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Factors affecting timing of surgery following neoadjuvant chemoradiation for esophageal cancer

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ABSTRACT

Background: Neoadjuvant chemoradiation with esophagectomy is standard management for locally advanced esophageal cancer. Studies have shown that surgical timing following chemoradiation is important for minimizing postoperative complications, however in practice timing is often variable and delayed. Although postoperative impact of surgical timing has been studied, less is known about factors associated with delays.
Materials and methods: A retrospective review was performed for 96 patients with esophageal cancer who underwent chemoradiation then esophagectomy between 2018 and 2020 at a single institution. Univariable and stepwise multivariable analyses were used to assess association between social (demographics, insurance) and clinical variables (pre-operative weight, comorbidities, prior cardiothoracic surgery, smoking history, disease staging) with time to surgery (≤8 weeks "on-time" vs. >8 weeks "delayed").
Results: Fifty-one patients underwent esophagectomy within 8 weeks of chemoradiation; 45 had a delayed operation. Univariate analysis showed the following characteristics were significantly different between on-time and delayed groups: weight loss within 3 months of surgery (3.9 ± 5.1 kg vs. 1.5 ± 3.6 kg; P = 0.009), prior cardiovascular disease (29% vs. 49%; P = 0.05), prior cardiothoracic surgery (4% vs. 22%; P = 0.01), history of ever smoked (69% vs. 87%; P = 0.04), absent nodal metastasis on pathology (57% vs. 82%; P = 0.008). Multivariate analysis demonstrated that prior cardiothoracic surgery (OR 8.924, 95%CI 1.67–47.60; P = 0.01) and absent nodal metastasis (OR 4.186, 95%CI 1.50–11.72; P = 0.006) were associated with delayed surgery.
Conclusions: Delayed esophagectomy following chemoradiotherapy is associated with prior cardiothoracic surgery and absent nodal metastasis. Further investigations should focus on understanding how these factors contribute to delays to guide treatment planning and mitigate sources of outcome disparities.

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1. Introduction

Guidelines for management of locally advanced esophageal cancer include neoadjuvant chemoradiation therapy followed by surgery, with an ongoing debate regarding optimal surgical timing [1–8]. Prior research has found consistent benefits in progression-free survival and overall survival for patients receiving neoadjuvant chemoradiation plus surgery versus surgery alone [3, 8,9]. Even though neoadjuvant chemoradiation is a standard component in treating locally advanced esophageal cancer, the time interval between neoadjuvant chemoradiation and esophagectomy that occurs is variable; however, many studies use an 8-week cutoff [10–12]. Despite ongoing debate regarding optimal timing of esophagectomy following neoadjuvant chemoradiation, neither the National Comprehensive Cancer Network nor the Society of Thoracic Surgeons have specified guidelines for timing.

Prior studies have raised concern that timing of esophagectomy following neoadjuvant therapy is important for maximizing pathologic complete response and overall survival and minimizing 30-day mortality [10–12]. However, there remains limited investigation into patient and clinical factors associated with delayed receipt of esophagectomy. Some have argued that patients with increased comorbidities and weight loss may have more delays in surgery due to medical and nutritional optimization [13–16]. In addition, patients with lower clinical stage may be more likely to receive timely operations following neoadjuvant therapy [14,15]. Currently, the association of a patient's demographics, clinical factors, and tumor stage with the timing of esophagectomy following neoadjuvant chemoradiation is unclear.

In this single-center retrospective review, we evaluate all patients undergoing neoadjuvant chemoradiation followed by esophagectomy for locally advanced esophageal cancer. The aim of this study is to evaluate the impact of factors such as preoperative physical fitness, patient comorbidities, or disease staging on the timing of surgery. We hypothesize that worsened physical fitness, increased patient comorbidities, and more advanced disease stages will be associated with delayed receipt of esophagectomy.

2. Materials and Methods

2.1. Data source/patient population

Data for this study were collected from a retrospective database of all patients with esophageal cancer who underwent esophagectomy at a single institution between July 2018 to April 2020. The data set used in this analysis represented single institution data capture for the Society of Thoracic Surgeons General Thoracic Surgery Database. One hundred eighteen patients were identified and 96 patients underwent neoadjuvant chemoradiation therapy prior to esophagectomy. Patients who received only chemotherapy were excluded from analysis (N = 22). Surgical approaches included all minimally invasive and open esophagectomies performed using *trans*-hiatal, Ivor-Lewis and McKeown techniques. This study was determined to be exempt by the University of Michigan Institutional Review Board (HUM00012731).

2.2. Outcomes

Timing of esophagectomy following neoadjuvant therapy was determined by identifying the completion date of neoadjuvant thoracic radiation therapy or chemotherapy (using the later date if the patient underwent both therapy options) from the date of esophagectomy. This time interval was calculated in days and converted to weeks for the purpose of this study. Patients who received esophagectomy within 8 weeks were considered to have surgery "on-time" whereas patients who received esophagectomy beyond 8 weeks were considered to have surgery "delayed". This dichotomy of 8 weeks was used based on previous studies that have indicated this interval as an important cutoff in the association between timing of esophagectomy and clinical outcomes [10–12].

2.3. Variable selection

Factors thought to contribute to operative delay included: patient demographics (age at surgery, sex, insurance), current weight, weight loss within 3 months of surgery, hypertension, prior cardiovascular disease, diabetes, prior cardiothoracic surgery, history of anticoagulant therapy, creatinine level, having ever smoked (former or current smoker), and clinical and pathologic disease staging. Prior cardiothoracic surgery included any prior cardiothoracic surgery, prior sternotomy, prior VATS/Robotic cardiothoracic surgery, prior pulmonary resection, or prior thoracotomy. Type of insurance was categorized as either public (Medicare, Medicaid, Military) or private (commercial, health maintenance organization, none/self). Prior cardiovascular disease was defined as any diagnosis of congestive heart failure, coronary artery disease, myocardial infarction, atrial fibrillation, valvular disease, vascular disease, or deep vein thrombosis listed in the patient's medical history. Clinical and pathologic disease staging were defined according to the tumor-node-metastasis classification of the American Joint Committee for Cancer Staging, Eighth Edition [13]. Clinical primary tumor status was analyzed as presence of tumor invasion at least beyond the muscularis propria (cT > T2). Pathologic primary tumor status was analyzed as presence of tumor invasion at least beyond the lamina propria, muscularis mucosae, or submucosa (pT > T1). Pathologic regional lymph node status was analyzed as absence of regional lymph node metastasis (pN = N0).

2.4. Statistical analysis

We described characteristics of patients who had surgery "on-time" compared to surgery "delayed" using mean ± standard deviation for continuous variables and frequency (percent) for categorical variables. We assessed differences between on-time and delayed surgery using t-tests for continuous variables and chi-square test or Fisher's exact test for categorical variables. We tested which variables significant in bivariate analyses were associated with surgery being delayed using a multivariable logistic regression model. Finally, we constructed a multivariate model predicting delay in surgery using stepwise regression with p-value <0.05 for entry and >0.05 for exit to identify the most parsimonious multivariate model. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient demographics

A total of 96 patients were included in the study and the patient characteristics stratified by on-time or delayed surgery are described in Table 1. There was no significant difference in mean (SD) age between on-time compared to delayed groups (63 (10) years vs. 66 (10) years; OR 1.025, 95%CI 0.984–1.069; P = 0.24). Biological sex was similar between on-time compared to delayed groups (14% female vs. 24% female; OR 2.034, 95%CI 0.713–5.800; P = 0.18). Average weight prior to surgery was similar between on-time and delayed groups (85 ± 16 kg vs. 80 ± 18 kg; OR 0.984, 95%CI 0.960–1.008; P = 0.18). However, weight loss 3 months prior to surgery was significantly lesser in patients who underwent delay in resection (3.9 ± 5.1 kg vs. 1.5 ± 3.6 kg; OR 0.863, 95%CI 0.764–0.976; P = 0.01). Prior cardiovascular disease was the only comorbidity we observed with significant difference in prevalence (29% in on-time vs. 49% in delayed; OR 2.296, 95%CI 0.992–5.314; P = 0.05). There was a significant difference with regards to prior cardiothoracic surgery (4% in on-time, 22% in delayed; OR 6.999, 95%CI 1.443–33.941; P = 0.01). There was a significantly smaller portion of patients who have ever smoked in the on-time versus the delayed group (69% vs. 87%; OR 2.971, 95%CI 1.047–8.435; P = 0.04). Proportion of patients with pathologic regional lymph node status of pN = N0 was significantly less in the on-time group compared to the delayed group (57% vs. 82%; OR 3.509, 95%CI 1.365–9.018; P = 0.008).

3.2. Logistic regression model predicting delayed esophagectomy

Variables found to be significant in bivariate analysis of having operative delay were included in a multivariate logistic regression model shown in Table 2. After adjustment for multiple variables, logistical regression demonstrated weight loss in the past 3 months to not be significantly associated with higher odds of receiving delayed esophagectomy (OR 0.887, 95%CI 0.779–1.009; P = 0.07). There was also no significant association with prior cardiovascular disease (OR 1.730, 95%CI 0.634–4.718; P = 0.28), prior cardiothoracic surgery (OR 5.489, 95%CI 0.919–32.783; P = 0.06), or prior smoking (OR 2.123, 95%CI 0.693–6.502; P = 0.19). The only significant variable associated with higher odds of receiving delayed esophagectomy was pathologic regional lymph node status of pN = N0 (OR 3.344, 95%CI 1.147–9.753; P = 0.03).

Table 1
Baseline characteristics of patients associated with timing of surgery. Data are mean ± SD or N (%).

	= 8 weeks	>8 weeks	OR (95%CI)	p-value
N	51 (53%)	45 (47%)		
Age at surgery	63 ± 10	66 ± 10	1.025 (0.984–1.069)	0.2356
Sex				0.1794
Female	7 (14%)	11 (24%)	2.034 (0.713–5.800)	
Male	44 (86%)	34 (76%)		
Insurance				0.1931
Private (commercial, health maintenance organization, none/self)	20 (39%)	12 (27%)	0.563 (0.237–1.342)	
Public (Medicare, Medicaid, military)	31 (61%)	33 (73%)		
Weight (kilogram)	85 ± 16	80 ± 18	0.984 (0.960–1.008)	0.1829
Weight loss in past 3 months (kilogram)	3.9 ± 5.1	1.5 ± 3.6	0.863 (0.764–0.976)	0.0087
Hypertension	27 (53%)	30 (67%)	1.778 (0.776–4.071)	0.1718
Prior cardiovascular disease	15 (29%)	22 (49%)	2.296 (0.992–5.314)	0.0504
Diabetes	15 (29%)	13 (29%)	0.975 (0.404–2.356)	0.9551
Prior cardiothoracic surgery[a]	2 (4%)	10 (22%)	6.999 (1.443–33.941)	0.0111
History of anticoagulant therapy[a]	4 (8%)	8 (18%)	2.54 (0.710–9.093)	0.2162
Creatinine level	0.87 ± 0.23	0.82 ± 0.22	0.365 (0.053–2.515)	0.3026
Hemoglobin level	12.3 ± 1.6	12.2 ± 1.4	0.929 (0.706–1.223)	0.6051
Ever smoked	35 (69%)	39 (87%)	2.971 (1.047–8.435)	0.0359
Eastern Cooperative Oncology Group (ECOG) score > 1[a]	3 (6%)	4 (7%)	1.143 (0.219–5.971)	1.000
Clinical staging: primary tumor status cT > T2	38 (75%)	34 (76%)	1.057 (0.419–2.671)	0.9060
Pathologic staging: primary tumor status pT > T1	30 (59%)	20 (44%)	0.560 (0.249–1.259)	0.1593
Pathologic staging: regional lymph node status pN = N0	29 (57%)	37 (82%)	3.509 (1.365–9.018)	0.0075

[a] Cell sizes <5 so Fisher's Exact p-value listed instead of Chi-Square p-value.

Table 2
Logistic regression results using all variables significant in bivariate analysis in model predicting having surgery delayed (>8 weeks).

	OR (95% CI)	p-value
Weight loss in past 3 months (kilogram)	0.887 (0.779–1.009)	0.0683
Prior cardiovascular disease	1.730 (0.634–4.718)	0.2845
Prior cardiothoracic surgery	5.489 (0.919–32.783)	0.0619
Ever smoked	2.123 (0.693–6.502)	0.1874
Pathologic staging: regional lymph node status pN = N0	3.344 (1.147–9.753)	0.0271

3.3. Stepwise logistic regression model predicting delayed esophagectomy

In an effort to find the most parsimonious model to predict delay in surgery, only prior cardiothoracic surgery (OR 8.924, 95%CI 1.67–47.60; P = 0.01) and pathologic regional lymph node status of pN = N0 were predictive of delayed esophagectomy following chemoradiation (OR 4.186, 95%CI 1.50–11.72; P = 0.01), see Table 3.

4. Discussion

In this study, our findings expand upon understanding of patient and clinical factors associated with delayed esophagectomy. There are two key findings: history of prior cardiothoracic surgery and early-stage disease without nodal involvement were predictive of delayed esophagectomy following chemoradiation. There was no association between patient social factors with timing of surgery.

In review of clinical factors, our data indicates that history of prior cardiothoracic surgery is predictive of delayed esophagectomy following chemoradiation. From our review, there are no studies that have focused on describing this specific relationship, however it is a trend that is seen with many malignancies that undergo neoadjuvant chemoradiation therapy [14]. This is thought to be due to a need for medical optimization and longer recovery from chemoradiation treatment prior to surgery. Our study also found that early-stage esophageal cancer with absence of regional lymph node metastasis on pathology was significantly associated with higher odds of receiving delayed surgery following neoadjuvant therapy. Similar findings have been shown in previous studies. A study by Levinsky et al. which used a time inflection point of 90 days to distinguish timely surgery versus delayed surgery showed significantly higher proportions of esophageal cancer cases with absence of nodal involvement on pathology and well-differentiated tumors in patients with increased time to surgery [15]. This association of absence of nodal metastasis and delayed surgery was significant despite no difference in preceding chemotherapy and radiation treatment approaches. Another study conducted a retrospective review demonstrating that patients receiving surgery after 56 days had a higher proportion of absent nodal disease and increased rate of pathologic downstaging, but no difference in margin positivity and lower overall survival [16]. It is possible that this association between lack of nodal involvement and delayed surgery is a result of less aggressive disease requiring less urgency for surgical management or the absence of nodal disease may lead to changes in patient or surgeon decision making. Lastly, our data found no significant association between patient comorbidities, smoking, or weight loss within 3 months of surgery on timing of esophagectomy. Some studies have demonstrated similar findings when looking at comorbidities as a whole using the Charlson-Deyo score, however data from one study by Kim et al. suggests that coronary artery disease alone is associated with delays in esophagectomy while, as also evident in our results, diabetes and weight loss are not associated with delays in surgery [10,15,17].

Our study found no significant association between insurance type with delayed timing of esophagectomy. This contrasts with findings from prior studies which have found that public insurance (Medicaid, Medicare, other government) was associated with longer time to surgery [15,18]. One prior study demonstrated that in addition to public insurance, racial and ethnic minorities (non-Hispanic Black or Hispanic patients) and low household income were predictive of longer times to surgery [18]. This discrepancy may be explained by inherent biases of our small sample size and data drawn from a single institution with limited diversity in its patient population that may limit generalizability with regards to social factors. However, patients who are racial and ethnic minorities, lower income, or on public insurance have already been found to experience delays in surgery in larger data sets, which reflects that such groups experience worse access to care and health outcomes than privately insured individuals [19,20].

An important factor to consider with regards to surgeries performed within the year of 2020 includes the impact of delayed medical care related to responses to the COVID-19 pandemic. Within our study, only one surgery occurred after March 11, 2020. This was the date that the World Health Organization declared COVID-19 a global pandemic. Within the state of Michigan, this was also the initial date that the state governor made the first public announcement discouraging non-essential travel and gatherings of greater than 100 people. On March 13, 2020, the Michigan state governor implemented an official ban for gatherings of greater than 250 people. After March 16' 2020, subsequent bans and shut-downs were implemented to prevent the spread of COVID-19. All but one of the patients

Table 3
Stepwise logistic regression results having available all variables significant in bivariate analysis in model predicting having surgery delayed (>8 weeks).

	OR (95% CI)	p-value
Prior cardiothoracic surgery	8.924 (1.673–47.597)	0.0104
Pathologic staging: regional lymph node status pN = N0	4.186 (1.496–11.717)	0.0064

included in our study underwent surgery prior to March 11, 2020. Given that there was only one surgery that occurred after this date, response to the COVID-19 pandemic was not a significant contributing factor for delays in surgery.

It remains unclear why delayed receipt of surgery following chemoradiation therapy is associated with worse outcomes. However, it appears that identifiable factors can place patients at risk for prolonged intervals to esophagectomy. There are several avenues for future interventions that can help minimize delays in surgery. For instance, the use of nurse navigators, electronic record alerts for delays or incomplete treatment, as well as regular data feedback regarding completion of timely treatment to the interdisciplinary team providing care to cancer patients has been demonstrated to improve care for all patients with breast and lung cancer, in addition to reducing disparities, and should be considered for esophageal cancer [21–23]. In addition, there may be specific patients and sub-populations where delays in esophagectomy are necessary including those that require optimization of nutritional status, functional status, and co-morbidities prior to undergoing surgery [24]. In addition, there is a need for ongoing research to understand if there is an association or potential causal relationship between delay in surgery and improved pathologic response for patients with esophageal cancer. providers, a thorough understanding of factors that may contribute to longer times to surgery following neoadjuvant therapy can inform treatment planning for medical, radiation, and surgical oncologists to optimize timing of therapy.

Our study should be considered in light of multiple limitations. First, this is a single-center study that may be limited in its generalizability to patients outside of high-volume esophagectomy surgical practices. Despite this, understanding the association of patient factors with variation in timing of esophagectomy even in optimal care settings provides insight for future practice changes. Second, although our overall sample size was small, this cohort had all clinical information abstracted from their charts rather than a claims-based data-source, allowing for more accurate assessment of clinically important factors for timely esophagectomy. In addition, our data set did not include pre-operative clinical variables, such as dysphagia, pre-operative feeding tube placement or respiratory status, which may represent unmeasured confounders in our analysis. In addition, while we include information regarding baseline weight and mean weight changes in the prior 3 months, there may be important nutrition factors such albumin that may be more specific for patients' nutritional status. Furthermore, our analysis does not include surgeon, hospital or healthcare system factors that may also be unmeasured confounders affecting time to receipt of surgery. Lastly, specific treatment regimens with regards to chemotherapy and radiation doses were not included in our dataset.

Nevertheless, this may be an avenue for future research with regards to the effects of specific toxicities associated with chemoradiation regimens on optimization of surgical timing.

5. Conclusion

In summary, this study suggests there are identifiable patient factors associated with prolonged timing of esophagectomy following neoadjuvant chemoradiation. Specifically, our study found that absence of esophageal cancer spread to regional lymph nodes by pathology and history of prior cardiothoracic surgery were significant predictors of delayed receipt of surgery. Understanding of the factors that place patients at risk of a prolonged interval between completion of neoadjuvant therapy and esophagectomy can help to inform providers regarding medical optimization and to help mitigate potential sources of disparities in outcomes amongst patients with esophageal cancer.

Ethics approval

This study protocol was approved and determined to be exempt by the University of Michigan Institutional Review Board (HUM00012731). All methods were performed in accordance with relevant guidelines and regulations.

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Data availability statement

Data associated with this study has not been deposited into a publicly available repository. Data may be made available on request.

CRediT authorship contribution statement

Shannon J. Jiang: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Andrada C. Diaconescu:** Writing – review & editing, Investigation, Conceptualization. **Dyke P. McEwen:** Visualization, Validation, Formal analysis. **Laura N. McEwen:** Visualization, Validation, Formal analysis. **Andrew C. Chang:** Data curation. **Jules Lin:** Data curation. **Rishindra M. Reddy:** Data curation. **William R. Lynch:** Data curation. **Sidra Bonner:** Writing – review & editing, Writing – original draft, Supervision. **Kiran H. Lagisetty:** Writing – review & editing, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Sidra Bonner receives funding from the NIH T32 Multidisciplinary Program in Lung Disease at the University of Michigan If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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