of perforation) could allow for a risk-adjusted comparison of treatment outcomes. Another benefit of such a clinical registry would be to monitor the quality of care and give providers feedback about their performance. Doing so may address the main hypothesis that arises from our current investigation—esophageal stenting is inferior to surgical repair in the community-at-large because of the lack of a comprehensive treatment plan that addresses mediastinal and pleural contamination, appropriate antibiotic use, and nutrition. Finally, administering such a clinical registry would allow surgeons and gastroenterologists to take a leadership role in addressing growing concerns about off-label use of medical devices. Examples such as the STS/ACC TVT Registry™

(https://www.ncdr.com/webncdr/tvt/publicpage/data-collection) provide a precedent for multi-disciplinary collaboration for building a disease-based registry for the purposes of quality improvement and scientific advancement with an eye towards achieving better patient outcomes.

Acknowledgements: We would like to thank the University of Washington, Division of Cardiothoracic Surgery and Megan Zadworny, MHA for support in completing this research. Dr. Thornblade is supported by a training grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK070555. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Table: Patient characteristics, outcomes, and costs by management of esophageal perforation

	Surgical Repair n = 449	Stent n = 100	Surgical Drainage n = 110	All patients n = 659	p-value
Demographics					
age, mean (SD)	49 (11)	51 (11)	48 (11)	49 (12)	0.17
female, n (%)	183 (41)	43 (43)	46 (42)	272 (41)	0.91
Charlson Comorbidity Index, n (%)					**0.02**
0	205 (46)	36 (36)	40 (36)	281 (43)	
1	125 (28)	22 (22)	32 (29)	179 (27)	
≥2	119 (27)	42 (42)	38 (35)	199 (30)	
Health Insurance Type, n (%)					0.53
HMO or Capitated POS	56 (13)	12 (12)	13 (12)	81 (13)	
Low deductible insurance	334 (78)	74 (76)	87 (83)	495 (78)	
High deductible insurance	40 (9)	11 (11)	5 (5)	56 (9)	
EGD within 2 weeks prior, n (%)					
Therapeutic	77 (17)	32 (32)	18 (16)	127 (19)	**0.002**
Diagnostic	77 (17)	17 (17)	24 (22)	118 (18)	0.87
Any	154 (34)	49 (49)	42 (38)	245 (37)	**0.02**
6-month Healthcare Utilization					
Length of Stay, median (IQR)	12 (8-20)	13 (5-27)	16 (10-25)	13 (8-22)	**0.03**
Readmission*, n (%)	159 (36)	52 (54)	38 (38)	249 (39)	**0.004**
6-month total costs, $USD					
Median (IQR)	$126,573 (75,583-234,386)	$192,321 (93,922-319,313)	$156,894 (85,819-352,652)	$145,942 (78,182-264,105)	**0.005**
Mean (SD)	$225,445 (337,748)	$248,978 (216,302)	$231,845 (201,070)	$230,084 (302,445)	0.78
6-month out of pocket costs, median (IQR)	$4,987 (2,539-8,418)	$5,906 (3,577-9,071)	$4,551 (2,573-8,009)	$5,034 (2,796-8,470)	0.12
mean (SD)	$6,864 (8,882)	$7,008 (6,043)	$5,897 (4,730)	$6,724 (7,941)	0.48
Outcomes					
Discharge to home*, n (%)	346 (79)	72 (72)	74 (74)	492 (77)	0.73
Death, n (%)					
Index hospitalization	8 (2)	4 (4)	10 (9)	22 (3)	**0.001**
Subsequent hospitalization	5 (1)	8 (8)	2 (2)	15 (2)	**<0.001**
Any	13 (3)	12 (12)	12 (11)	37 (6)	**<0.001**

***** among those who survived their initial hospitalization

Figure 1: Trends in Management of Benign Esophageal Perforation

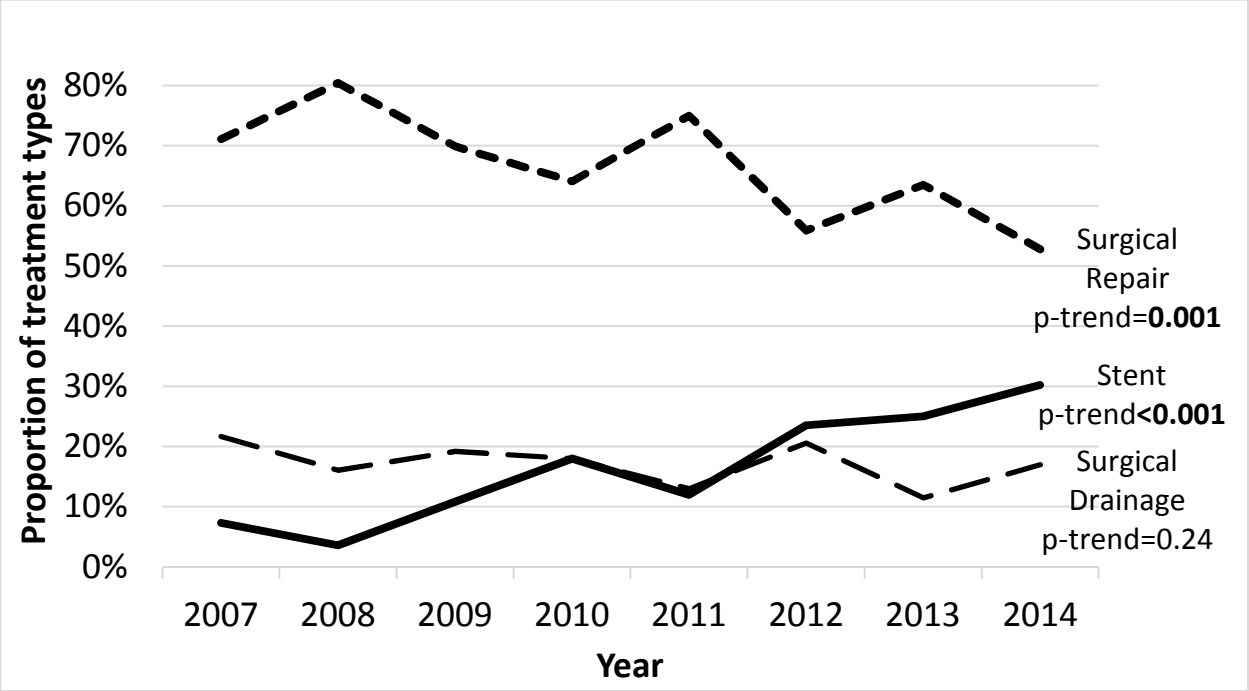


Figure 2a: Trends in Outcomes for Patients with Esophageal Perforation

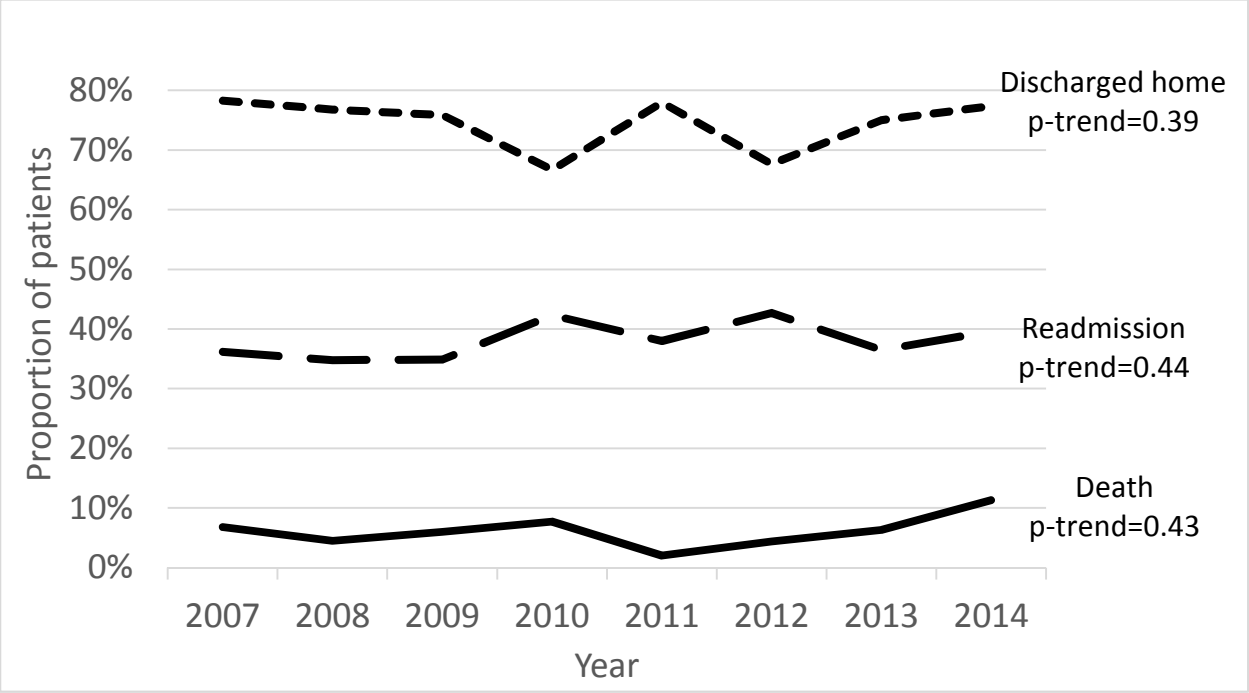
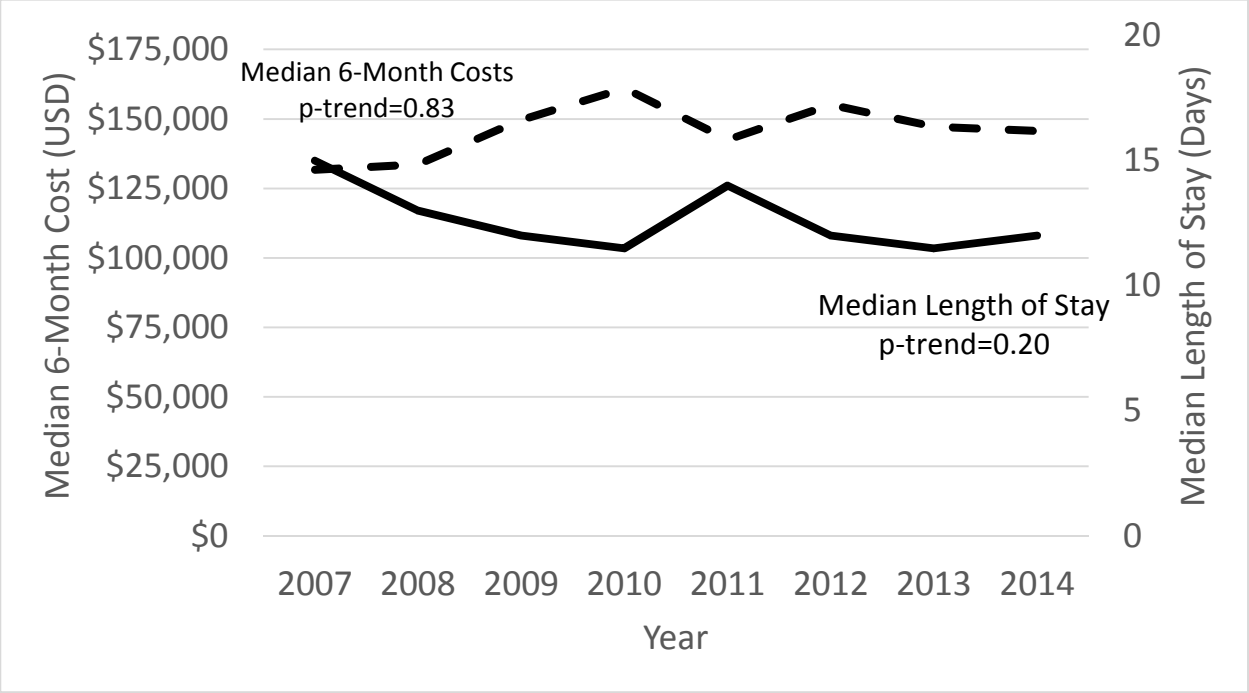


Figure 2b: Trends in Utilization for Patients with Esophageal Perforation



Thesis Discussion: As healthcare continues to develop, clinician researchers must develop and apply new skills to assess the value and effectiveness of new technologies. In the developing world, the burden of surgical disease has been increasingly recognized as an important and modifiable cause of morbidity and mortality.[82] Health services researchers who will inform policy in healthcare development in both high- and low/middle-income countries will need to apply statistical and epidemiological methods to comparative effectiveness studies.

In the first part of this thesis, I applied logistic regression and non-inferiority methods to national clinical registry data to further ascertain the safety of an innovative and minimally invasive approach to major liver resection and helped to define for which groups of patients this approach may be most appropriate. In the second part of this thesis, I used a national claims database to assess the "off-label" use of an esophageal stent to treat perforations of the esophagus which have historically been treated surgically. Because of significant uncontrolled confounding by indication present in claims data, this study required an alternative approach to assessing outcomes associated with stents. We applied a temporal trend analysis of stent use compared with conventional surgical repair and looked for trends in outcomes over time. In both studies, new technology was not universally found to be superior to existing approaches to these surgical problems, revealing the importance of such comparisons.

By choosing the appropriate methodology to fit the data source and clinical question, comparative effectiveness studies can provide useful information about potentially costly or ineffective approaches to surgery. These methods will be useful for policy makers and clinicians in determining whether or not to adopt a new technology into routine practice.

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