The Use of Single-agent Versus Multiple-agent Concurrent Chemoradiotherapy in the Treatment of Locally Advanced Rectal Cancer

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Abstract

Purpose: The use of concurrent chemoradiotherapy is frequently recommended in the treatment of locally advanced rectal cancer however the ideal chemotherapy regimen remains unknown and there is variability in chemotherapy agents used among different institutions. We sought to examine differences in overall survival between patients receiving single versus multiple-agent concurrent chemoradiotherapy.

Methods: The National Cancer Database was used to identify 31,025 patients with rectal cancer who received concurrent chemoradiotherapy between 01/2006 through 12/2016. We compared patients who received single-agent chemotherapy with those who received multiple-agent concurrent chemoradiotherapy. The primary outcome of interest was overall survival. The groups were compared using univariate analysis and Cox proportional hazard models to adjust for potential confounding factors.

Results: 18,544 patients received single-agent and 12,481 patients received multiple-agent chemotherapy. The former were older with more comorbidities as evidenced by their higher Charlson-Deyo Scores. Those receiving multiple-agent chemotherapy were more likely to have clinical Stage III disease (52.9% vs 43.3%, p<0.001) and less likely to have well-differentiated cancer (6.9% vs 7.7%, p<0.001). The rates of negative resection margin were identical (p=0.225) between the two groups. On multivariable analysis after adjusting for comorbidities, radiation dose, and resection margins, single-agent chemotherapy was associated with worse overall survival (HR 1.09, 95% CI 1.057-1.124, p<0.001).

Conclusion: Multiple-agent chemoradiotherapy is associated with improved overall survival in locally advanced rectal cancer, however chemotherapy regimen does not affect resection margins. The modest overall survival benefit with multiple agent chemotherapy must be balanced with the potential associated toxicity.

Introduction

Concurrent chemoradiotherapy for rectal cancer has changed considerably over the last few years. Existing guidelines recommend chemoradiation in the treatment of locally advanced rectal cancer (T3 or above and N1 or above without evidence of metastatic disease), as it is associated with a decrease in locoregional recurrence, however it has not been clearly associated with an overall survival benefit [1, 2]. Specifically, for chemotherapy, the current NCCN guidelines recommend the administration of concurrent chemoradiotherapy followed by adjuvant chemotherapy for Stage II and Stage III rectal cancer, however the optimal neoadjuvant and adjuvant regimens remain unclear and treatment protocols vary from one center to another [3]. Even though the addition of neoadjuvant chemotherapy has been associated with an increase in pathologic complete response rates and a decrease in locoregional recurrence rates, there has been no proven benefit in terms of overall survival [4, 5].

Today, 5-fluorouracil (5-FU) or capecitabine-based agents remain the most commonly used regimens for neoadjuvant therapy in rectal cancer. Several studies have examined the addition of a second agent such

as oxaliplatin to the existing regimens, however the results have not been conclusive. For instance, some studies including the CAO/ARO/AIO-04 randomized controlled trial have found that the addition of oxaliplatin leads to improved overall survival and improved pathologic complete response rates, however this has not been supported by other trials such as the STAR-01 trial [6-8]. The latter study not only showed similar overall survival and pathologic response rates, but also emphasized the enhanced toxicity related to the use of an additional chemotherapeutic agent. As a result of equivocal data, currently the addition of a second agent in neoadjuvant therapy for rectal cancer is not recommended by NCCN guidelines [3].

Given the clinical equipoise in selecting the best form of neoadjuvant treatment in rectal cancer, in this study we sought to examine differences in overall survival in patients who received single-agent neoadjuvant chemotherapy versus those who received multiple-agent neoadjuvant chemotherapy for locally advanced rectal cancer using the National Cancer Database (NCDB). In addition, we evaluated the association between neoadjuvant chemotherapy and likelihood of negative circumferential margin.

Materials And Methods

Study Design – Inclusion and Exclusion Criteria

Our study protocols were considered exempt by our institutional review board. We analyzed all patients who were diagnosed with adenocarcinoma of the rectum between 01/2006 through 12/2016 in the NCDB. The diagnosis of rectal cancer was identified using the code C20.9 and subsequently the histology codes that were used to capture patients with adenocarcinoma included: 8000, 8140, 8144, 8210, 8211, 8261, 8262, 8263, 8480, 8481, 8482, and 8490. This yielded a total of 31,025 patients who were eventually included in our analysis. We excluded patients with alternative histopathologic diagnoses and those with Stage IV disease.

The NCDB is a nationwide cancer epidemiology program that captures approximately 70% of all incident cancers in the United States. It is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Neither the American Cancer Society nor the American College of Surgeons have verified or are responsible for the methodology used in the present study or its conclusions.

Covariates

We captured several variables including patient demographic characteristics including age, gender, race, income, and insurance status. Patient comorbidities were assessed using the Charlson-Deyo index, which is a weighted score derived from 15 comorbid conditions that have been correlated with survival. Cancer-specific variables were also captured including the tumor grade and the American Joint Committee on Cancer (AJCC) Stage. Patient treatment variables including type of surgery, administration of chemotherapy and radiation therapy were also collected. The overall patient population was divided into two separate cohorts for the purpose of the analysis. One group comprised patients who received single-

agent chemoradiotherapy and the other group included patients who received multiple-agent chemoradiotherapy.

Primary Outcome:

The primary outcome of interest was overall survival. The NCDB captures survival as vital status meaning alive or dead at the time of last contact.

Statistical analysis

The statistical analysis was performed using SAS software (SAS institute Inc, Cary, NC). Statistical significance was defined as $p<0.05$. Continuous variables were summarized as means with standard deviations and categorical variables as counts with percentages. Continuous variables were compared using the 2-sided t-test or the Mann Whitney U test as appropriate and categorical variables were compared using the chi-square test. Subsequently, we performed survival analysis with Kaplan-Meier curves comparing the two groups using a log-rank test and then performed multivariable Cox hazard regression analyses to calculate hazard ratios controlling for all potential confounders. Overall survival was the dependent variable and the independent variables included age, gender, race, Charlson-Deyo Score, insurance status, income, AJCC stage, tumor grade, preoperative chemotherapy (single versus multiple-agent), type of surgery (partial versus total proctectomy), negative resection margin, and chemotherapy administered pre-op (versus both pre-op and post-op). The results of the Cox regression analysis were reported as hazard ratios (HR) with the corresponding 95% confidence intervals (CI) and p values.

Results

Patient Population and Univariate analysis

We included a total of 31,025 patients in our study. Of them, 18,544 patients received single-agent concurrent chemoradiotherapy and 12,481 received multiple-agent concurrent chemoradiotherapy. The characteristics of the two groups are summarized in Table 1. Patients receiving multiple-agent chemotherapy were younger, more frequently of white race, and more likely to have private insurance as compared to patients treated with single-agent chemotherapy (Table 1). They had less baseline comorbidities as evidenced by the lower Charlson-Deyo Score with 80% of patients in the multiple-agent group having a score of 0 versus 75.1% in the single-agent group ($p<0.001$). In terms of the tumor characteristics, patients who received single-agent chemotherapy were more likely to have well-differentiated (grade 1) cancer, whereas patients who received multiple-agent treatment were more likely to have clinical Stage III disease ($p<0.001$). Of note, there was no difference between the two groups in the time between the cancer diagnosis to the time they underwent surgery (42 vs 46 days, $p=0.2$) and there was no difference in the number of patients who needed to undergo a total proctectomy as compared to partial proctectomy (32% vs 31% respectively, $p=0.09$). In addition, there was no statistically significant difference in the neoadjuvant radiation dose between the two groups ($p=0.1$).

Patients in the single-agent treatment cohort had a slightly higher pathologic complete response rate (2.9% versus 2.3%, p<0.001). Yet, the rates of negative resection margins were identical between the two groups (93.9% for both, p=0.225). Those who received single-agent chemotherapy had higher overall 30- and 90-day mortality rates (1.2% vs 0.2% and 2.3% vs 0.7% respectively, p<0.001), as well as longer hospital length of stay (6.7 vs 5.5 days, p<0.001) after resection.

Multivariable and Survival Analysis

After adjusting for possible confounders, the administration of single versus multiple-agent chemoradiotherapy was not predictive of positive resection margin (OR 1.044, 95% CI 0.934 - 1.167, p=0.449). The only independent predictors of positive resection margin in our multivariable analysis were clinical Stage II and Stage III compared to Stage I disease, high-grade tumors, need for total proctectomy compared to partial proctectomy, and no insurance coverage. Lastly, patients among the higher quartile income (>63,000$) were significantly less likely to have positive resection margins. These results are summarized in Table 2.

In terms of survival, on unadjusted analysis, Kaplan-Meier curves showed no significant difference in overall survival between patients receiving single versus multiple-agent chemoradiotherapy treatment (Log rank p=0.4496). The Kaplan Meier curves are reproduced in Figure 1. However, our Cox proportional hazards analysis demonstrated that the administration of single-agent chemotherapy was independently associated with decreased overall survival (HR 1.09, 95% CI 1.057 - 1.124, p<0.001). Other factors that were associated with overall survival included age at the time of diagnosis, white race, black race, income in the lowest quartile, high grade cancer, partial (versus total proctectomy), and systemic therapy administered both pre and post-op (versus only pre-op). The results of the Cox regression analysis are summarized in Table 3.

Discussion

In this study of a large epidemiologic database from the American College of Surgeons and American Cancer Society, we identified a large proportion of patients with locally advanced rectal cancer who continue to undergo chemoradiotherapy with single-agent chemotherapy. Those who received single-agent chemotherapy had worse overall survival compared to those who received multiple-agent chemotherapy after adjusting for covariates such as patient characteristics, tumor variables, radiation dose, and type of surgery. Interestingly, even though we observed a significant difference in overall survival, we did not find any difference in positive resection margins, nor any clinically significant difference in pathologic complete response rates with additional chemotherapeutic agents.

Single versus multiple-agent chemotherapy has been widely debated in rectal cancer clinical practice [9]. In the ACCORD 12/0405 PRODIGE 2 randomized controlled trial a total of 598 patients were randomized into two arms; chemoradiotherapy with capecitabine versus chemoradiotherapy with capecitabine and oxaliplatin [10, 11]. At 3 years the investigators identified no significant difference between the two groups in terms of local recurrence, overall survival, or disease-free survival. As a result, they concluded

against the addition of oxaliplatin to the chemotherapy treatment protocols. The authors did mention that the follow-up was short and that the study was not adequately powered to detect differences <10%. Other studies have investigated different aspects such as chemotherapy-related toxicity following the addition of chemotherapeutic agents. Aschele and colleagues published the STAR-01 randomized phase 3 trial in 2011 [8]. They randomized a total of 747 patients with resectable, locally advanced (cT3-4 and or cN1-2) rectal adenocarcinoma into two groups. The first group (379 patients) was randomized to receive pelvic radiation and fluorouracil alone and the second group (368 patients) was assigned to receive the above with the addition of oxaliplatin. They demonstrated a statistically significant increase in the incidence of toxicity in the oxaliplatin group, without a significant impact on pathologic complete response. Thus, they also recommended against the addition of oxaliplatin to the chemoradiotherapy regimen. The above findings were corroborated by the results of the NSABP R04 trial, which concluded that adding oxaliplatin to neoadjuvant capecitabine did not improve locoregional control or survival but did add considerable toxicity [12].

In contrast, the German CAO/ARO/AIO-04 study was a phase III, multicenter, randomized controlled trial published in 2015 [6, 7]. The authors enrolled 1,236 patients with Stage II or Stage III rectal adenocarcinoma, of whom 623 received preoperative radiotherapy and fluorouracil followed by surgery and adjuvant fluorouracil (control group) and the remaining 613 received preoperative radiotherapy plus fluorouracil and oxaliplatin followed by surgery and adjuvant fluorouracil, leucovorin, and oxaliplatin (investigational group). The authors found a significant improvement in disease-free survival for patients in the investigational group and recommended the addition of oxaliplatin to the classic fluorouracil-based neoadjuvant chemotherapy protocols. The results of this study are supported by our findings that multiple-agent chemoradiotherapy regimens lead to improved overall survival in patients with locally advanced rectal adenocarcinoma.

Our study provides important data with its main strength being the very large sample size that the NCDB offers with more that 31,000 patients, a large cohort of patients with locally advanced rectal cancer that received treatment in the United States from 01/2006 through 12/2016. This sample size enabled us to detect a statistically significant difference in long-term outcomes between patients receiving single as compared to those receiving multiple-agent chemoradiotherapy. We identified a difference in overall survival favoring the multiple-agent chemotherapy group even after adjusting for clinically important variables including baseline comorbidities, radiation dose, and surgical procedure. The NCDB unfortunately does not provide data on important factors such as disease-free survival, locoregional recurrence or distant metastases, and systemic toxicity, however the results of our study imply that randomized controlled trials with longer follow-up or potentially larger sample size might be needed to identify significant statistical and clinical differences in outcomes.

The addition of oxaliplatin has been shown to have radiation-sensitizing properties and enhance the activity of 5-FU, ultimately leading to improved survival in patients with rectal cancer when offered in the adjuvant setting [13, 14]. The results of our study show that there may also be an advantage to using multiple-agent chemoradiotherapy in the neoadjuvant setting. If it is not simply a matter of sample size,

perhaps we should turn our attention and research efforts to identifying subsets of patients with locally advanced rectal cancer that could benefit the most from multiple-agent chemotherapy. For instance, a post-hoc analysis of the CAO/ARO/AIO-04 study revealed that the addition of oxaliplatin significantly improved disease free-and overall survival in patients with rectal cancer younger than 60, however did not confer a survival benefit in patients older than 70 [15]. In our study the patients who received multiple-agent chemotherapy were more frequently diagnosed with poorly differentiated tumors or Stage III disease. It is possible that such patients with more advanced disease have a survival benefit with additional chemotherapeutic agents.

Our study has a few limitations that warrant discussion. The main limitation is the potential bias secondary to its retrospective nature. As a result, there are potential confounding variables that have not been completely accounted for. In addition, the NCDB only includes patients who were treated at one of the CoC centers many of which are academic or comprehensive cancer centers, hence the generalizability of our results is somewhat limited. Furthermore, the NCDB does not capture several outcomes of interest including local or distant recurrence, disease-specific survival, and surgical complications such as leak rates etc. Lastly, the NCDB does not provide any details about the specific chemotherapy regimens such as the exact drugs that were used and dosing/administration schedules, hence there is inevitably a degree of bias that cannot be accounted for in the analysis. However, the strength of the NCDB is in its large population of patients, approximately 70% of all cancer diagnoses in the USA and the standard data collection. For these reasons, we maintain the value of these data in clinical decision making.

Conclusion

Multiple-agent chemoradiotherapy is associated with improved overall survival in locally advanced rectal cancer, however it does not affect resection margins, nor does it lead to improved pathologic complete response. Further research is warranted to identify the ideal chemoradiotherapy regimen and subsets of patients who would benefit most from a multi-agent modality.

Declarations

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Code availability: n/a

Ethics approval: Our study protocols were considered exempt by our Institutional Review Board.

Consent to participate: n/a

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Tables

Table 1: Univariate analysis comparing patients who received single-agent vs multiple-agent chemotherapy.

Variable	Single-agent chemotherapy (n=18,544)	Multiple-agent chemotherapy (n=12,481)	p-value
Age at diagnosis	61.9 (12.2)	57.1 (11.4)	<0.001
Male gender	11,547 (62.3)	7,781 (62.3)	0.896
Race			<0.001
White	15,852 (85.5)	10,830 (86.8)	
Black	1,653 (8.9)	964 (7.7)	
Other	1,039 (5.6)	687 (5.5)	
Insurance status			<0.001
Not Insured	855 (4.6)	605 (4.9)	
Private Insurance / Managed Care	8,379 (45.2)	7,382 (59.2)	
Medicaid	1,309 (7.1)	989 (7.9)	
Medicare	7,604 (41.0)	3,269 (26.2)	
Other Government	187 (1.0)	132 (1.1)	
Median income			<0.001
Less than 38,000 $	3,341 (18.0)	2,032 (16.3)	
38,000 – 48,000 $	4,630 (25.0)	2,966 (23.8)	
48,000 – 63,000 $	4,914 (26.5)	3,451 (27.7)	
> 63,000 $	5,572 (30.1)	3,993 (32.0)	
Charlson-Deyo Score			<0.001
0	13,922 (75.1)	9,979 (80.0)	
1	3,466 (18.7)	2,019 (16.2)	
≥2	813 (4.4)	345 (2.8)	
Well differentiated cancer (Grade 1)	1,431 (7.7)	855 (6.9)	<0.001
Clinical Stage			<0.001
1	1,144 (6.2)	557 (4.5)	
2	7,272 (39.2)	4,017 (32.2)	
3	8,022 (43.3)	6,597 (52.9)	
Diagnosis to chemotherapy initiation in days	38.3 (26.1)	36.4 (27.1)	<0.001

At least two courses of chemotherapy given both pre and postop	3,552 (19.2)	7,300 (58.5)	<0.001
Diagnosis to radiation initiation in days	39.2 (25.1)	41.0 (32.6)	<0.001
Radiation dose (50.4 Gy)	14,965 (80.7)	10,172 (81.5)	0.113
Diagnosis to surgery in days	141.2 (42.2)	140.6 (46.6)	0.217
Partial proctectomy (vs total)	12,650 (68.2)	8,629 (69.1)	0.087
Pathologic complete response	543 (2.9)	287 (2.3)	<0.001
Negative resection margin	17,403 (93.9)	11,716 (93.9)	0.225
Hospital length of stay, in days	7.6 (6.7)	6.9 (5.5)	<0.001
30-day mortality (all-cause)	191 (1.2)	22 (0.2)	<0.001
90-day mortality (all-cause)	376 (2.3)	73 (0.7)	<0.001

Table 2. Multivariable regression analysis to identify independent predictors of positive resection margin.

Variable	Odds Ratio (OR)	95% Confidence Interval (95% CI)	P value
Age at diagnosis	0.995	0.989 - 1.002	0.145
Female gender	1.007	0.909 - 1.115	0.896
Race			
Black (vs white)	1.117	0.94 - 1.328	0.208
Other (vs white)	0.885	0.698 - 1.121	0.31
Charlson-Deyo Score			
1 (vs 0)	1.096	0.964 - 1.246	0.16
2 (vs 0)	0.802	0.601 - 1.072	0.136
3 (vs 0)	1.223	0.847 - 1.766	0.283
Insurance status			
Not Insured (vs Private Insurance / Managed Care)	1.387	1.121 - 1.717	0.003
Medicaid (vs Private Insurance / Managed Care)	1.474	1.239 - 1.754	<0.001
Medicare (vs Private Insurance / Managed Care)	1.1	0.948 - 1.276	0.209
Other Government (vs Private Insurance / Managed Care)	1.358	0.863 - 2.136	0.185
Median income			
38,000 - 48,000 $ (vs < 38,000 $)	0.996	0.856 - 1.159	0.962
48,000 - 63,000 $ (vs < 38,000 $)	0.927	0.793 - 1.084	0.342
> 63,000 $ (vs < 38,000 $)	0.821	0.695 - 0.971	0.022
High grade cancer (vs low grade)	1.198	1.056 - 1.359	0.005
Clinical Stage			
II (vs I)	1.429	1.085 - 1.88	0.011
III (vs I)	1.68	1.281 - 2.204	<0.001
Total proctectomy (vs partial)	1.781	1.611 - 1.969	<0.001
At least two courses of chemotherapy given both pre and postop (vs only preop)	1.004	0.895 - 1.126	0.949

Single agent chemotherapy (vs multiple)	1.044	0.934 - 1.167	0.449

Table 3. Cox regression model predicting overall survival.

Variable	Hazard Ratio (HR)	95% Confidence Interval (95% CI)	P value
Age at diagnosis	0.997	0.996 - 0,999	0.003
Male gender	1.011	0.983 - 1.04	0.441
Race			
White	0.896	0.843 - 0.952	<0.001
Black	0.921	0.852 - 0.995	0.037
Charlson-Deyo Score			
0	1.029	0.898 - 1.18	0.681
1	1.001	0.871 - 1.152	0.985
≥2	1.06	0.906 - 1.24	0.469
Insurance status			
Not Insured	0.808	0.697 - 0.937	0.005
Private Insurance / Managed Care	0.763	0.667 - 0.873	<0.001
Medicaid	0.955	0.827 - 1.102	0.528
Medicare	0.755	0.658 - 0.866	<0.001
Other Government	0.863	0.715 - 1.041	0.123
Median income			
Less than 38,000 $	1.327	1.07 - 1.645	0.01
38,000 - 48,000 $	0.978	0.933 - 1.026	0.365
48,000 - 63,000 $	0.965	0.926 - 1.006	0.091
> 63,000 $	0.982	0.946 - 1.019	0.329
High Grade Cancer	1.089	1.053 - 1.126	<0.001
Clinical Stage			
1	0.567	0.54 - 0.596	<0.001
2	0.745	0.701 - 0.792	<0.001
3	0.885	0.859 - 0.913	<0.001
Partial proctectomy (vs total)	1.066	1.034 - 1.099	<0.001
Negative resection margin	0.895	0.745 - 1.075	0.237
At least two courses of chemotherapy given both	0.827	0.802 - 0.854	<0.001

pre and postop (vs only preop)			
Single agent chemotherapy (vs multiple)	1.09	1.057 - 1.124	<0.001

Figures

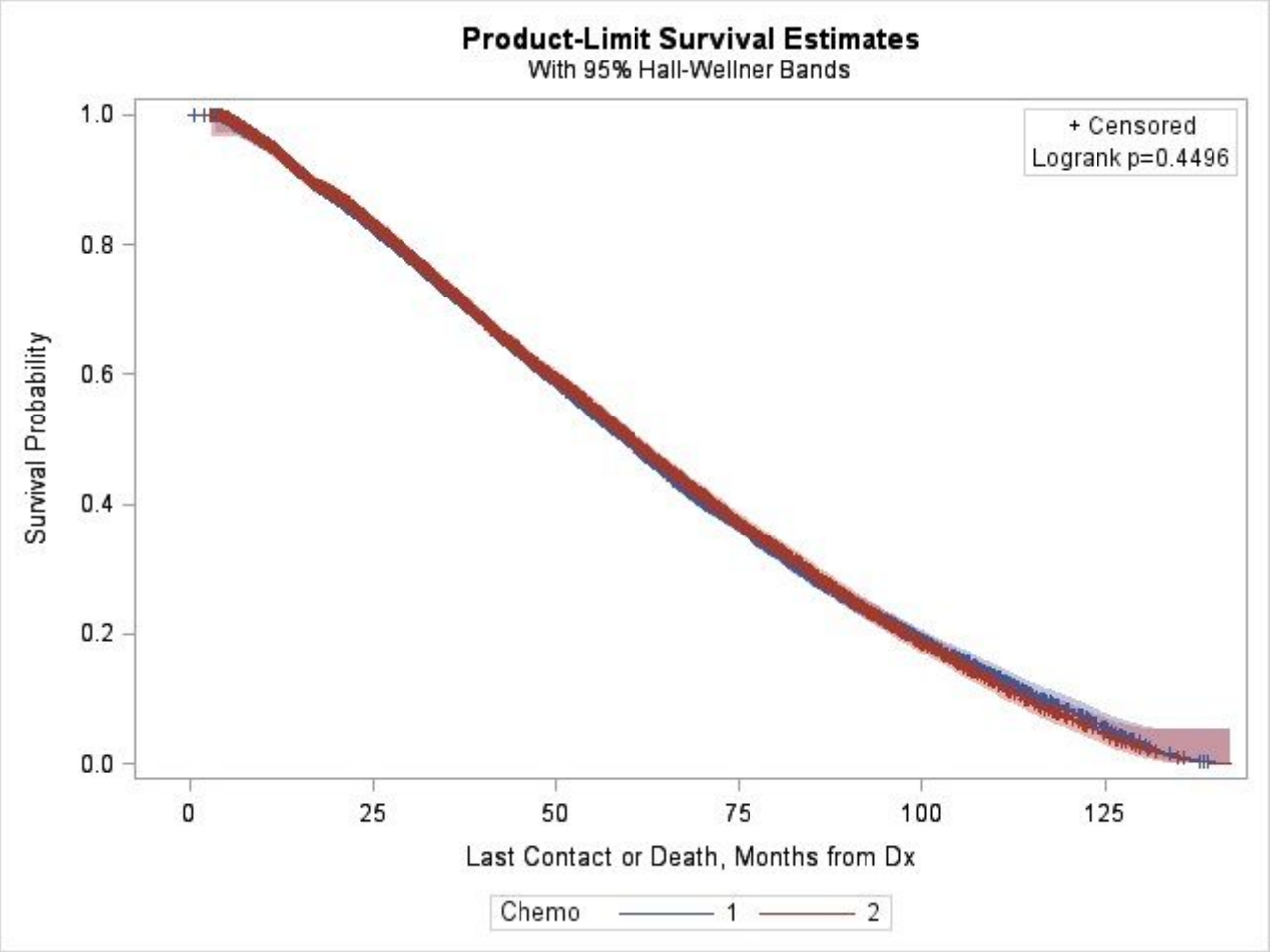

Figure 1

Kaplan Meier curves comparing overall survival between patients receiving single-agent neoadjuvant chemotherapy (blue line) and multiple-agent neoadjuvant chemotherapy for locally advanced rectal cancer