JAMA Surgery | Original Investigation | PACIFIC COAST SURGICAL ASSOCIATION

Association of Intervals Between Neoadjuvant Chemoradiation and Surgical Resection With Pathologic Complete Response and Survival in Patients With Esophageal Cancer

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IMPORTANCE Pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (CRT) may be a clinical prognostic marker of superior outcomes. In patients with esophageal cancer, pCR is associated with increased survival. While mechanisms for increasing the likelihood of pCR remain unknown, in other solid tumors, higher rates of pCR have been associated with longer time intervals between CRT completion and surgical procedures.

OBJECTIVE To determine the association between time intervals from the completion of CRT to surgical procedure with rates of pCR in patients with esophageal cancer.

DESIGN, SETTING, AND PARTICIPANTS A prospectively maintained multidisciplinary foregut database was reviewed for consecutively enrolled patients with esophageal cancer from January 2000 to July 2015 presenting for surgical evaluation at a single National Cancer Institute–designated cancer center within a quaternary academic medical center.

INTERVENTIONS Included patients successfully completed neoadjuvant CRT followed by esophagectomy.

MAIN OUTCOMES AND MEASURES Rate of pCR by logistic regression based on a categorized time interval (ie, 0 to 42, 43 to 56, 57 to 70, 71 to 84, 85 to 98, and 99 or more days) from the completion of CRT to surgical resection, adjusted for clinical stage, demographic information, and CRT regimen.

RESULTS Of the 234 patients who met inclusion criteria, 191 (81.6%) were male, and the median (range) age was 64 (58-70) years; 206 (88.0%) were diagnosed as having adenocarcinoma, and 65 (27.9%) had a pCR. Patients in the 85 to 98–day group had significantly increased odds of a pCR compared with other groups (odds ratio, 5.46; 95% CI, 1.16-25.68; $P = .03$). No significant differences in survival were seen between time groups overall or among patients with residual tumor.

CONCLUSIONS AND RELEVANCE This study suggests that a time interval of 85 to 98 days between CRT completion and surgical resection is associated with significantly increased odds of a pCR in patients with esophageal cancer. No adverse association with survival was detected as a result of delaying resection, even in patients with residual tumor.

Invited Commentary

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JAMA Surg. doi:10.1001/jamasurg.2016.2743
Published online September 14, 2016.

Esophageal cancer is the sixth most common cause of cancer death worldwide.[1] This highly morbid disease continues to increase in incidence in the United States, where it accounts for more than 15 000 deaths annually.[2] Since the addition of neoadjuvant chemoradiotherapy (CRT) prior to surgical procedures, improved survival is now being seen compared with previous treatment regimens that favored surgical procedures alone.[3,4] Nevertheless, the prognosis for this disease remains grim, with an overall estimated 5-year survival rate of 18%,[5] illustrating the urgent need to further refine treatment strategies.

Even with the addition of neoadjuvant CRT, individual patients can have varied responses to treatment. In the ideal case, a very robust treatment effect can result in the elimination of all residual tumor from the surgical specimen,[6] termed a *pathologic complete response* (pCR). However, when tumor persists or even progresses during treatment, this represents an incomplete response. Unfortunately, while we know that those patients who achieve a pCR have significantly improved survival compared with those with residual disease,[6-8] it remains unclear what factors either predict or increase the likelihood of a pCR.[9,10]

Contemporary treatment plans for patients with esophageal cancer suggest that esophagectomy be performed within 6 to 8 weeks of the completion of neoadjuvant therapy.[3,11,12] However, studies of other solid tumors, such as pancreatic[13] and rectal cancer,[14-17] have found that longer time intervals between CRT and surgical procedures are associated with increased rates of pCR. However, evaluations of this phenomenon in patients with esophageal cancer have produced mixed results. Consequently, the aim of the current study was to identify an optimal time after the completion of neoadjuvant therapy that might maximize the rate of pCR in patients with esophageal cancer.

Key Points

Question What is the effect of the timing of esophagectomy after the completion of neoadjuvant chemoradiotherapy on the rates of pathologic complete responses in patients with esophageal cancer?

Findings This review of a prospectively maintained single National Cancer Institute–designated cancer center database demonstrated that a wait time of 85 to 98 days between chemoradiotherapy and esophagectomy was associated with the highest rate of pathologic complete response in patients with esophageal cancer without a significant effect on survival.

Meaning Delaying surgical procedures for 85 to 98 days may increase rates of pathologic complete responses and improve outcomes for patients with this morbid disease.

Methods

Study Design and Participants

We performed a retrospective review of a prospectively maintained esophageal disease registry from a single National Cancer Institute–designated cancer center, under institutional review board approval (IRB 1759). We selected patients with cancers of the mid or distal esophagus who completed neoadjuvant CRT under the direction of their oncologists between January 2000 and July 2015. Patients were then restaged according to institutional guidelines, and those who were deemed to be resectable (regardless of the apparent degree of response to CRT) and appropriate surgical candidates by the operating surgeon were offered esophagectomy, allowing them to be enrolled and analyzed. Those with incomplete or inaccurate information on induction CRT treatment timing and those who declined a surgical procedure were excluded from this analysis. Individual patient demographic information as well as operative and postoperative variables were extracted and used for subsequent analyses, with each patient's clinical record being reviewed to obtain missing variables. The Oregon Health and Science Institutional Review Board provided approval for this study, and written informed consent was obtained from all patients in line with institutional procedures at the time of their enrollment in the registry.

Time Interval Designation

The time-to-operation variable was defined as the number of days from the last day of preoperative chemotherapy or radiation (whichever was later) to surgical resection. This variable was categorized into the following groups: 0 to 42 days, 43 to 56 days, 57 to 70 days, 71 to 84 days, 85 to 98 days, and 99 or more days. These categories were chosen based on several considerations. We chose to have a larger number of groups so that it would be possible to detect a trend in the chance of pCR by wait time until operation. The first 2 boundaries, 42 and 56 days, were chosen so that our results could be compared with existing studies that generally evaluate wait times of approximately 6 to 8 weeks. Subsequent boundaries were chosen at 14-day intervals until 99 days, the latest boundary for which the last group could maintain an adequate size.

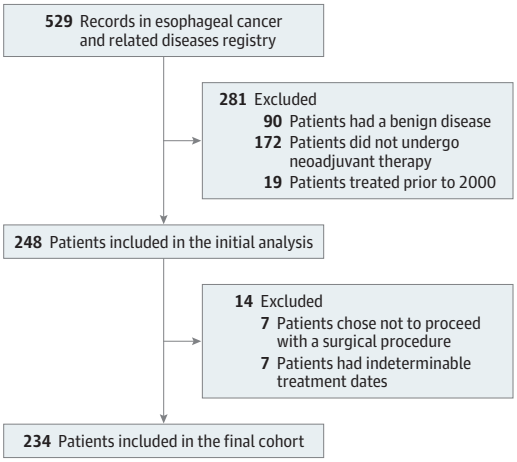
Comorbidities

Patient comorbidities were calculated using an age-adjusted Charlson Comorbidity Index score. The Charlson Comorbidity Index is an evidence-based method for categorizing comorbidities in a manner in which each of 17 comorbidities carries a specific weight based on the adjusted risk of mortality for that condition. The sum of all the weights results in a single comorbidity score for a patient, which reflects an estimate of their 1-year mortality risk.[18]

Statistical Analysis

Baseline demographic and clinical characteristics were examined and compared across the various time groups. Continuous-valued characteristics were summarized in terms of quantiles and were compared across groups using the Kruskal-Wallis test. Categorical-valued characteristics were compared using the χ^2 test or Fisher exact test, as appropriate. Counts were categorized and compared in the same way. Clinical characteristics included age, sex, race/ethnicity, preoperative

Figure 1. Patient Enrollment Flow Map



diagnosis, clinical stage, lymph node status, types of neoadjuvant therapies administered, and Charlson Comorbidity Index score.

A logistic regression model was then formulated to evaluate the association between the chance of pCR and time from the end of neoadjuvant therapy to esophagectomy. To address potential confounding, the model was adjusted for histologic subtype (ie, adenocarcinoma or squamous cell carcinoma), clinical stage, type of neoadjuvant therapies, patient age, and sex. The time from the end of neoadjuvant therapy to esophagectomy was modeled categorically, with the 0 to 42-day group serving as the reference group.

To investigate whether overall survival time following esophagectomy differed across these groups, a Cox proportional hazards model was formulated, adjusting for clinical factors. Finally, a subgroup analysis was carried out to examine whether survival time differed across the groups among patients who did not have a pCR. Statistical significance was set at $P < .05$.

Results

Patient Demographic Information

Of the 529 patients in the registry at the time of our query, 234 patients with esophageal cancer had completed neoadjuvant CRT with restaging indicative of resectable disease and were scheduled for esophagectomy (**Figure 1**). Demographic and clinical characteristics of the patients who met inclusion criteria were stratified by groups defined by time intervals between the end of neoadjuvant CRT and the esophagectomy (**Table 1**). The sample was predominantly white (228 [97.4%]) and male (191 [81.6%]), and the median (range) age at time of operation was 64 (58-70) years. Most patients (206 [88.0%]) were diagnosed as having an adenocarcinoma, with the remainder diagnosed as having a squamous cell carcinoma (28 [12.0%]).

The distribution of patient ages differed somewhat across the groups, as patients in the shortest time group tended to be younger (Kruskal-Wallis test: $P = .06$; Table 1). In addition, the frequency of neoadjuvant radiation differed across the groups; only 20 of 26 patients (76.9%) in the shortest time-to-operation group received concurrent radiation, while 225 of 234 patients overall (96.2%) received it (Fisher exact test: $P = .001$). However, there were no other notable differences across the groups in terms of sex, race/ethnicity, histologic subtype, clinical stage, or nodal status. Examination of comorbidities through the Charlson Comorbidity Index revealed median scores of 4 to 5.5, with a range of 2 to 12 ($P = .03$). Including all major and minor complications, 131 patients (56.5%) experienced a complication, with no significant differences in this rate across the groups ($P = .13$).

Of the 234 patients deemed appropriate surgical candidates, 232 (99.1%) successfully completed esophagectomy. Of the 2 patients in whom complete surgical resection failed, one experienced cardiac death 93 days after completing his neoadjuvant CRT. The second patient's surgical procedure was delayed for medical reasons, and progressive disease was found 104 days after completing neoadjuvant CRT, resulting in the cancellation of his procedure. The first patient was excluded from pCR analyses because it is unknown whether he had a pCR, but he was included in the survival analysis. The second was categorized as not achieving a pCR due to his recurrence and was included in all analyses.

Time From Completion of CRT to Surgical Resection

The median (range) wait time from the completion of neoadjuvant CRT to esophagectomy was 60 (17-217) days. There was no notable difference in time to operation between patients who had a pCR on the final pathology and those who did not (Mann-Whitney test: $P = .30$).

Eighteen patients (7.7%) in our cohort had extended wait times of 99 or more days. There were several reasons for the extended wait times in our sample; 7 patients were delayed for medical optimization (ie, for cardiac intervention or pulmonary optimization), 8 experienced complications during CRT that delayed surgical fitness (ie, infections, poor tolerance, or a need for other surgical procedures), 3 were late referrals, and 3 experienced other delays.

Pathologic Complete Response

In our cohort, 65 patients (27.9%) had a pCR, although there was substantial variation in this rate across the time-to-operation groups (**Table 2**). While most groups had pCR rates ranging from 19.2% to 33.3%, our 85 to 98-day group was noted to be a high outlier, with 8 of 19 patients (42.1%) achieving a pCR. After adjusting for patient age and sex as well as preoperative histology, clinical stage of the tumor, neoadjuvant therapy type, and chemotherapy agents administered, the odds of a pCR was systematically higher for all groups compared with the 0 to 42-day reference group (**Table 3**). However, only the 85 to 98-day group showed a significant difference from the other groups, with an estimated odds ratio for pCR of 5.46 (95% CI, 1.16-25.68; $P = .03$). Importantly, this effect did not appear to be monotonic, as the estimated odds of pCR for the 99 or more-day group was closer to the null value. This pattern could indicate that the adjusted odds of pCR may have an

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%)							P Value
		Time From End of Neoadjuvant Therapy to Surgical Procedure, d						
	Total (N = 234)	0-42 (n = 26)	43-56 (n = 73)	57-70 (n = 75)	71-84 (n = 22)	85-98 (n = 20)	≥99 (n = 18)	
Age, median (interquartile range), y	64 (58-70)	59.5 (54-66)	63 (57-68)	67 (61-71)	62.5 (56-66)	65.5 (59-73)	63.5 (59-72)	.06[a]
Male	191 (81.6)	24 (92.3)	56 (76.7)	62 (82.7)	18 (81.8)	15 (75.0)	16 (88.9)	.49
Race/ethnicity								
Native American	2 (0.9)	0	1 (1.4)	1 (1.3)	0	0	0	
Asian	3 (1.3)	1 (3.8)	0	1 (1.3)	1 (4.5)	0	0	.78[b]
White	228 (97.4)	25 (96.2)	71 (97.3)	73 (97.3)	21 (95.5)	20 (100)	18 (100)	
Other	1 (0.4)	0	1 (1.4)	0	0	0	0	
Preoperative diagnosis								
Adenocarcinoma	206 (88.0)	25 (96.2)	63 (86.3)	67 (89.3)	17 (77.3)	17 (85.0)	17 (94.4)	.39
Squamous cell carcinoma	28 (12.0)	1 (3.8)	10 (13.7)	8 (10.7)	5 (22.7)	3 (15.0)	1 (5.5)	
Clinical stage								
I	4 (1.7)	1 (3.8)	1 (1.4)	2 (2.7)	0	0	0	
II	74 (31.6)	12 (46.2)	22 (30.1)	21 (28.0)	6 (27.3)	6 (30.0)	7 (38.9)	.64
III	145 (62.0)	11 (42.3)	47 (64.4)	49 (65.3)	16 (72.7)	13 (65.0)	9 (50.0)	
IV	8 (3.4)	1 (3.8)	3 (4.1)	2 (2.7)	0	0	2 (11.1)	
Unknown	4 (1.7)	1 (3.8)	0	1 (1.3)	0	1 (5.0)	0	
No. of nodes removed								
0	9 (3.8)	0	2 (2.7)	3 (4.0)	0	3 (15.0)	1 (5.6)	
1-5	16 (6.8)	2 (7.7)	3 (4.1)	5 (6.7)	3 (13.6)	1 (5.0)	2 (11.1)	
6-10	21 (9.0)	6 (23.1)	5 (6.8)	2 (2.7)	3 (13.6)	2 (10.0)	3 (16.7)	.07
11-20	101 (43.2)	9 (34.6)	32 (43.8)	44 (58.7)	7 (31.8)	4 (20.0)	5 (27.8)	
21-30	63 (26.9)	7 (26.9)	23 (31.5)	16 (21.3)	6 (27.3)	6 (30.0)	5 (27.8)	
≥31	24 (10.3)	2 (7.7)	8 (11.0)	5 (6.7)	3 (13.6)	4 (20.0)	2 (11.1)	
No. of positive nodes								
0	132 (56.4)	14 (53.8)	40 (54.8)	44 (58.7)	12 (54.5)	11 (55.0)	11 (61.1)	
1-5	83 (35.5)	10 (38.5)	30 (41.1)	27 (36.0)	6 (27.3)	6 (30.0)	4 (22.2)	.49
6-10	11 (4.7)	1 (3.8)	2 (2.7)	3 (4.0)	3 (13.6)	1 (5.0)	1 (5.6)	
≥11	8 (3.4)	1 (3.8)	1 (1.4)	1 (1.3)	1 (4.5)	2 (10.0)	2 (11.1)	
Charlson Comorbidity Index score, median (interquartile range)	5 (4-6)	4 (3-7)	4 (3-6)	5 (4-6)	4 (4-5)	5 (4-6.5)	5.5 (5-8)	.03[a]
Chemotherapy regimen								
Carboplatin and paclitaxel with or without other agents	106 (45.3)	7 (26.9)	28 (38.4)	37 (49.3)	10 (45.5)	12 (60.0)	12 (66.7)	
Cisplatin and fluorouracil with or without other agents	67 (28.6)	8 (30.8)	25 (34.2)	20 (26.7)	8 (36.4)	4 (20.0)	2 (11.1)	.50
Other	36 (15.4)	6 (23.1)	13 (17.8)	10 (13.3)	3 (13.6)	2 (10.0)	2 (11.1)	
Unknown	25 (10.7)	5 (19.2)	7 (9.6)	8 (10.7)	1 (4.5)	2 (10.0)	2 (11.1)	
Neoadjuvant radiation	225 (96.2)	20 (76.9)	71 (97.3)	74 (98.7)	22 (100)	20 (100)	18 (100)	.001[b]
Any complication	131 (56.0)	14 (53.8)	44 (60.3)	41 (54.7)	7 (31.8)	13 (65.0)	12 (66.7)	.13

[a] Value calculated by Kruskal-Wallis test of equal distributions.

[b] Value calculated by Fisher exact test.

inverted U shape over the time to operation or that there may be an inflection point in the odds of pCR if surgical procedure is delayed too long.

Survival

Patients with a pCR on final pathology had significantly better survival than those with residual disease, with a median

Table 2. Absolute Rates of Pathologic Complete Response

Time From End of Neoadjuvant Therapy to Surgical Procedure, d	Pathologic Complete Response		
	Total, No.	Yes, No. (%)	No, No. (%)
0-42	26	5 (19.2)	21 (80.8)
43-56	73	21 (28.8)	52 (71.2)
57-70	75	20 (26.7)	55 (73.3)
71-84	22	5 (22.7)	17 (77.3)
85-98	19	8 (42.1)	11 (57.9)
≥99	18	6 (33.3)	12 (66.7)
Total	233	65 (27.9)	168 (72.1)

(interquartile range) survival time of 8.7 (2.3->12.9) years for those with a pCR and only 2.0 (0.82-13.3) years for those with residual tumor at resection. Although the estimated odds of pCR in the 85 to 98-day group was much greater than in the 0 to 42-day reference group, this did not translate into a survival advantage. Rather, Kaplan-Meier analysis showed no evidence that the risk of death differed significantly across the time-to-operation groups after adjusting for age, sex, clinical stage, neoadjuvant therapy type, and chemotherapy agent (Wald test of coefficients: $P = .47$) (**Figure 2**A). Likewise, we did not detect a survival difference across groups for patients with residual tumor at the time of their resection ($P = .17$) (Figure 2A).

Discussion

Our study suggests that a time interval of 85 to 98 days between the completion of neoadjuvant CRT and surgical resection is associated with significantly increased odds of a pCR in patients with esophageal cancer. Further, 8 of 19 patients (42.1%) in the 85 to 98-day group achieved a pCR, a considerable increase from previously published pCR rates, which are generally no higher than 30%.[19]

Neoadjuvant therapy has well described tumoricidal effects on solid cancers. However, to our knowledge, the precise effects of neoadjuvant therapies on the immune system and their mechanisms for inducing pCR remain to be elucidated.[20,21] It has been well documented in several solid tumors, including esophageal cancer, that higher levels of immune cell infiltration into tumors predict a better response to neoadjuvant CRT and thus a higher likelihood of a pCR.[22] Because CRT induces cell death, it elicits an immune response specific to the cancer, which increases immune surveillance and tumoricidal capacity[23] for several months following the completion of CRT, extending beyond the traditional surgical timing of 6 to 8 weeks.[24] The findings of increased pCR rates with longer time intervals between the completion of CRT and esophagectomy may be evidence of this increased tumoricidal capacity in the postneoadjuvant therapy setting. By proceeding with esophagectomy within the currently recommended time frame, we may be redirecting the immune system's capability toward recovering from a major operation rather than continuing in its tumoricidal role. Thus, we may be limiting its potential anticancer capacity. Increasing the interval between the completion of CRT and esophagectomy may provide the time needed for the immune system to exert its maximum effect on tumor regression. However, more formal evaluations of the timing of immune recovery in the weeks following CRT are necessary to fully answer this question.

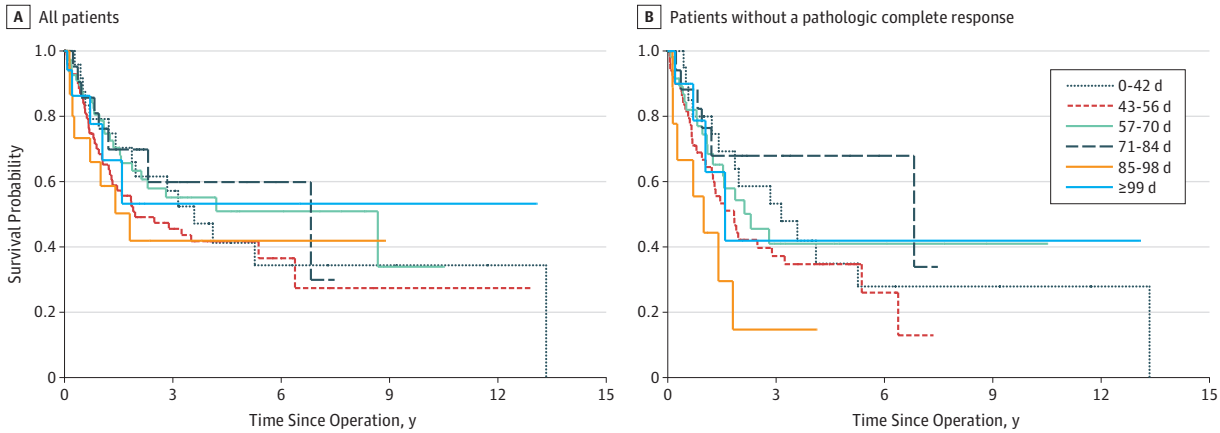
Table 3. Logistic Regression Analysis Examining the Influence of Patient Factors on Pathologic Complete Response

Characteristic	Odds Ratio (95% CI)
Time from end of neoadjuvant therapy to surgical procedure, d	
0-42	1 [Reference]
43-56	2.23 (0.62-7.95)
57-70	2.10 (0.58-7.64)
71-84	1.70 (0.35-8.21)
85-98	5.46 (1.16-25.68)
≥99	3.55 (0.73-17.21)
Clinical stage	
Stage 1B	1 [Reference]
Stage 2A	0.40 (0.05-3.54)
Stage 2B	0.41 (0.04-3.81)
Stage 3A	0.23 (0.03-1.92)
Stage 3B	0.27 (0.03-2.77)
Stage 3C	0.43 (0.03-6.94)
Stage 4	0.09 (0-1.94)
Unknown stage	NA
Chemotherapy agent	
Carboplatin and paclitaxel with or without other agents	1 [Reference]
Cisplatin and fluorouracil with or without other agents	2.10 (0.98-4.5)
Other regimen	1.78 (0.69-4.56)
Unknown regimen	4.44 (1.59-12.41)
Neoadjuvant radiation	0.64 (0.12-3.40)
Age, y	
18-59	1 [Reference]
60-69	1.69 (0.77-3.67)
≥70	1.31 (0.56-3.07)
Male sex	1.21 (0.52-2.79)
Histologic subtype	
Adenocarcinoma	1 [Reference]
Squamous cell carcinoma	1.62 (0.62-4.26)

Abbreviation: NA, not applicable.

Our findings in this study differ from the findings of other investigators. While a number of studies have also suggested a trend toward an increased chance of pCR with increasing time between neoadjuvant CRT and surgical procedures in patients with esophageal cancer,[25-30] others found no significant differences in the rates of pCR between patients who underwent "early" resection (before 7 to 8 weeks) and those who had "late" resections (after 7 to 8 weeks).[19,31] However, it should be noted that these studies have generally modeled the time to operation as a dichotomous variable, with the cutoffs remaining fairly early in the treatment cycle (usually at 6 to 8 weeks). Consequently, previous studies have not been able to analyze the finer differences between multiple time groups, particularly patients who waited for considerably longer time intervals. Our current study

Figure 2. Survival Probability Based on Time Interval Between Chemoradiotherapy and Surgical Resection



No. at risk

0-42 d	26	13	5	3	1	21	10	4	3	1
43-56 d	73	25	5	1	1	52	15	3		
57-70 d	75	19	8	1		55	8	4	1	
71-84 d	22	6	2			17	6	2		
85-98 d	19	4	1			11	1			
≥99 d	18	2	2	1	1	12	1	1	1	1

Kaplan-Meier estimate of the probability of survival after esophagectomy, stratified by groups defined by time between the end of neoadjuvant therapy and esophagectomy. A, The Wald test of coefficients for all patients demonstrated $P = .47$. B, The Wald test of coefficients for patients without a pathologic complete response demonstrated $P = .17$.

was able to explore this more thoroughly because of the large number of patients at our center experiencing extended surgical wait times. This was a result of our setting as a tertiary care esophageal cancer specialty center with high rates of referrals of medically complex individuals who required preoperative optimization, delaying their time to resection.

Our findings also differ from the published literature with respect to survival and complications. In comparison to previous authors' suggestions that longer wait times might be associated with worse overall survival and increased complications,[19] we found no effect on mortality and no increase in complications in the longer time interval groups, including in analysis of both major complications, such as anastomotic leak, as well as minor complications. The mortality finding also held true in those patients in the longer wait time groups who did not achieve a pCR (ie, had residual disease); subgroup analysis did not demonstrate a difference in survival in the extended wait time groups (Figure 2B).

The lack of a mortality difference between our time groups is perhaps surprising, given the evidence that supports that a notable survival benefit should accompany higher rates of pCR.[6-8] In fact, our data show high rates of pCR but no improved survival in patients who waited 85 to 98 days between CRT and resection. This may be a reflection of the disproportionate number of medically complex patients in this time group. Although we could not determine the direction of the trend, Charlson Comorbidity Index scores varied significantly between our groups ($P = .03$). This may reflect the fact that the later resection groups were not there because of preference or chance but because of the need to optimize medical comorbidities or recover from complications of CRT, which may have put them at an inherent disadvantage in terms of survival. An additional consideration is that the benefit of a pCR is likely related to disease-specific survival rather than the overall survival captured in our database. Even if a pCR does fully eliminate the cancer, patients with multiple comorbidities in the longer time groups may have increased overall mortality unrelated to their esophageal disease, which could be diluting the survival benefit of a pCR. It remains plausible that delaying resection, if proven to improve rates of pCR as suggested in this study, could improve survival if done in a healthier population unhindered by significant medical comorbidities. This idea will require prospective randomized evaluation to be fully addressed.

There are a number of limitations to this study. One of the most important sources of bias was that patients may have been allocated to the wait time groups for reasons that are related to the chance of a pCR (and survival), such as their comorbidities. In addition, the study is retrospective and subject to the bias and confounding inherent in this model, although the study was conducted using data collected prospectively under a single institution with standardized protocols for staging, treatment, and specimen analysis, and our group has demonstrated a consistent internal validation of pCR determination.[32] We are further limited by our relatively small sample size, with only 234 patients meeting the strict criteria for inclusion, and by relatively low numbers of patients in each of the time groups. With only 18 to 75 patients in each time group, validation in a larger separate cohort is warranted. However, it should be noted that in our population who were deemed to be surgical candidates after the completion of neoadjuvant CRT and restaging, all but 2 were successfully taken to procedure. This low exclusion rate gives reasonable fidelity to our study population and limits potential introduction of bias into the later groups.

Even if our findings are validated, there are many future studies that will be needed to more fully elucidate the role of predicting and promoting pCR in the management of patients with esophageal cancer. Serial assessment of noninvasive biomarkers, including cell-free tumor DNA, may help to clarify how pCR correlates with the actual burden of residual, immeasurable disease. Such an approach would also allow clinicians to intervene early and switch to another therapeutic regimen if the biomarker turns out to be predictive of pathologic incomplete response. In addition, there are patients who will not respond to CRT based on intrinsic tumor resistance. It may be worthwhile to enrich the population of patients who have a more favorable molecular signature for response and/or resistance to CRT.

Conclusions

The findings of this study show that a time interval of 85 to 98 days between the completion of neoadjuvant chemoradiation and surgical resection is associated with the greatest chance of a pCR in patients with esophageal cancer. To optimize rates of pCR with the goal of improving survival in this disease, delaying surgical procedures until 85 to 98 days after the completion of neoadjuvant CRT may be a reasonable approach. Validation of our observations in similar cohorts, ideally through a multi-institutional, prospective, randomized evaluation, is warranted to address the issues of bias.

ARTICLE INFORMATION

Accepted for Publication: May 20, 2016.

Published Online: September 14, 2016. doi:10.1001/jamasurg.2016.2743

Author Contributions: Dr Dolan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Haisley, Laird, Nabavizadeh, Gatter, Vaccaro, Thomas, Hunter, Dolan.
Acquisition, analysis, or interpretation of data: All Authors.
Drafting of the manuscript: Haisley, Laird, Nabavizadeh, Hunter, Dolan.
Critical revision of the manuscript for important intellectual content: All Authors.
Statistical analysis: Haisley, Laird, Hunter.
Obtaining funding: Hunter.
Administrative, technical, or material support: Gatter, Thomas, Hunter.
Study supervision: Nabavizadeh, Holland, Vaccaro, Thomas, Schipper, Hunter, Dolan.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Dolan's authorship in this publication was supported by the Oregon Clinical and Translational Research Institute and grant UL1TR000128 from the National Center for Advancing Translational Sciences of the National Institutes of Health.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Previous Presentation: This work was presented at the 87th Annual Pacific Coast Surgical Association Meeting; February 14, 2016; Kohala Coast, Hawaii.

Additional Contributions: We acknowledge the contributions of our biostatistician Dr Laird, as well as Hope Hardaker, MPH (Division of Gastrointestinal and General Surgery, Department of Surgery), and Charlie Borzy, BS, CCRC (Division of Gastrointestinal and General Surgery, Department of Surgery), our support staff at Oregon Health and Science University who maintain and update our database. No contributors were compensated for their work.

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