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Timing of Esophagectomy after Neoadjuvant Chemoradiation Therapy Affects the Incidence of Anastomotic Leaks

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Background: Neoadjuvant chemoradiation therapy (nCRT) has become the standard of care for esophageal cancer patients prior to esophagectomy. However, the optimal timing for surgery after completion of nCRT remains unclear. **Methods:** A retrospective review was performed of patients who underwent esophagectomy with cervical anastomosis for esophageal cancer at a single institution between January 2000 and June 2015. Patients were categorized into 3 cohorts: those who did not receive nCRT prior to esophagectomy (no nCRT), those who underwent esophagectomy within 35 days after nCRT (≤35d), and those who underwent esophagectomy more than 35 days after nCRT (>35d). **Results:** A total of 366 esophagectomies were performed during the study period, and 348 patients met the inclusion criteria. Anastomotic leaks occurred in 11.8% of all patients included in the study (41 of 348). Within each cohort, anastomotic leaks were detected in 14.7% of patients (17 of 116) in the no nCRT cohort, 7.3% (13 of 177) in the ≤35d cohort, and 20.0% (11 of 55) in the >35d cohort (p=0.020). Significant differences in the occurrence of anastomotic leaks were observed between the no nCRT and ≤35d cohorts (p=0.044), and between the ≤35d and >35d cohorts (p=0.007). **Conclusion:** Esophagectomy with cervical anastomosis within 35 days of nCRT resulted in a lower percentage of anastomotic leaks.

Key words: 1. Esophageal neoplasms
2. Esophagectomy
3. Anastomotic leak
4. Chemoradiotherapy
5. Neoadjuvant therapy

Introduction

Neoadjuvant chemoradiation therapy (nCRT) followed by surgery is a common treatment for locally advanced esophageal cancer. Recent studies have suggested that this treatment may improve survival and provide better local control [1-11], although several reports have shown no significant benefit [12-16]. Despite these inconsistencies, routine nCRT prior to esophagectomy is becoming a standard practice.

There are concerns that nCRT may make surgery

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more difficult because it can cause fibrosis and increase postoperative complications [17]. Moreover, nCRT could potentially influence the rates of anastomotic leaks, which are a complication of esophagectomy associated with serious morbidity and mortality [18]. However, a recent multicenter study showed that nCRT had no impact on anastomotic leaks in patients who underwent surgery 6–8 weeks after completing treatment [19]. Further, a study by Kim et al. [20] demonstrated that perioperative morbidity and mortality did not differ for esophagectomies performed less than or more than 8 weeks following nCRT treatment. Although combined-modality treatment regimens may lead to better outcomes, the data currently available are not conclusive regarding the optimal timing of surgery following nCRT, and prior studies have not specifically focused on the implications of anastomotic leaks [20-25]. The aim of our study was to determine whether the timing of esophagectomy following nCRT affected the incidence of anastomotic leaks.

Methods

This study was reviewed and approved by the Institutional Review Board and informed consent was waived. A prospectively collected database of all patients undergoing esophagectomy for esophageal cancer from January 2000 to June 2015 at the University of Iowa Hospitals and Clinics was retrospectively reviewed. The histological subtypes of esophageal cancer included adenocarcinoma, squamous cell, neuroendocrine, poorly differentiated, and gastrointestinal stromal tumor. Patients with a cervical esophagogastric anastomosis were included in the study; patients with an intrathoracic anastomosis were excluded. A detailed chart review was performed and the following data were recorded for each patient: age/sex; smoking history; previous history of diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), renal failure, or hypertension; prior abdominal/thoracic surgery; prior esophageal surgery; prior coronary artery bypass graft (CABG); weight loss greater than 4.5 kg; and body mass index (BMI). As part of staging, all patients underwent computerized tomography scanning of the chest and abdomen, positron emission tomography scanning, and endoscopic ultrasonography.

1) Patient categorization

Clinically significant anastomotic leaks were defined as any anastomoses that required drainage, and/or neck wound infections requiring jejunal feeds and/or parenteral nutrition. Cervical anastomoses were performed using the modified Collard technique. Briefly, the anastomosis was performed by stapling the posterior wall with an endo GIA stapler (Medtronic, Minneapolis, MN, USA) and oversewing the anterior wall with 2 absorbable monofilament layers of suture. Patients underwent a thin barium esophagram on postoperative day 5–7. All patients with a leak identified on the esophagram were included in the leak group. Patients with neck wounds that were erythematous and/or draining had the incisions opened at the bedside and were considered to have anastomotic leaks.

Patients with identified anastomotic leaks were divided into 3 cohorts based on the timing of esophagectomy: those who did not receive nCRT (no CRT), those who underwent esophagectomy within 35 days of completing nCRT (≤35d), and those who underwent esophagectomy more than 35 days after nCRT (>35d). The cutoff point for being at an increased risk for an anastomotic leak rate following nCRT was determined using logistic regression, which was performed by analyzing all of the patients who developed an anastomotic leak and taking each time point in days from surgery to determine whether there was an increased risk for a leak. The time point when there was a trend towards a greater risk for an anastomotic leak was calculated. Patients who underwent surgery more than 35 days after nCRT had a higher risk of an anastomotic leak than those who underwent surgery at 35 days or less (odds ratio, 2.95; 95% confidence interval [CI], 1.25–7.00; p=0.014).

2) Statistical analysis

Categorical data were analyzed using the chi-square test or the Fisher exact test, as appropriate. Continuous variables were analyzed using analysis of variance. Intergroup comparisons of quantitative variables were analyzed using the Kruskal-Wallis test. Data were expressed as number of patients, with the percentage in parentheses, or median with interquartile range. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using IBM SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline characteristics of patients who underwent esophagectomy without nCRT, ≤35 days following nCRT, or >35 days following nCRT

Characteristic	Esophagectomy without nCRT (n=116)	Esophagectomy ≤35 days post-nCRT (n=177)	Esophagectomy >35 days post-nCRT (n=55)	p-value[a)]
Age at surgery (yr)	66.7±11.4 (32–88)	61.0±9.6 (25–82)	60.3±9.7 (27–79)	<0.001[b)]
Sex (male)	92 (79)	149 (84)	49 (89)	0.252
Never smoked	31 (27)	34 (19)	9 (16)	0.447
Ever smoked				
Current smoker	24 (21)	40 (23)	15 (27)	
Former smoker	61 (52)	103 (58)	31 (56)	
Diabetes	20 (17)	36 (20)	11 (20)	0.796
Chronic obstructive pulmonary disease	15 (13)	21 (12)	4 (7)	0.565[c)]
Coronary artery disease	25 (22)	31 (18)	15 (27)	0.272
Renal failure	3 (3)	2 (1)	1 (2)	0.543[c)]
Hypertension	66 (57)	85 (48)	29 (53)	0.327
Prior abdominal surgery	55 (47)	61 (35)	19 (35)	0.066
Prior thoracic surgery	11 (10)	15 (9)	4 (7)	0.901[c)]
Prior esophageal surgery	8 (7)	6 (3)	1 (2)	0.296[c)]
Prior coronary artery bypass graft	10 (9)	13 (7)	6 (11)	0.699
Weight loss >4.5 kg	39 (34)	120 (68)	29 (53)	<0.001
Body mass index at surgery (kg/m^2)	28.8±6.4 (16.0–45.6)	27.7±6.4 (14.2–57.8)	27.7±6.4 (18.7–50.2)	0.360[d)]

Values are presented as mean±standard deviation (min–max) or number (%).
nCRT, neoadjuvant chemoradiotherapy.
[a)]By chi-square test. [b)]By Kruskal-Wallis. [c)]By Fisher exact test. [d)]By analysis of variance.

Actuarial survival rates for the 3 cohorts were calculated using the Kaplan-Meier method.

Results

Within the timeframe of this study, a total of 366 esophagectomies were performed to treat esophageal cancer. The most common type of procedure performed was transhiatal esophagectomy (n=330). Other techniques included the Mckeown 3-hole esophagectomy (n=25) and the Ivor Lewis esophagectomy (n=11). Several patients were excluded, for the following reasons: the 11 patients who underwent an Ivor Lewis esophagectomy were excluded due to the presence of an intrathoracic anastomosis, 5 patients were excluded due to delayed cervical anastomosis after spit fistula formation during the initial operation, and 2 patients were excluded because radiation therapy was administered with curative intent at high doses (6,000 cGy and 7,440 cGy). Intrathoracic anastomoses were excluded, as the majority of our patients had cervical anastomoses and intrathoracic anastomoses only occurred in a small fraction (<5%) of our cohort. The small number would only confound the data and would not allow a meaningful comparison.

A total of 348 patients met the inclusion criteria. Overall, 348 anastomoses were assessed for leaks using radiographic imaging unless clinical evidence of a leak was present. The median dose of radiation was 5,040 cGy (range, 4,140–5,600 cGy). Chemotherapy consisted of a platinum-based regimen; the most common agents used were cisplatin/5-fluorouracil and carboplatin/paclitaxel. The median time to surgery after completion of neoadjuvant treatment was 28 days. The 30-day operative mortality rate was 2.3% (8 of 348).

Patients were divided into 3 cohorts based on the timing of surgery following nCRT: no nCRT cohort, ≤35d cohort, and >35d cohort. The cutoff of 35 days was determined using logistic regression to determine the time at which the incidence of anastomotic leaks increased. Table 1 summarizes the demographic characteristics for each cohort. The pathologic staging of the tumors for each cohort is summarized in Table 2. The mean age of patients who did not receive nCRT was higher (66.7 years) than that of patients who received nCRT (60.3 years in

Table 2. Pathologic staging of all patients who underwent esophagectomy in this study

TNM staging	Esophagectomy without nCRT (n=116)	Esophagectomy ≤35 days post-nCRT (n=177)	Esophagectomy >35 days post-nCRT (n=55)
T0	-	45 (25.4)	21 (38.2)
Tis	18 (15.5)	6 (3.4)	-
T1	35 (30.2)	19 (10.7)	7 (12.7)
T2	15 (12.9)	32 (18.1)	12 (21.8)
T3	38 (32.8)	73 (41.2)	14 (25.5)
T4	10 (8.6)	2 (1.1)	1 (1.8)
N0	68 (58.6)	119 (67.2)	38 (69.1)
N1	34 (29.3)	33 (18.6)	16 (29.1)
N2	10 (8.6)	21 (11.9)	1 (1.8)
N3	4 (3.4)	4 (2.3)	-
Complete response	-	41 (23.2)	19 (34.5)
Stage 0	18 (15.5)	6 (3.4)	-
Stage IA/B, IIA	38 (32.8)	39 (22.0)	14 (25.5)
Stage IIB	23 (19.8)	46 (26.0)	11 (20.0)
Stage IIIA	17 (14.7)	22 (12.4)	10 (18.2)
Stage IIIB	8 (6.9)	19 (10.7)	1 (1.8)
Stage IIIC	12 (10.3)	4 (2.3)	-

Values are presented as number (%).
TNM, tumor–node–metastasis; nCRT, neoadjuvant chemoradiotherapy.

Table 3. Timing of esophagectomy after nCRT and its effect on anastomotic leak incidence

Timing of nCRT	With anastomotic leak	p-value[a)]	Pairwise comparison	Post-hoc adjusted p-value
No nCRT (n=116)	17 (14.7)	0.020	No nCRT vs. ≤35 days	0.044
nCRT ≤35 days prior to surgery (n=177)	13 (7.3)		No nCRT vs. >35 days	0.378
nCRT >35 days prior to surgery (n=55)	11 (20.0)		≤35 days vs. >35 days	0.007

Values are presented as number (%), unless otherwise stated.
nCRT, neoadjuvant chemoradiotherapy.
[a)]By chi-square test.

the >35d cohort and 61.0 years in the ≤35d cohort; $p<0.001$). No differences in sex, smoking history, diabetes, COPD, CAD, renal failure, hypertension, prior abdominal/thoracic surgery, prior esophageal surgery, prior CABG, and BMI were observed among the cohorts. Weight loss of over 4.5 kg was more common in patients who received nCRT (53% in the >35d cohort and 68% in the ≤35d cohort) than in those in the no nCRT group (33%, $p<0.001$).

Among all patients who were included, anastomotic leaks occurred in 11.8% (41 of 348). Among the 41 patients with anastomotic leaks, 11 leaks (26.8%) were found radiographically on the initial evaluation. The neck incision was opened at the bedside if a patient had clinical signs of a cervical anastomotic leak, and no further radiographic examination was performed. Anastomotic leaks were observed in 10.3% of patients (24 of 232) who received nCRT, but in 14.7% (17 of 116) of no nCRT group (p=0.247). A comparison of anastomotic leaks among the 3 cohorts demonstrated a significant difference between the no nCRT cohort and the ≤35d cohort (p=0.044), whereas no significant difference was observed between the no nCRT and >35d cohorts (p=0.378). When esophagectomy was performed within 35 days of nCRT, anastomotic leaks occurred in 7.3% of patients (13 of 177), whereas they occurred in 20.0% of patients (11 of 55) who had surgery more than 35 days following nCRT (p=0.007) (Table 3). Among the patients who re-

Table 4. Effects of anastomotic leaks on the median length of the hospital stay and on 30-day operative mortality

Variable	Anastomotic leak (n=41)	No anastomotic leak (n=307)	p-value
Median length of stay (25th–75th percentile) (day)	20 (9.5–29)	6 (5–9)	<0.001
No. of 30-day operative mortality (%)	3 (7.3)	5 (1.6)	0.056

Table 5. Effects of nCRT on the median length of the hospital stay and on 30-day operative mortality among patients with an anastomotic leak

Variable	Anastomotic leak with nCRT (n=24)	Anastomotic leak without nCRT (n=17)	p-value
Median length of stay (25th–75th percentile) (day)	10 (7.3–21.8)	26 (18–64.5)	0.041
No of 30-day operative mortality (%)	0	3 (17.6)	0.064

nCRT, neoadjuvant chemoradiotherapy.

Table 6. Effects of timing of nCRT on median length of the hospital stay and on 30-day operative mortality

Variable	Esophagectomy ≤35 days after nCRT (n=177)	Esophagectomy >35 days after nCRT (n=55)	p-value
Median length of stay (25th–75th percentile) (day)	6 (5–8)	7 (6–13)	<0.001
No. of 30-day operative mortality (%)	2 (1.1)	0	0.581

nCRT, neoadjuvant chemoradiotherapy.

ceived nCRT, the median time to surgery after completion of treatment was longer (35 days) for those with an anastomotic leak than for those who had no detectable leak (28 days).

The median hospital stay following surgery was longer among patients with an anastomotic leak (20 days) than those without a leak (6 days, p<0.001). The 30-day operative mortality rate was 7.3% (3 of 41) for patients with an anastomotic leak and 1.6% (5 of 307) for patients without an anastomotic leak (p=0.056) (Tables 4–6). The median survival by group was 52.3 months (95% CI, 26.5–78.1 months) in the no nCRT cohort, 38.7 months (95% CI, 20.0–57.3 months) in the ≤35d cohort, and 24.2 months (95% CI, 18.4–30.1 months) in the >35d cohort, (p=0.101) (Fig. 1). The 5-year survival rates were 49.1% (57 of 116) in the no nCRT cohort, 46.9% (83 of 177) in the ≤35d cohort, and 30.9% (17 of 55) in the >35d cohort. The 90-day mortality rates were 10.3% (12 of 116) in the no nCRT cohort, 3.4% (6 of 177) in the ≤35d cohort, and 10.9% (6 of 55) in the >35d cohort.

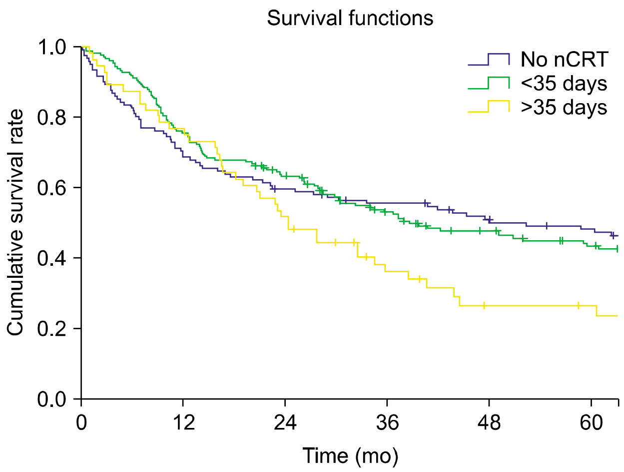

Fig. 1. Kaplan-Meier curve for overall survival (p=0.101). nCRT, neoadjuvant chemoradiotherapy.

Discussion

Currently, the effects of nCRT on postoperative complications following esophagectomy are unclear. In some retrospective studies, neoadjuvant therapy was found to be associated with postoperative complications [5,26]. For example, adverse effects on working capacity were observed in a retrospective trial in which surgical resection was performed 4–6 weeks after the completion of neoadjuvant therapy [26]. In contrast, other studies have failed to find any negative effects on surgical morbidity [1,2,12-15,19,27]. Randomized trials comparing surgery alone to neoadjuvant chemo-radiotherapy have failed to demonstrate any adverse effects of nCRT therapy on surgical complications [11,16]. In these trials, resection was performed within 3–4 weeks of completion of nCRT, and patients' survival improved. In a retrospective trial that demonstrated harm following neoadjuvant therapy, surgical resection was frequently performed 4-6 weeks after neoadjuvant therapy was completed [26].

Extending the time between nCRT and esophagectomy has been theorized to increase tumor regression, leading to improved tumor resectability and an increase in the pathologic complete response (pCR). Some studies have concluded that a longer interval between nCRT and esophagectomy resulted in higher rates of pCR [23,25], whereas others have reported no significant improvement [20-22]. In a multicenter trial in Europe, no difference in the occurrence of anastomotic leaks was observed when surgery was performed 6–8 weeks after the completion of nCRT therapy [19]. Additionally, a study by Kim et al. [20] found no significant difference in postoperative morbidity and mortality in esophagectomies performed within or after 8 weeks of receiving nCRT.

In contrast, a report that evaluated the 30- and 90-day mortality rates after esophagectomy using data from the American College of Surgeons National Cancer Database found a positive effect on operative mortality when esophagectomy was delayed after neoadjuvant therapy (90 days versus 30 days) [24]. The results from our study suggest that a short delay (≤35 days) in esophagectomy after the completion of nCRT reduces the occurrence of anastomotic leaks. Patients who did not receive nCRT were also noted to have a higher rate of anastomotic leaks than those in the ≤35d group. No nCRT group was significantly older, with a mean age of 66.7 years, than the patients in the ≤35d group, who had a mean age of 61.0 years. While older age may have been a contributing factor to the higher anastomotic leak rate among patients who did not receive nCRT, age alone is unlikely to be the only contributing factor. This is a limitation of the study, and further investigation is needed to identify factors leading to differences in the leak rate between these 2 cohorts.

This study specifically analyzed the effects of timing of nCRT prior to surgery on the rate of anastomotic leaks, whereas prior studies have analyzed perioperative complications more generally. Our data showing that patients who underwent surgery within 35 days of nCRT had a lower rate of anastomotic leaks provide a clear time frame during which to perform surgery after nCRT. Furthermore, anastomotic leaks significantly increased the length of the hospital stay post-esophagectomy compared to patients who did not have a leak. However, differences in the occurrence of anastomotic leaks due to nCRT did not affect overall survival; no difference in the survival rate was observed between patients who received nCRT and those who did not (Fig. 1). Thus, our data suggest that reducing the time to esophagectomy following nCRT to less than 35 days positively affects postoperative outcomes such as the occurrence of anastomotic leaks. However, each patient must be evaluated on an individual basis, accounting for all clinical variables such as performance status, in order to determine the best time for surgery after nCRT.

Although prior studies have used 30 days, 60 days, 90 days, 4 weeks, or 8 weeks after nCRT as the time frame for surgery, our study categorized 35 days as the cutoff between the 2 groups of patients who received nCRT. This cutoff period was derived by performing a logistic regression analysis of the data to determine when patients started to have an increased incidence of anastomotic leaks. Patients were categorized into quartiles, which resulted in the following classifications of days after nCRT to surgery: 12–23 days, 24–28 days, 29–35 days, and >35 days. The >35 days group showed a significantly increased rate of anastomotic leaks. This time frame may not be equivalent to that used in prior studies, but one of the primary goals of this study was to examine the effect of timing after nCRT prior to surgery and its impact on anastomotic leaks. Therefore, having a time frame distinct from those used in previously reported studies was justified.

Although our data demonstrate a reduction in the number of anastomotic leaks in patients who had a preoperative interval of ≤35 days following completion of nCRT, some limitations should be kept in mind. This study was performed retrospectively and did not account for differences in baseline demographics (such as patient age) or in preoperative weight loss between those who did or did not receive nCRT. Confounding variables such as preoperative albumin and transfusion requirements, which can affect the occurrence of anastomotic leaks, were not collected in the database [28]. Our dataset also did not include tumor regression response data, and we were thus unable to analyze how the timing of esophagectomy following nCRT affected tumor response. In addition, patients undergoing surgery >35 days after nCRT may have had worse performance status, resulting in both delayed surgery and a higher incidence of leaks. Further investigation is needed to determine the factors associated with the increased anastomotic leak rates in this cohort of patients.

Our analysis did not include information on the radiation field used during neoadjuvant radiation therapy. The size of the radiation field can have a significant impact on development of anastomotic leakage, especially if the cranial level of the radiation field includes the location of the cervical anastomosis. The exact cranial level of the radiation field could not be determined for many members of our patient cohort, as some underwent neoadjuvant radiation therapy at another institution, due to proximity and the patient's convenience. Although the radiation field incorporated the malignancy and there were limited variations on the field extending beyond the margins of the tumor, a lack of quantification of the radiation field is a limitation of the study.

The study spans more than 15 years of data, and there may have been differences in decision-making in terms of the operators' choice of surgical technique and in the preoperative and postoperative management of patients that could have affected the incidence of anastomotic leaks. We also recognize that the vascularity of the gastric conduit and tension placed during anastomosis may have varied among the operators and patients included in the study. However, given the rigorous training that all operators underwent, as well as the standardization of surgical technique, anastomoses were performed only if there was adequate blood supply to the gastric conduit, and they were performed in a way that minimized tension on the conduit. These factors were not readily quantifiable retrospectively, which represents another limitation of the study.

Despite these limitations, our current practice has incorporated the findings of our study, so that esophagectomies are now performed within 35 days of nCRT. Further investigation will help to determine the optimal time interval during which to proceed with surgery following nCRT, as well as characterizing the effects of this timing on tumor regression and overall survival.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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