Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Effect of time interval between Neoadjuvant Chemoradiation and Esophagectomy surgery on pathological complete response of patients with Esophageal Cancer

Fereidoon Amanat Yazdi
Tehran University of Medical Sciences
Fatemeh Moosaie
Tehran University of Medical Sciences
Nima Taghizadeh Mortezaei
International Surgical Research Association (ISRA), Universal Scientific Education and Research Network (USERN), Tehran University of Medical Sciences
Soha Mohammadi
International Surgical Research Association (ISRA), Universal Scientific Education and Research Network (USERN), Tehran University of Medical Sciences
Seyede Marzie Fatemi Abhari
Alborz University of Medical Sciences
Ali Moosaie
Tehran University of Medical Sciences
Amirmohsen Jalaeefar
Tehran University of Medical Sciences
Mohammad Shirkhoda
mshirkhoda@sina.tums.ac.ir

Tehran University of Medical Sciences

Article

Keywords: Esophageal cancer, Neoadjuvant Chemoradiation, Esophagectomy, pathological complete response, Time to Surgery

Posted Date: June 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9960534/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Esophageal cancer carries a poor prognosis, and despite the widespread adoption of neoadjuvant chemoradiation (nCRT) followed by esophagectomy, survival outcomes have barely budged. A key question that remains unresolved in clinical practice is how long to wait between completing nCRT and proceeding to surgery. Pathological complete response (pCR), the absence of viable tumor cells at resection, is a strong marker of treatment success, and there is reason to believe that a longer interval might allow tumor regression to fully mature. To explore this, we retrospectively analyzed 147 esophageal cancer patients treated at a tertiary cancer center with nCRT followed by esophagectomy. The overall pCR rate was 49.6%. Neither demographic nor clinical variables significantly predicted pCR. Across all time-interval classifications, patients who waited longer before surgery showed consistently higher pCR rates, those operated within 4–8 weeks had an odds ratio of just 0.43 for achieving pCR compared to those waiting beyond 12 weeks. Yet none of these trends crossed the threshold of statistical significance. The pattern held in subgroup analysis restricted to esophageal squamous cell carcinoma. These results neither confirm nor refute delaying surgery, but the consistent directional trend warrants further investigation through prospective trials with larger, more heterogeneous cohorts.

Introduction

Esophageal cancer is the eighth most common cancer in the world and the sixth leading cause of cancer death [1–3]. It is the most common cancer in developing regions including Asia, Africa, and Latin America [1,4]. Despite its prevalence, esophageal cancer 5-year survival rates have not significantly improved in recent years [2,5]. In esophageal cancer at stages higher than T1 and with lymph node involvement, the standard treatment includes neoadjuvant chemoradiotherapy followed-esophagectomy and then adjuvant treatment, a combination known as trimodality therapy [6]. Using neoadjuvant chemoradiation (nCRT) in esophageal cancer reduces tumor burden, increases resectability, and leads to long-term survival [7]. Previous studies have shown that nCRT followed by esophageal resection surgery enhances survival rate compared to esophagectomy alone in patients with advanced stages of esophageal cancer [8–11].

Pathologic complete response (pCR) after neoadjuvant treatment was first introduced as a prognostic factor in rectal squamous cell carcinoma (SCC) [12–14]. Moreover, the interval between neoadjuvant radiotherapy and surgery and its correlation with the reduction of the pathological tumor stage after neoadjuvant treatment and resectability was first described in rectal cancers [15]. An interval of more than eight weeks has been identified as an effective factor for pCR post-surgery in rectal cancers [16–18].

Achieving pCR allows the postponement or elimination of esophageal surgery without the risk of cancer progression following neoadjuvant treatment. The pCR of esophageal cancer to treatment is assessed using the Japanese classification of esophageal cancer. A complete response is defined if no viable tumor cells are found in the pathological specimen of esophagectomy and in its lymph nodes [19].

Clinically, the interval between nCRT and esophagectomy surgery varies, with the time to surgery (TTS) between 4 and 8 weeks [20,21]. There are several inevitable factors secondary to nCRT that justify delaying TTS, such as patients' compromised physical condition, suboptimal nutritional status, uncontrolled comorbidities, and the occurrence of severe treatment-induced adverse events, specifically radiation-associated pneumonia and cardiotoxicity [21,22].

The objective of this study is to assess the influence of the time interval between the completion of nCRT and esophagectomy on achieving pCR in patients with esophageal cancer. By investigating whether extending the interval before surgery enhances the pCR rate, this study aims to identify an optimal timing strategy that could potentially improve treatment outcomes for esophageal cancer patients.

Results

Patient characteristics

In this study, 53.7% of the participants were women. The mean age of the participants was 58.96 with a deviation of 11.01 years. The minimum age was 27 years and the maximum age was 79 years. The frequency distribution analysis demonstrated that most participants in this study were diagnosed with ESCC, accounting for 130 (88.4%) of all cases studied compared to 17 EAC patients (11.6%). 76.2% of the patients were in the 3rd stage of the disease. The majority of patients (91.8%) in the study, had lymph node involvement. Most of the patients participating in the study (93.9%) had T3/T4 tumor size, and 6.1% had T1/T2 tumor size. Of the 147 patients participating in the study, 57 had operative time of less than 6 hours and 90 (61.3%) had a duration of more than 6 hours. Additionally, most of the patients participating in the study (75.5%) had a hospitalization period of less than 2 weeks (Table 1).

Table 1
Patient Characteristics.

Variables		Total patients with esophageal cancer (N = 147)	Patients with pCR (N = 73)	*P-value*
Sex	Male	68 (46.3)	34 (50)	0.939
	Female	79 (53.7)	39 (49.4)	
Age	< 60	78 (53.06)	38 (48.7)	0.808
	> 60	69 (46.94)	35 (50.7)	
Hospitalization Period	< 2 weeks	111 (75.5)	57 (51.4)	0.472
	> 2weeks	36 (24.5)	16 (44.4)	
Operative time	< 6 hours	57 (38.7)	30 (52.6)	0.566
	> 6 hours	90 (61.3)	43 (47.4)	
Type	SCC	130 (88.4)	70 (53.8)	0.01
	Adenocarcinoma	17 (11.6)	3 (17.6)	
Stage	□	12 (8.16)	9 (72.8)	0.066
	□I	112 (76.2)	56 (50)	0.187
	□	23 (15.6)	8 (34.8)	Ref

Data are presented as N (%)

cPR: complete pathologic response

Stratification of pCR Across Demographic and Clinical Variables

Out of the 147 patients participating in the study, 73 had a positive pCR and 74 had a negative pCR. The frequency distribution results showed that (50.3%) of the patients participating in the study had a negative pCR.

The pCR outcomes among the male patients were equally distributed, with half demonstrating positive pCR. Similarly, among the female patients, there was a relatively even distribution between positive and negative pCR outcomes, with a slightly higher percentage of them having a negative pCR (50.6% vs 49.4%). Gender did not show a statistically significant difference between the two groups with positive and negative pCR (P-value 0.535). Also, 48.7% of the patients younger than 60 and 50.7% of the patients who were older than 60 years had a positive pCR. The mean age of the individuals in the group with positive pCR was 59.32 and in the group with negative pCR was 58.6. The average age between the two groups did not show a statistically significant difference (P-value 0.693). After adjustments for

confounding variables, it was demonstrated that there was no statistically significant relationship between gender and age with pCR.

The majority of patients had a surgery time of more than 6 hours and were hospitalized for less than two weeks. The pCR rate was higher in the patients with less than 6 hours (52.6% vs. 47.4%), and fewer than 2 weeks' hospitalization (51.4% vs. 44.4%); however, these variables did not make a significant difference regarding pCR. Furthermore, the regression analysis showed that there was no statistically significant relationship between the hospitalization period and the operative time in patients with pCR.

Regarding tumor stage, the highest pCR rate was observed in patients with stage 2 tumors. The pCR rate was 72.8%, 50%, and 34.8% among the patients with stage 2, 3, and 4 tumors, respectively. Although, considering the higher frequency of patients with stage 3 tumors in this study (76.2%), the highest frequency among patients with positive pCR belongs to this group. Additionally, 53.8% of ESCC patients and 17.6% of EAC patients had a positive pCR. However, there was no significant relationship between the tumor stage and the pCR, the relationship between the positive pCR and the type of tumor was significant, so the patients who had esophageal SCC had a more positive pCR (Table 1).

Effect of Time to surgery on pCR in patients with esophageal cancer

In the first interval categorization, patients with esophageal cancer, including ESCC and EAC, were almost evenly distributed between subcategories. Within this timeframe, there is an increasing trend in pCR rates by delaying the time between CRT and surgery. The comparison between 4–8 weeks and more than 12 weeks' intervals revealed that those who undertook surgery within 4–8 weeks have greatly lower odds of achieving pCR; however, this significance is only marginal (OR = 0.43, CI = 0.20–0.97, P-value = 0.06). Similarly, patients in the 9–12 weeks' interval have lower odds of achieving pCR than those who had surgery after 12 weeks of CRT, though this difference is not statistically significant (OR = 0.7, CI = 0.26–1.37, p-value = 0.22). According to the second interval classification based on an 8-week cutoff, two-thirds of the participants had a TTS of more than eight weeks. Compared to the prolonged interval group, patients who had surgery in less than eight weeks of CRT had lower odds of achieving complete pCR, although the difference was insignificant (OR = 0.56, CI = 0.27–1.12, p-value = 0.09). Based on the third interval grouping, 100 individuals experienced a TTS in less than 12 weeks, while the remaining 47 patients surpassed the 12-week cut-off. Similar to other interval classifications, the shorter TTS cohort had a lower pCR rate and notably reduced chances of achieving pCR compared to delayed TTS group; however, the difference was not significant (OR = 0.55, CI = 0.28–1.11, p-value = 0.10).

Accordingly, it was revealed that there was no statistically significant relationship between the positive pCR and any of the divisions of the interval between the completion of nCRT and esophagectomy. Furthermore, analyzing the pCR in terms of mean days between nCRT and surgery demonstrated no significant difference (p-value = 0.465) between patients with positive and negative pCR groups. On average, patients with positive pCR had a TTS of 82.19 days, while those with negative pCR had a TTS of 78.66 days (Table 2, Fig. 1)

Table 2
Effect of time to surgery in pathologic complete response among patients with esophageal cancer including esophageal SCC and adenocarcinoma.

TTS	Number of patients, N (%)	Patients with pCR, N (%)	OR	95% CI	*P-value*
First Interval					
4–8 weeks	51 (34.7)	20 (39.2)	0.43	0.20–0.97	0.064
9–12	49 (33.3)	25 (51)	0.7	0.26–1.37	0.228
> 12 weeks	47 (32)	28 (59.6)	Ref	-	-
Second Interval					
≤ 8 weeks	52 (35.37)	21 (40.4)	0.56	0.27–1.12	0.098
> 8 weeks	95 (64.63)	52 (54.7)	Ref	-	-
Third Interval					
≤ 12 weeks	100 (68)	45 (45)	0.55	0.28–1.11	0.101
> 12 weeks	47 (32)	28 (59.6)	Ref	-	-

TTS; Time to Surgery; pCR; pathologic Complete Response, OR; Odds Ratio; CI; Confidence Interval, Ref; Reference.

Effect of Time to surgery on pCR in patients with ESCC

Among ESCC patients, the average TTS in the group with positive pCR was 60.02 days, and in the group with negative pCR, it was 58.31 days. The analysis showed that TTS did not show a statistically significant difference between the two groups (*P-value* 0.371).

Subgroup analysis within the ESCC cohort, using the same interval categorization, revealed varying pCR rates. Patients treated within 4–8 weeks showed a trend towards lower odds of achieving pCR compared to those treated after 12 weeks (OR = 0.47, CI = 0.12–1.12, p-value = 0.09). Also, the 9–12 weeks' interval cohort showed slightly reduced odds of pCR compared to the reference group, although this difference was not statistically significant (OR = 0.84, CI = 0.35–1.98, p-value = 0.69).

Identical patterns emerged in the subsequent analysis, divided into second and third intervals. Patients with surgery within 8 weeks watched to have lower odds of achieving pCR than those treated later (OR = 0.52, CI = 0.25–1.08, p-value = 0.08). Likewise, the third interval cohort, consisting of patients with TTS within 12 weeks, demonstrated reduced odds of pCR compared to those with longer 12 weeks TTS, though this difference was not statistically significant (OR = 0.63, CI = 0.30–1.31, p-value = 0.22). In short; Similarly, in ESCC patients, the regression analysis outcomes indicated no statistically significant

association was observed between positive pCR and any subcategories within the time interval between nCRT and surgery (Table 3, Fig. 1).

Table 3
Effect of time to surgery in pathologic complete response in patients with esophageal SCC.

TTS	Number of patients with esophageal SCC, N (%)	Patients with pCR, N (%)	OR	95% CI	*P-value*
First Interval					
4–8 weeks	44 (33.84)	19 (43.2)	0.47	0.12–1.12	0.090
9–12	35 (26.9)	19 (54.3)	0.84	0.35–1.98	0.691
> 12 weeks	51 (39.23)	32 (62.7)	Ref	-	-
Second Interval					
≤ 8 weeks	44 (33.84)	19 (43.2)	0.52	0.25–1.08	0.083
> 8 weeks	86 (66.15)	51 (59.3)	Ref	-	-
Third Interval					
≤ 12 weeks	86 (66.15)	43 (50)	0.63	0.30–1.31	0.220
> 12 weeks	44 (33.84)	27 (61.4)	Ref	-	-
SCC; Squamous cell carcinoma, TTS; Time to Surgery; pCR; pathologic Complete Response, OR; Odds Ratio; CI; Confidence Interval, Ref; Reference.					

Discussion

Studies have shown that pCR in patients undergoing combined tri-modality treatment for esophageal cancer is a valuable tool for measuring the rate of improvement, tumor recurrence, metastasis, as well as the survival rate [23–25]. In other studies, patients with locally advanced esophageal cancer were examined at multiple intervals, with the primary goal similar to this study [15,26–32]. In this study, we performed data analysis by dividing the TTS intervals into two different midpoint times and categorizing it into 4-week interval, to minimize selection bias among study participants; however, in all cases the same results were obtained. Considering the high prevalence of esophageal SCC in our study population, we also assessed the relationship between TTS and pCR over various intervals in this subgroup of our patients; however, no significant relationship was observed between these two variables. In rectal cancer, current recommendations suggest performing surgery 6–8 weeks after nCRT, as this interval significantly improved tumor downstaging compared to a 2-week interval [12]. Similarly, the concept of

allowing time for recovery from nCRT-related adverse events and reach the maximum therapeutic effect before proceeding with esophagectomy is now widely accepted. However, there is a lack of consensus on the optimal interval that maximizes oncological benefits, as studies on this topic have produced conflicting results [26,33].

Several studies revealed a lack of a significant correlation between the TTS and pCR after surgery, which is consistent with our findings [20,26,27,29,31–37]. A systematic literature review by Lin et al. included five studies with a combined cohort of 1,016 patients of both histological subtypes of esophageal cancer. They categorized patients based on a 7–8 weeks cut-off and found that a longer interval was associated with a potentially detrimental impact on 2-year overall survival (OS) and margin positivity. However, pCR, anastomotic leak rate, and postoperative morbidity were similar between the groups [34]. Klevebro et al. analyzed data from 643 patients with esophageal cancer and categorized them into two groups according to a median TTS of 49 days. In addition to the differences in pCR and OS rates being insignificant, the study found no significant differences in margin positivity, postoperative complications, and 90-day mortality between the longer and shorter interval groups. However, the majority of the patients (72.6%) in this study had EAC, which may be a distinguishing factor [20]. Overall, we think that if altered genetic factors in the development of carcinoma cells are included as variables, the results will change.

Notably, the cohorts in most of the studies with similar findings consisted only of ESCC patients, which revealed no significant difference between their extended and shorter TTS interval groups regarding pCR and survival indices [26,31,33,35–37]. Wang et al. conducted a retrospective study on 665 ESCC patients, dividing them into four groups based on 4-week intervals. Their findings indicated that surgery within one month after nCRT was linked to significantly lower positive surgical margin rates; a significant increase in postoperative mortality counteracts this advantage. They also found that the group with a TTS of 8 to 12 weeks had the lowest mortality rates and hazard ratio (HR) for OS and the highest pCR rate. However, the statistical significance was only observed in surgical mortality [36]. Furukawa et al. studied 134 ESCC patients from a Japanese hospital, classified them into short—and long-interval cohorts based on an 8-week cut-off, and found no significant difference regarding pCR, OS, and recurrence-free survival rates between the two groups. However, they suggest that due to the significantly higher incidences of respiratory morbidity by prolonging the TTS, it is better to proceed with esophagectomy within eight weeks after nCRT [33]. Wakita et al. conducted a study involving 131 patients with thoracic esophageal cancer, 129 of whom had ESCC, and categorized them into two groups based on a median TTS of 39 days. They observed that extending the TTS did not impact pCR and OS rates; however, it significantly raised the incidence of postoperative complications, including anastomotic leakage and recurrent laryngeal nerve palsy [26]. In contrast, two separate studies examined ESCC patients and found no significant differences in surgical complications or perioperative mortality between their long- and short-interval defined cohorts [35,37].

The results of our study conflict with some studies that revealed a significantly higher pCR rate with prolonging TTS for EC [15,22,28,38–42]. Shapiro et al. investigated 325 patients, 75% of whom had EAC and received the same nCRT protocol. They showed that a TTS interval of more than 45 days was associated with a higher pCR rates; however, it increased surgical complications, and had no impact on OS or disease-free survival (DFS) rates [28]. Liu et al. reviewed 161 esophageal cancer patients and revealed that the prolonged time interval group achieved a significantly higher pCR rate; however, there was no association between a prolonged time interval and OS or DFS [40]. Ranney and Franko analyzed 2,444 and 4,284 patients with EAC in their respective studies and found that extending the interval between nCRT and surgery led to significantly higher rates of pCR; however, it also worsened the OS and postoperative mortality [41,42]. Similarly, Azab et al. demonstrated that the improved pCR after surgery does not result in an improved survival rate, and there is a higher rate of mortality after surgery [38]. A systematic review by Qin et al. included 13 studies with a pooled cohort of 15,086 EC patients and found that a TTS longer than 7–8 weeks was significantly associated with an improved pCR rate. However, this extended interval increased the mortality rate and worsened 2-year and 5-year OS [39]. The lack of improvement in the several responses despite the improvement in the local response can be a sign of the systemic nature of esophageal cancer [43]. In other words, we should look for factors that indicate a systemic response to treatment and then check the relationship of these factors with TTS.

In studies with results that differ from ours, the majority of esophageal cancer patients had adenocarcinoma histology, and the same chemoradiation regimen was applied. Given these differences in cohort characteristics, the discrepancies in the effect of TTS on pCR may be explained. Moreover, the subgroup analyses in Qin's systematic review demonstrated a significant association between the extended interval and both pCR and surgical mortality rates only in adenocarcinoma patients [39]. Xiao's study is the only one among those with differing results from ours that only included the SCC histology subtype. They examined 224 patients and showed a significant association between prolonged TTS and improved pCR; however, they showed no significant difference in survival benefits and postoperative complications between long and short-interval groups [22]. Similarly, our study revealed a rising trend in pCR rates with delayed surgery among ESCC patients. However, unlike Xiao's study, the differences weren't significant, possibly due to our cohort's absence of stage 1 tumors, contrasting with Xiao's cohort, where they constituted 57.14% of patients. Karthyarth et al. conducted a systematic review and meta-analysis assessing the effects of early and delayed esophagectomy following nCRT. The pooled estimate of cohort studies revealed no difference in pCR rates, OS, mortality, and complications between the two groups. However, analyzing data of 9723 patients from registry-based studies demonstrated different results, indicating that the delayed surgery group had better pCR rates with no improvement in survival, and increased rate of mortality and major complications [44].

The discrepancies observed in the findings regarding the impact of delaying TTS on pCR, OS, and post-surgical complications across different studies underscore the critical need for further research and investigation; Especially the relationship between tumor biology and the factors considered in this research. To better understand the impact of TTS on pCR, we divided the TTS into different time intervals

and grouped patients accordingly to better understand the impact of TTS on pCR. Specifically, the intervals were categorized into 4-week groups, allowing for more precise comparisons while reducing selection bias. This approach ensured that we could identify trends or differences in pCR across various time periods, making the results more reliable and relevant to clinical practice. Also, we focused on ESCC, which has different biological characteristics and treatment responses compared to EAC. By including both cancer types and focusing on ESCC, we provided a better understanding of how TTS may affect this subtype, which is less frequently studied. Similar to other studies, the present study had limitations. The insufficient number of patients, the retrospective nature of the study, and the incompleteness of the patient profile information are among the study's shortcomings. Additionally, due to the limited availability of patients' information and history of multiple chemoradiation regimens, it was impossible to categorize patients based on their CRT regimen. We suggest conducting trials with the design of incorporating varied time intervals and confounding factors such as patient's demographic characteristics, underlying diseases, comprehensive biopathological tumor features, and other personalized factors influencing their response to treatment and survival.

The results of the study showed that the interval between the completion of nCRT and esophagectomy surgery cannot predict the pCR to treatment in patients with esophageal cancer. Moreover, data analysis did not show a significant relationship between TTS interval and pCR in individuals with esophageal SCC.

Methods

Study Design

The present study is a retrospective cohort study, conducted on esophageal cancer patients referred to the Tehran Cancer Institute from 2016 to 2022. It aims to investigate the relationship between the interval from nCRT to surgery and pCR after surgery, along with the association between tumor characteristics such as the type and stage of the tumor and pCR.

Study population

The study population was selected from patients with esophageal cancer referred to the Tehran Cancer Institute from 2016 to 2022. Using Cochran's formula and based on the sample size of Chiu et al. [27] and Anvari et al. [45] studies, with a 95% confidence level and maximum error of 0.08, 126 samples were determined, adjusted by an additional 15% to account for potential sample loss, resulting in a required sample size 147 patients. The sampling method was convenient and continuous. Inclusion criteria include patients with a definitive diagnosis of esophageal cancer without metastasis, based on pathology and paraclinical findings, patients who underwent nCRT and surgery minimally after 28 days from nCRT, and patients with squamous cell carcinoma or adenocarcinoma with involvement of the trunk and distal esophagus. Exclusion criteria include esophageal cancer with gastric or gastroesophageal junction involvement, tumor progression or systemic metastasis in re-staging after post-neoadjuvant

treatment, impossibility to undergo surgery, failure to receive neoadjuvant treatment, death during treatment, and cases requiring emergency or salvage surgery.

Data Collection

After obtaining ethics committee approval and necessary permissions, data from 147 patients who completed chemoradiation and esophagectomy, based on inclusion criteria, were collected from patients' medical records. Data collection involved using checklists for demographic (age, gender, etc.) and clinical characteristics (tumor type, size, lymph node involvement, disease stage, interval between chemoradiation completion and surgery, surgery duration, hospitalization duration, and pCR of the tumor). Primary the pCR was determined using the TNM formula of the AJCC staging system's 8th edition, with T0N0M0 indicating a positive pCR.

Patients were classified based on the TTS in esophageal cancer into three intervals: three groups with 4 weeks cut-off (4–8, 9–12, and > 12 weeks), an average of 8 weeks, and an average of 12 weeks, and the effect of interval on post-operative pathology results was investigated. Considering the prevalence of esophageal squamous cell carcinoma (ESCC) than esophageal adenocarcinoma (EAC), the relationship between the interval and pCR outcomes post-operatively was investigated separately.

Statistical Analysis

Data were analyzed using SPSS version 26, utilizing descriptive statistics (mean, variance, standard deviation) and inferential statistics (chi-square, independent t-test, analysis of variance). The Kolmogorov–Smirnov test was used to assess the normality of the data, and logistic regression analyzed the relationship between pCR, adjusted for confounding variables (i.e., age, sex, cancer type and staging). A significance level of < 0.05 was used for all tests.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Tehran University of Medical Sciences with the ethics code of IR.TUMS.IKHC.REC.1398.062, and followed the guidelines of the Helsinki Declaration and the Ministry of Health and Medical Education. Given the retrospective nature of this study, individual informed consent was waived by the ethics committee.

Consent to publish

The participants have given their consent for the publication of their data and study findings.

Additional Information

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Author Contribution

Authors' contributions statementF.AY. conceived the study and conducted data acquisition and statistical analysis and reviewed and edited the manuscript. F.M. conceived the study, performed statistical analysis, and wrote, reviewed, and edited the manuscript. N.TM. contributed to visualization, and wrote, reviewed, and edited the manuscript. S.M. wrote, reviewed, and edited the manuscript. SM.FA., A.M. and A.J. reviewed and edited the manuscript. M.S. conceived the study and provided supervision and manuscript review. All authors contributed to the article and approved the final version of the Manuscript.

Acknowledgments

Not applicable

Data Availability

Data availabilityData is provided within the manuscript and the datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. The global. regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol. Hepatol.* **5**, 582–597. 10.1016/s2468-1253(20)30007-8 (2020).
2. Uhlenhopp, D. J., Then, E. O., Sunkara, T. & Gaduputi, V. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. *Clin. J. Gastroenterol.* **13**, 1010–1021 (2020).
3. Liu, C. Q. et al. Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. *Thorac. cancer*. **14**, 3–11 (2023).

4. Santucci, C. et al. Global trends in esophageal cancer mortality with predictions to 2025, and in incidence by histotype. *Cancer Epidemiol.* **87**, 102486. https://doi.org/10.1016/j.canep.2023.102486 (2023).
5. Then, E. O. et al. Esophageal cancer: an updated surveillance epidemiology and end results database analysis. *World J. Oncol.* **11**, 55 (2020).
6. Hategan, M. et al. Trimodality therapy and definitive chemoradiotherapy for esophageal cancer: a single-center experience and review of the literature. *Dis. Esophagus*. **28**, 612–618. 10.1111/dote.12242 (2015).
7. Ruol, A. et al. Trends in management and prognosis for esophageal cancer surgery: twenty-five years of experience at a single institution. *Arch. Surg.* **144**, 247–254. 10.1001/archsurg.2008.574 (2009). discussion 254.
8. Tepper, J. et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J. Clin. Oncol.* **26**, 1086–1092. 10.1200/jco.2007.12.9593 (2008).
9. van Hagen, P. et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl. J. Med.* **366**, 2074–2084. 10.1056/NEJMoa1112088 (2012).
10. Yuan, M. et al. The optimal treatment for resectable esophageal cancer: a network meta-analysis of 6168 patients. *Front. Oncol.* **11**, 628706 (2021).
11. Chen, H. S., Lin, C. H., Wu, S. C. & Wang, B. Y. Survival Comparison Among Neoadjuvant Chemoradiotherapy Followed by Esophagectomy, Definitive Chemoradiotherapy, and Esophagectomy Alone for Esophageal Squamous Cell Carcinoma. *Annals Surg. Oncology*, 1–11 (2022).
12. Zorcolo, L. et al. Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. *Ann. Surg. Oncol.* **19**, 2822–2832. 10.1245/s10434-011-2209-y (2012).
13. Martin, S. T., Heneghan, H. M. & Winter, D. C. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br. J. Surg.* **99**, 918–928. 10.1002/bjs.8702 (2012).
14. Maas, M. et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol.* **11**, 835–844. 10.1016/s1470-2045(10)70172-8 (2010).
15. Shaikh, T. et al. Increased time from neoadjuvant chemoradiation to surgery is associated with higher pathologic complete response rates in esophageal cancer. *Ann. Thorac. Surg.* **99**, 270–276. 10.1016/j.athoracsur.2014.08.033 (2015).
16. Kalady, M. F. et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann. Surg.* **250**, 582–589. 10.1097/SLA.0b013e3181b91e63 (2009).

17. Probst, C. P. et al. Extended Intervals after Neoadjuvant Therapy in Locally Advanced Rectal Cancer: The Key to Improved Tumor Response and Potential Organ Preservation. *J. Am. Coll. Surg.* **221**, 430–440. 10.1016/j.jamcollsurg.2015.04.010 (2015).
18. Chen, K. T. et al. Neoadjuvant chemoradiation and duration of chemotherapy before surgical resection for pancreatic cancer: does time interval between radiotherapy and surgery matter? *Ann. Surg. Oncol.* **21**, 662–669. 10.1245/s10434-013-3396-5 (2014).
19. Doki, Y. et al. Japanese Classification of Esophageal Cancer, 12th Edition: Part II. *Esophagus*, (2024). 10.1007/s10388-024-01048-w
20. Klevebro, F. et al. Association between time interval from neoadjuvant chemoradiotherapy to surgery and complete histological tumor response in esophageal and gastroesophageal junction cancer: a national cohort study. *Dis. Esophagus*. **33** 10.1093/dote/doz078 (2020).
21. Li, J. et al. Optimal Time-to-Surgery Recommendations Based on Primary Tumor Volume Regression for Patients with Resectable Esophageal Cancer after Neoadjuvant Chemoradiotherapy: A Retrospective Study. *Annals Surg. Oncology*, 1–10 (2024).
22. Xiao, X. et al. Longer Time Interval from Neoadjuvant Chemoradiation to Surgery is Associated with Poor Survival for Patients Without Clinical Complete Response in Oesophageal Cancer. *Ann. Surg. Oncol.* **30**, 886–896. 10.1245/s10434-022-12758-9 (2023).
23. Chirieac, L. R. et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* **103**, 1347–1355. 10.1002/cncr.20916 (2005).
24. Stahl, M. et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J. Clin. Oncol.* **27**, 851–856. 10.1200/jco.2008.17.0506 (2009).
25. Su, F., Yang, X., Yin, J., Shen, Y. & Tan, L. Validity of using pathological response as a surrogate for overall survival in neoadjuvant studies for esophageal cancer: A systematic review and meta-analysis. *Ann. Surg. Oncol.* **30**, 7461–7471 (2023).
26. Wakita, A. et al. Verification of the Optimal Interval Before Esophagectomy After Preoperative Neoadjuvant Chemoradiotherapy for Locally Advanced Thoracic Esophageal Cancer. *Ann. Surg. Oncol.* **28**, 2101–2110. 10.1245/s10434-020-09206-x (2021).
27. Chiu, C. H. et al. Interval between neoadjuvant chemoradiotherapy and surgery for esophageal squamous cell carcinoma: does delayed surgery impact outcome? *Ann. Surg. Oncol.* **20**, 4245–4251. 10.1245/s10434-013-3139-7 (2013).
28. Shapiro, J. et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. *Ann. Surg.* **260**, 807–813. 10.1097/SLA.0000000000000966 (2014). discussion 813 – 804.
29. Ruol, A. et al. Interval between neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma of the thoracic esophagus: does delayed surgery have an impact on outcome? *Ann. Surg.* **252**, 788–796. 10.1097/SLA.0b013e3181fc7f86 (2010).

30. Nilsson, K. et al. Surgical Morbidity and Mortality From the Multicenter Randomized Controlled NeoRes II Trial: Standard Versus Prolonged Time to Surgery After Neoadjuvant Chemoradiotherapy for Esophageal Cancer. *Ann. Surg.* **272**, 684–689. 10.1097/SLA.0000000000004340 (2020).
31. Tsang, J. S. et al. Appropriate timing for surgery after neoadjuvant chemoradiation for esophageal cancer. *Dis. Esophagus*. **30**, 1–8. 10.1093/dote/dox062 (2017).
32. Kim, J. Y. et al. Does the timing of esophagectomy after chemoradiation affect outcome? *Ann. Thorac. Surg.* **93**, 207–212. 10.1016/j.athoracsur.2011.05.021 (2012). discussion 212 – 203.
33. Furukawa, T. et al. Impact of Interval Between Neoadjuvant Chemoradiation and Surgery Upon Morbidity and Survival of Patients with Squamous Cell Carcinoma of Thoracic Esophagus. *Anticancer Res.* **38**, 5239–5245. 10.21873/anticanres.12848 (2018).
34. Lin, G., Han, S. Y., Xu, Y. P. & Mao, W. M. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in esophageal cancer: a meta-analysis of published studies. *Dis. Esophagus*. **29**, 1107–1114. 10.1111/dote.12432 (2016).
35. Franko, J. & McAvoy, S. Timing of esophagectomy after neoadjuvant chemoradiation treatment in squamous cell carcinoma. *Surgery* **164**, 455–459. 10.1016/j.surg.2018.04.026 (2018).
36. Wang, B. Y. et al. Clinical impact of the interval between chemoradiotherapy and esophagectomy in esophageal squamous cell carcinoma patients. *Ann. Thorac. Surg.* **99**, 947–955. 10.1016/j.athoracsur.2014.10.037 (2015).
37. Kuo, Y. H. et al. Impact of the interval between neoadjuvant concurrent chemoradiotherapy and esophagectomy in the modern era: a population-based propensity-score-matched retrospective cohort study in Asia. *World J. Surg. Oncol.* **17** 10.1186/s12957-019-1712-7 (2019).
38. Azab, B. et al. Impact of Chemoradiation-to-Surgery Interval on Pathological Complete Response and Short- and Long-Term Overall Survival in Esophageal Cancer Patients. *Ann. Surg. Oncol.* **26**, 861–868. 10.1245/s10434-018-6897-4 (2019).
39. Qin, Q. et al. Does timing of esophagectomy following neoadjuvant chemoradiation affect outcomes? A meta-analysis. *Int. J. Surg.* **59**, 11–18. 10.1016/j.ijsu.2018.09.013 (2018).
40. Liu, J. et al. Longer interval between neoadjuvant chemoradiotherapy and surgery is associated with improved pathological response, but does not accurately estimate survival in patients with resectable esophageal cancer. *Oncol. Lett.* **25**, 155. 10.3892/ol.2023.13741 (2023).
41. Franko, J., Voynov, G. & Goldman, C. D. Esophagectomy Timing After Neoadjuvant Therapy for Distal Esophageal Adenocarcinoma. *Ann. Thorac. Surg.* **101**, 1123–1130. 10.1016/j.athoracsur.2015.09.044 (2016).
42. Ranney, D. N. et al. Surgical resection after neoadjuvant chemoradiation for oesophageal adenocarcinoma: what is the optimal timing? *Eur. J. Cardiothorac. Surg.* **52**, 543–551. 10.1093/ejcts/ezx132 (2017).
43. Wang, Y., Yang, W., Wang, Q. & Zhou, Y. Mechanisms of esophageal cancer metastasis and treatment progress. *Front. Immunol.* **14**, 1206504. 10.3389/fimmu.2023.1206504 (2023).

44. Karthyarth, M. N. et al. Early versus delayed surgery following neoadjuvant chemoradiation for esophageal cancer: a systematic review and meta-analysis. *Esophagus* **20**, 390–401. 10.1007/s10388-023-00989-y (2023).
45. Anvari, K. et al. Treatment of Esophageal Carcinoma by Pre-operative Chemo-radiotherapy Modality Cancer Research Center, Mashhad University of Medical Sciences. *Med. J. mashhad Univ. Med. Sci.* **52**, 173–179. 10.22038/mjms.2009.5434 (2009).

Figures

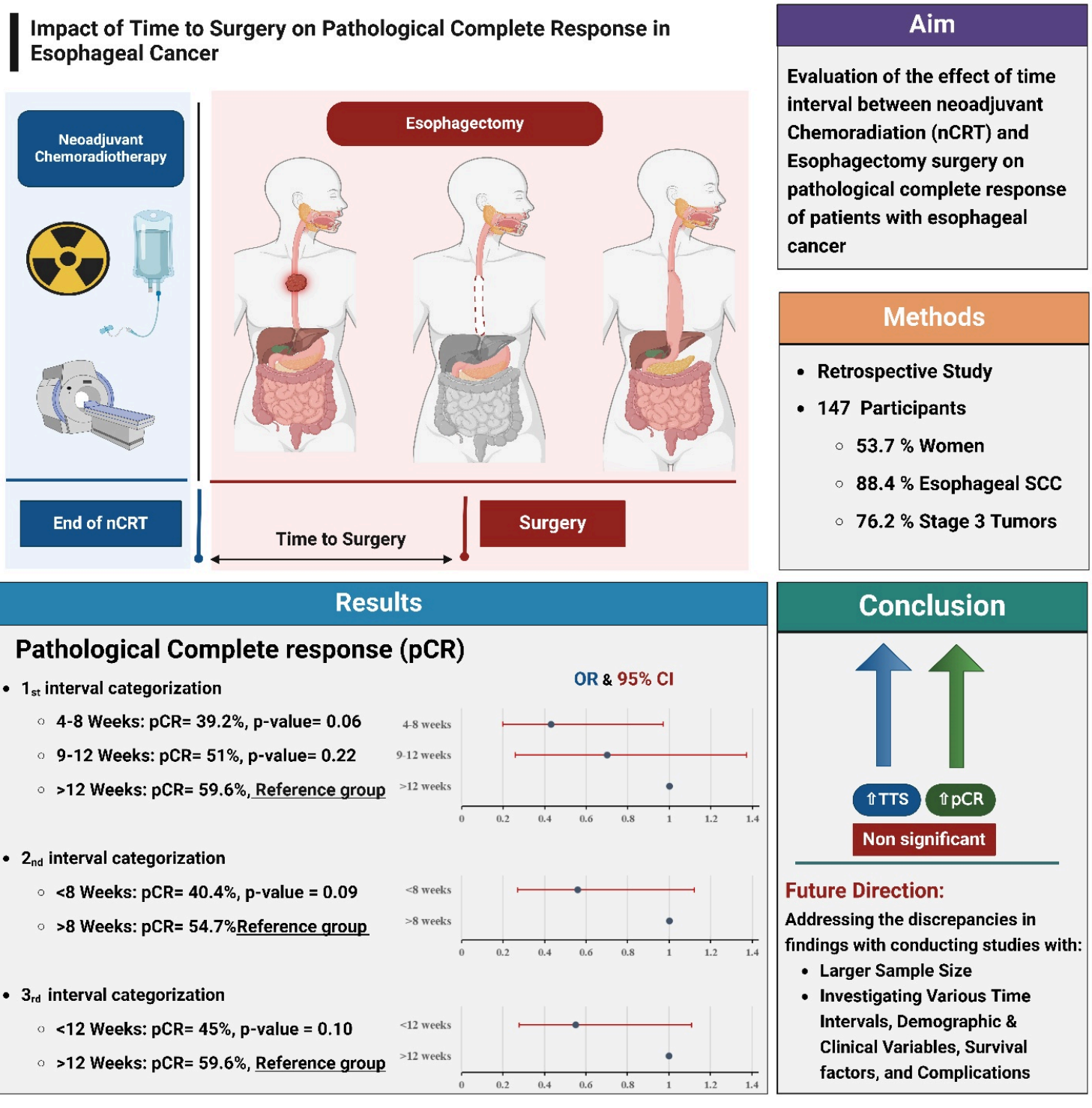


Figure 1

Time to Surgery and Its Impact on Pathological Complete Response in Esophageal Cancer