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ORIGINAL ARTICLE

Adjuvant Chemotherapy Improves Survival Following Resection of Locally Advanced Rectal Cancer with Pathologic Complete Response

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Abstract

Background Controversy exists over the use of adjuvant chemotherapy for locally advanced (stages II–III) rectal cancer (LARC) patients who demonstrate pathologic complete response (pCR) following neoadjuvant chemoradiation. We conducted a retrospective analysis to determine whether adjuvant chemotherapy imparts survival benefit among this population.

Methods The National Cancer Database (NCDB) was queried to identify LARC patients with pCR following neoadjuvant chemoradiation. The cohort was stratified by receipt of adjuvant chemotherapy. Multiple imputation and a Cox proportional hazards model were employed to estimate the effect of adjuvant chemotherapy on overall survival.

Results There were 24,418 patients identified in the NCDB with clinically staged II or III rectal cancer who received neoadjuvant chemoradiation. Of these, 5606 (23.0%) had pCR. Among patients with pCR, 1401 (25%) received adjuvant chemotherapy and 4205 (75%) did not. Patients who received adjuvant chemotherapy were slightly younger, more likely to have private insurance, and more likely to have clinically staged III disease, but did not differ significantly in comparison to patients who did not receive adjuvant chemotherapy with respect to race, sex, facility type, Charlson comorbidity score, histologic tumor grade, procedure type, length of stay, or rate of 30-day readmission following surgery. On adjusted analysis, receipt of adjuvant chemotherapy was associated with a lower risk of death at a given time compared to patients who did not receive adjuvant chemotherapy (HR 0.808; 95% CI 0.679–0.961; $p = 0.016$).

Conclusion Supporting existing NCCN guidelines, the findings from this study suggest that adjuvant chemotherapy improves survival for LARC with pCR following neoadjuvant chemoradiation.

Keywords Locally advanced rectal cancer · Pathologic complete responders · Chemoradiation · Adjuvant therapy · NCCN guidelines

Introduction

Neoadjuvant chemoradiation followed by oncologic surgical resection has emerged in the last two decades as the standard management strategy for patients presenting with locally advanced, or stage II or III, rectal cancer (LARC).[1] A number of well-designed clinical trials have established the benefit of neoadjuvant chemoradiation over other treatment strategies in this population,[2–4] and the use of this multiple modality approach has pushed 5-year overall survival rates for LARC to over 70%, whereas historically these rates ranged from 40 to 60%.[5] Prior to the widespread adoption of neoadjuvant chemotherapy, the benefit of adjuvant chemotherapy for LARC had been well established.[6] However, in the modern era of neoadjuvant chemoradiation, the benefit of subsequent

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adjuvant chemotherapy, particularly regarding survival, for LARC is uncertain and a topic of intense debate.

Up to a third of contemporary patients who undergo surgical resection of LARC ultimately develop metastatic disease.[7,8] As such, it has been posited that adjuvant chemotherapy following neoadjuvant chemoradiation and resection may further treat micrometastatic disease and thereby reduce recurrence and improve survival. Reflecting this sentiment, current National Comprehensive Cancer Network (NCCN) guidelines recommend both neoadjuvant chemoradiation and adjuvant chemotherapy for patients presenting with clinically staged II or III disease.[1] However, there is an acknowledged lack of empirical evidence to support the use adjuvant chemotherapy in this setting. A number of studies, including several randomized trials and meta-analyses of these trials, have attempted to address this issue but have collectively provided mixed and inconclusive results.[7,9–15] Consequently, adjuvant chemotherapy for LARC following neoadjuvant chemoradiation remains controversial, with guideline adherence around 60%.[16,17]

Tumor downstaging with neoadjuvant therapy further complicates the decision to administer adjuvant chemotherapy. Tumor downstaging occurs in approximately half of LARC patients, with 15–25% of patients demonstrating a pathologic complete response (pCR) with no evidence of residual cancer in the surgical specimen.[18–21] Current NCCN guidelines dictate that decisions on adjuvant chemotherapy should be based on pre-treatment staging, not surgical pathology. However, incorporating tumor response to neoadjuvant chemoradiation in the decision to administer adjuvant chemotherapy is poorly defined at present. Administration of adjuvant chemotherapy to the subset of LARC patients who demonstrate pCR is particularly controversial, and adherence to the NCCN guidelines have been reported at 32–83%.[15] While pCR is a highly favorable prognostic factor limiting the enthusiasm to administer adjuvant therapy; the 5-year recurrence free and survival rates of pCR patients have been reported to be as high as 90%.[15,21,22] In this study, we sought to address the impact of adjuvant chemotherapy on survival benefit to LARC patients with pCR by conducting an analysis from a large cohort of patients from the National Cancer Database (NCDB).

Methods

Data Source

This study conducted an analysis of de-identified data files of the NCDB and was granted an exemption from approval by the Duke University Medical Center Institutional Review Board. The NCDB is a clinical oncology database collecting information from over 1500 committee on cancer (COC) accredited hospitals.[23] It is estimated that roughly 70% of newly diagnosed cancers within the USA are captured in this database. Collected data includes patient demographics and comorbidities, treatment regimens, postoperative length of stay and readmission, and long-term overall survival.

Study Population

The 2006–2011 NCDB data files were queried to identify patients who had clinically staged II or III rectal cancer and received neoadjuvant chemoradiation. Patients who did not undergo surgical resection or who had metastasis preoperatively (clinical metastasis (M) score = 1) were excluded. To limit the cohort to those who demonstrated a complete pathological response following neoadjuvant therapy, patients with evidence of neoplasm in the resected pathological specimen (pathological tumor (T) or node (N) score ≥ 1) or who had missing pathological T and N scores were excluded. Finally, we excluded patients with missing Charlson comorbidity scores, survival data, or who died within 30 days of surgical resection. The latter exclusion was made because such patients would not have been eligible to receive adjuvant chemotherapy.

Statistical Analysis

The treatment of interest is adjuvant chemotherapy. Unadjusted comparisons between the treatment and control groups of demographics, cancer characteristics, and other treatment factors were conducted using chi-square tests for categorical variables and two-sided *t* tests or Wilcoxon Rank Sum tests for continuous variables where appropriate.

Overall survival (OS) was defined as the time from surgery to death from any cause or last contact. A Kaplan-Meier analysis was performed to estimate the unadjusted effect of adjuvant chemotherapy on OS in this population. Multiple imputation was performed with five imputations using the Markov chain Monte Carlo (MCMC) method. Cox proportional hazards model were used to estimate the treatment effect adjusting for the following a priori selected variables: age, gender, race, Charlson comorbidity score, facility type (academic medical center or not), insurance type, socioeconomic status, clinical stage of cancer, preoperative histologic tumor grade, time from diagnosis to start of neoadjuvant chemotherapy, time from diagnosis to surgery, type of surgical procedure, length of hospital stay after surgery, and whether or not the patient was readmitted within 30 days of surgery. To address differences of the impact of adjuvant chemotherapy on OS between stages II and III, a test of the interaction of stage with adjuvant chemotherapy receipt was performed. As patients who received adjuvant therapy differed in key cancer and patient characteristics from those who did not receive therapy, a propensity matched analysis was performed. All statistical analysis was performed using SAS version 9.4

(Cary, NC) and a Kaplan Meier curve generated in R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value of 0.05 was used to define statistical significance with adjustments for multiple comparisons by the Bonferroni method where appropriate.

Results

There were 24,418 patients identified with clinically staged II or III rectal cancer who received neoadjuvant chemoradiation (Fig. 1). After exclusions for evidence of neoplasm in the pathological specimen or missing pathologic T and N scores ($n = 18{,}045$), evidence of preoperative metastatic disease ($n = 247$), lack of surgical resection ($n = 510$), and death within 30 days of surgery ($n = 40$), 5606 (23.0%) patients remained in the study cohort, comprising a group of patients who demonstrated pCR to neoadjuvant therapy and who were potential candidates for adjuvant chemotherapy.

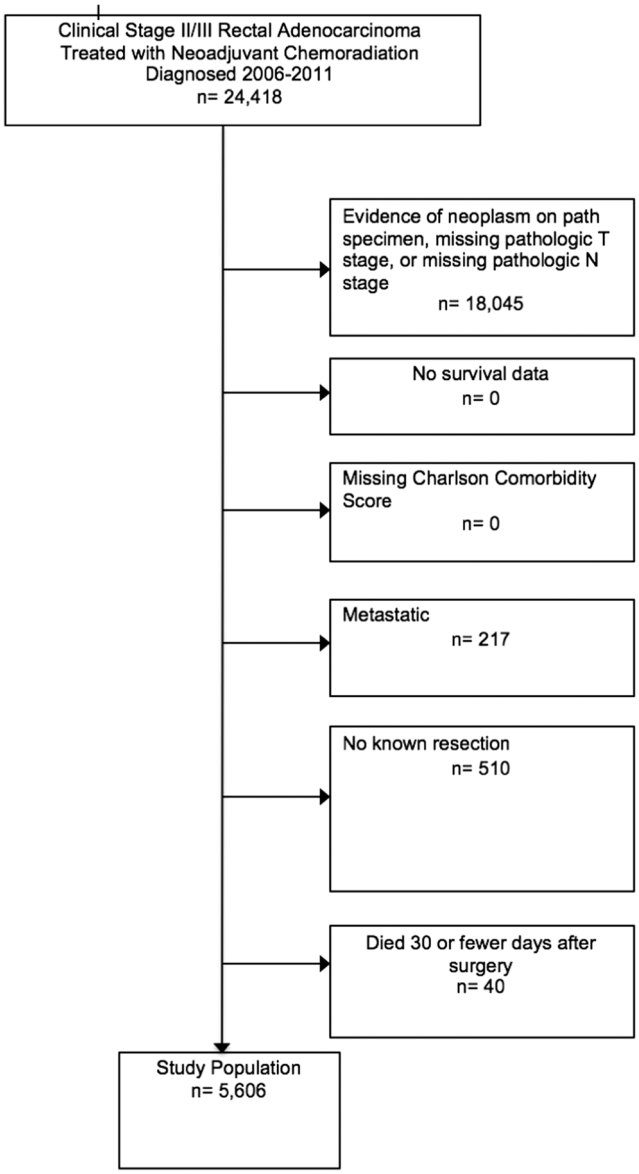

Fig. 1 Consort diagram for cohort inclusion

Among the study cohort, 1401 (25.0%) patients received adjuvant chemotherapy while the remaining 4205 (75.0%) patients did not. Patients who received adjuvant chemotherapy were slightly younger (mean age 57.5 vs. 61.4 years, $p < 0.001$), more likely to have private insurance (61.7% vs. 49.7%, $p < 0.001$) and more likely to have clinically staged III disease (53.7% vs. 47.6%, $p < 0.001$) compared to patients who did not receive adjuvant chemotherapy. The median time from diagnosis to surgery was also statistically different between groups (127 vs. 131 days, $p < 0.001$) with shorter times for the adjuvant chemotherapy patients. Race, sex, facility type, Charlson comorbidity score, preoperative histologic tumor grade, time for diagnosis to start of neoadjuvant chemotherapy, type of surgery, postoperative length of stay, and rate of 30-day readmission did not differ significantly between groups (Table 1).

Patients who received adjuvant chemotherapy had improved unadjusted overall survival compared those who did not (log-rank $p < 0.001$, Fig. 2). The five-year overall survival for patients who received adjuvant chemotherapy was *0.85* (*95% CI 0.83–0.88*); among those who did not receive adjuvant chemotherapy, the estimate was 0.77 (95% CI 0.76–0.79). There was no evidence that the relationship between adjuvant chemotherapy receipt and survival differed by clinical stage among complete responders. This was tested in the full model with the interaction term ($p = 0.54$) as well as a model that included only stage, adjuvant chemo receipt, and the interaction of the two variables ($p = 0.61$) (Fig. 3). In adjusted analysis, receipt of adjuvant chemotherapy was associated with a lower hazard of death compared to patients who did not receive adjuvant chemotherapy (HR 0.81; 95% confidence interval 0.68–0.96; $p = 0.016$).

A propensity matched analysis was performed to address the differences in stage, age, and insurance type for those who received adjuvant therapy. A large cohort of patients (75% of the total sample with complete survival data), 1379 adjuvant chemotherapy recipients, and 2726 non-recipients were included in the propensity matched cohort (Table 2). Survival curves are provided (Fig. 4). The hazard ratio (HR) for adjuvant chemotherapy vs no adjuvant chemotherapy (95% CI) is 0.81 (0.68–0.97, $p = 0.02$).

Discussion

In this study, we conducted an analysis of a large cohort of patients derived from the NCDB who had clinically staged II or III rectal cancer and demonstrated pCR following

Table 1 Baseline characteristics

Variable	*Overall* (*n* = *5606*)	*Adjuvant chemotherapy* (*n* = *1401*)	*No adjuvant chemotherapy* (*n* = *4205*)	*Adjusted p value*
Age, mean (SD)	60.4 (12.4)	57.5 (11.5)	61.4 (12.5)	< .0001
Race	87.23% White	87.65% White	87.09% White	0.1048
	7.15% Black	5.64% Black	7.66% Black	
	4.91% other	6.00% other	4.54% other	
	0.71% missing	0.71% missing	0.71% missing	
Sex	60.49% male	58.82% male	61.05% male	0.6950
	39.51% female	41.18% female	38.95% female	
Facility type	64.25% community center	64.10% community center	64.30% community center	1.0000
	35.50% Academic Medical Center	35.62% Academic Medical Center	35.46% Academic Medical Center	
	0.25% missing	0.29% missing	0.24% missing	
Charlson Comorbidity Score	81.54% 0	83.65% 0	80.83% 0	0.1048
	14.82% 1	13.85% 1	15.15% 1	
	3.64% 2	2.50% 2	4.02% 2	
Insurance Type	52.71% private	61.74% private	49.70% private	< .0001
	40.85% Medicare/Medicaid	32.69% Medicare/Medicaid	43.57% Medicare/Medicaid	
	4.00% not insured	3.35% not insured	4.21% not insured	
	1.52% missing	1.14% missing	1.64% missing	
	0.93% other government/unknown	1.07% other government/unknown	0.88% other government/unknown	
Stage	50.89% 2	46.32% 2	52.41% 2	0.0008
	49.11% 3	53.68% 3	47.59% 3	
Type of procedure	60.74% partial proctectomy	59.39% partial proctectomy	61.19% partial proctectomy	0.4403
	31.06% proctectomy	30.98% proctectomy	31.08% proctectomy	
	8.21% coloanal anastomosis	9.64% coloanal anastomosis	7.73% coloanal anastomosis	
Surgery hospital length of stay, median (SD)	6.0 (9.0)	6.0 (8.8)	6.0 (9.1)	0.1048
30-day readmission following surgery	87.96% no readmission within 30 days	87.51% no readmission within 30 days	88.11% no readmission within 30 days	1.0000
	7.40% readmission within 30 days	7.49% readmission within 30 days	7.37% readmission within 30 days	
	4.64% missing	5.00% missing	4.52% missing	
Days from Dx to surgery, median (SD)	130.0 (38.4)	127.0 (34.4)	131.0 (39.5)	< .0001
Grade	61.88% moderately differentiated, moderately well differentiated, intermediate differentiation	63.95% moderately differentiated, moderately well differentiated, intermediate differentiation	61.19% moderately differentiated, moderately well differentiated, intermediate differentiation	1.0000
	21.98% Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	20.13% Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	22.59% Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	
	8.70% poorly differentiated	8.21% poorly differentiated	8.87% poorly differentiated	
	6.90% well differentiated, differentiated, NOS	7.07% well differentiated, differentiated, NOS	6.85% well differentiated, differentiated, NOS	
	0.54% undifferentiated, anaplastic	0.64% undifferentiated, anaplastic	0.50% undifferentiated, anaplastic	
Days from Dx to first chemo date, median (SD)	33.0 (24.8)	32.0 (24.4)	33.0 (25.0)	1.0000

neoadjuvant chemoradiation to determine whether the administration of adjuvant chemotherapy improves survival among this population. Consistent with existing literature on the rate of pCR following neoadjuvant therapy,[18–21] 5606 (23%) patients from the initial 24,418 LARC patient cohort treated with neoadjuvant chemoradiation were reported to have pCR.

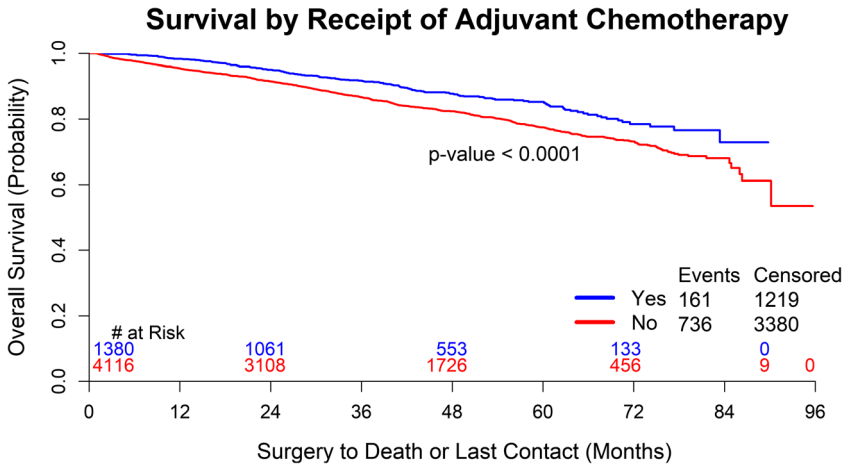

Fig. 2 Kaplan Meier curve for survival by receipt of adjuvant chemotherapy

Among these patients, a quarter ($n = 1401$) received adjuvant chemotherapy. In univariable analysis of patient characteristics, we observed that pCR patients who received adjuvant therapy were slightly younger, more likely to have private insurance, and to have clinically staged III (as opposed to clinically stage II disease) compared to those who did not. Unadjusted survival was improved among patients who received adjuvant chemotherapy as was the probability of 5-year survival. Moreover, our Cox proportional hazards model demonstrated a reduced risk of death from any cause with the receipt of adjuvant chemotherapy, even after adjustment for potential confounders.

These results support existing NCCN guidelines for administering adjuvant chemotherapy for LARC patients who demonstrate pCR following neoadjuvant chemoradiation. Contemporary use of neoadjuvant administration of chemotherapy and radiation for LARC made the benefit of adjuvant chemotherapy unclear. Retrospective analysis of the NCDB by Xu et al. primarily sought to determine current adjuvant chemotherapy guideline adherence in patients with LARC, determining poor adherence overall at 32% compared to the >80% rate reported by the NCCN datasets. Secondarily, they concluded a survival benefit exists for those who received adjuvant compared to those who did not across pathologic subtypes.[15] Additionally, a number of prospective randomized studies have attempted to address this question. The European Organization for Research and Treatment of Cancer (EORTC) trial 22,921 randomized 1011 patients into four groups: (1) neoadjuvant radiation, (2) neoadjuvant chemoradiation, (3) neoadjuvant radiation and adjuvant chemotherapy, (4) neoadjuvant chemoradiation and adjuvant chemotherapy.[4, 7] Early findings from this trial helped establish neoadjuvant chemoradiation as the standard-of-care in the management of LARC.[4] Subsequent results, published recently with a median follow-up over 10 years, have indicated that adjuvant chemotherapy, when added to neoadjuvant chemoradiation, does not

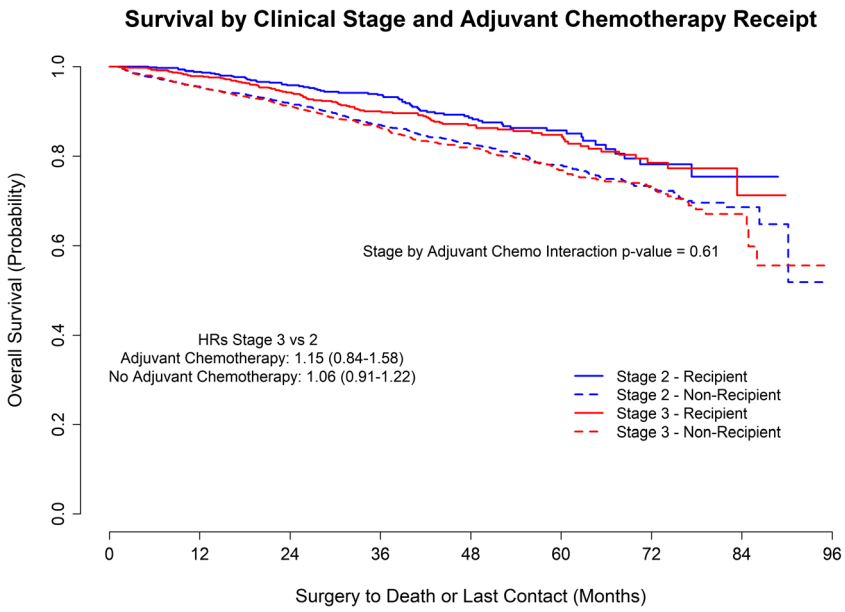

Fig. 3 Kaplan Meier curve for survival by stage and receipt of adjuvant chemotherapy. includes interaction

Table 2 Baseline characteristics after propensity matching

Variable	*Overall* (*n* = *4105*)	*Adjuvant chemotherapy* (*n* = *1379*)	*No adjuvant chemotherapy* (*n* = *2726*)	*Adjusted p value*
Age, mean(SD)	57.7 (11.6)	57.5 (11.5)	57.8 (11.6)	1.0000
Race	87.11% White	87.74% White	86.79% White	0.3533
	7.11% Black	5.73% Black	7.81% Black	
	5.09% other	5.95% other	4.66% other	
	0.68% missing	0.58% missing	0.73% missing	
Sex	60.85% male	58.81% male	61.89% male	0.6226
	39.15% female	41.19% female	38.11% female	
Facility type	64.09% community center	64.32% community center	63.98% community center	1.0000
	35.64% Academic Medical Center	35.39% Academic Medical Center	35.77% Academic Medical Center	
	0.27% missing	0.29% missing	0.26% missing	
Charlson Comorbidity Score	82.90% 0	83.47% 0	82.61% 0	1.0000
	14.01% 1	14.00% 1	14.01% 1	
	3.09% 2	2.54% 2	3.37% 2	
Insurance type	61.05% private	61.78% private	60.67% private	1.0000
	34.15% Medicare/Medicaid	32.78% Medicare/Medicaid	34.85% Medicare/Medicaid	
	3.02% not insured	3.26% not insured	2.90% not insured	
	1.78% other government/unknown	2.18% other government/unknown	1.58% other government/unknown	
Stage	53.18% 3	53.37% 3	53.08% 3	1.0000
	46.82% 2	46.63% 2	46.92% 2	
Type of procedure	61.22% partial proctectomy	59.46% partial proctectomy	62.11% partial proctectomy	1.0000
	29.79% proctectomy	30.96% proctectomy	29.20% proctectomy	
	8.99% coloanal anastomosis	9.57% coloanal anastomosis	8.69% coloanal anastomosis	
Surgery hospital length of stay, median (SD)	6.0 (8.7)	6.0 (8.9)	6.0 (8.6)	1.0000
30-day readmission following surgery	87.87% no readmission within 30 days	87.38% no readmission within 30 days	88.11% no readmission within 30 days	1.0000
	7.33% readmission within 30 days	7.61% readmission within 30 days	7.19% readmission within 30 days	
	4.80% missing	5.00% missing	4.70% missing	
Days from Dx to surgery, median (SD)	129.0(38.0)	127.0 (34.4)	130.0 (39.5)	< .0001
Grade	62.51% moderately differentiated, moderately well differentiated, intermediate differentiation	64.18% moderately differentiated, moderately well differentiated, intermediate differentiation	61.67% moderately differentiated, moderately well differentiated, intermediate differentiation	1.0000
	21.46% cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	20.01% cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	22.19% cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	
	8.67% poorly differentiated	8.27% poorly differentiated	8.88% poorly differentiated	
	6.87% well differentiated, differentiated, NOS	6.96% well differentiated, differentiated, NOS	6.82% well differentiated, differentiated, NOS	
	0.49% undifferentiated, anaplastic	0.58% undifferentiated, anaplastic	0.44% undifferentiated, anaplastic	
Days from Dx to first chemo date, median (SD)	32.0 (24.5)	32.0 (24.0)	33.0 (24.8)	1.0000

confer additional benefit with respect to recurrence-free or overall survival.[7] However, these results have not been considered definitive as only 43% of patients randomized to receive adjuvant chemotherapy completed the planned course of therapy. Two additional prospective randomized trials—the Chronicle trial ($n = 113$)[10] and the PROCTOR-SCRIPT trial ($n = 437$)[11]—also attempted to address the utility of adjuvant chemotherapy for LARC following neoadjuvant

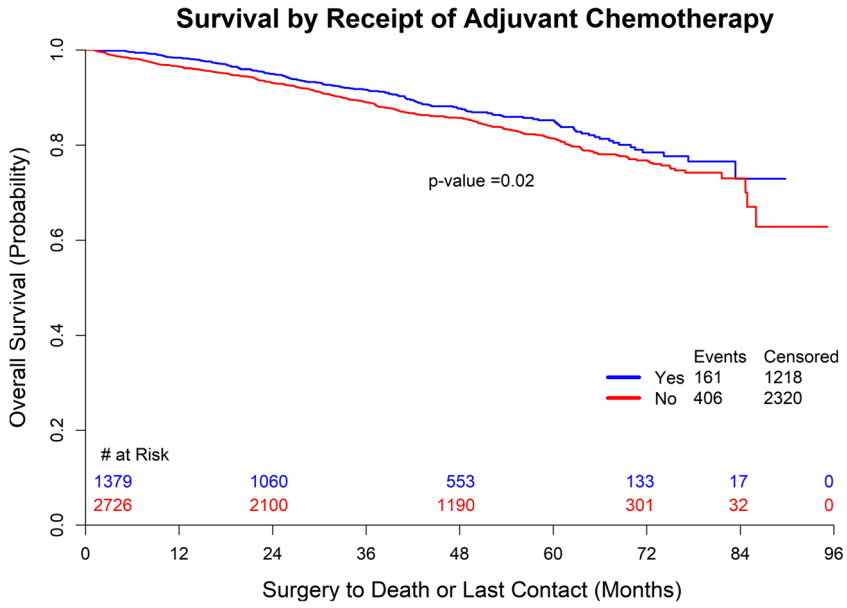

Fig. 4 Kaplan Meier curve for survival in propensity matched cohort

chemoradiation, but both were terminated prematurely for failure to accrue patients. Lastly, the Italian National Research Council conducted a randomized trial ($n = 655$) evaluating the efficacy of adjuvant chemotherapy following neoadjuvant chemoradiation and resection of LARC failing to demonstrate improvements in 5-year disease-free or overall survival.[24] Two meta-analyses of these four trials also did not demonstrate statistically significant improvement in recurrence or survival.[12, 25]

These trials and subsequent meta-analyses have been criticized for a number of reasons including being underpowered to detect small differences, and poor adherence to adjuvant chemotherapy protocols. Notably, all of these trials employed 5-fluorouracil and leucovorin (FL) adjuvant chemotherapy without oxaliplatin. The addition of oxaliplatin to FL, or FOLFOX, has established benefit when administered as an adjuvant regimen in colon cancer.[26] From extrapolation of colon cancer data, some have postulated that the addition of oxaliplatin to the adjuvant regimen for LARC may impart benefit that was not captured in prior studies. As such, two clinical trials—(ADORE)[27] and (CAO/ARO/AIO-04)[28]—have been published comparing FOLFOX vs. FL adjuvant chemotherapy following neoadjuvant chemoradiation and resection of LARC. Each trial demonstrated improved disease-free survival at 3 years and the ADORE also demonstrated improved overall survival at 3 years with the use of FOLFOX. The findings from these studies in large part underlie the current NCCN guidelines for FOLFOX as the preferred adjuvant chemotherapy regimen for LARC.[1]

Without considering adjuvant chemotherapy, current 5-year recurrence free and overall survival rates have been cited as high as 90%, resulting in lack of confidence in the benefit of additional chemotherapy.[20] This line of thinking has been bolstered by a recent analysis by Maas and colleagues of a pooled group over 3000 patients from 13 institutions. This study failed to demonstrate a 5-year survival benefit with the use of adjuvant chemotherapy in pCR patients, but did find benefit with adjuvant chemotherapy among patients who demonstrated intermediate or poor pathologic response.[14] The authors concluded that adjuvant chemotherapy may not be beneficial among the pCR and that an individualized approach, factoring in tumor response to neoadjuvant therapy, may be appropriate for decisions surrounding the use of adjuvant chemotherapy for LARC patients. It should be noted that the study by Maas and colleagues included relatively few patients with pCR, most of whom received their treatment prior to common use of adjuvant FOLFOX. Although data specifying adjuvant chemotherapy regimen is not available in the NCDB, as the cohort from the present study is composed of patients treated between 2006 and 2011, there is strong likelihood that adjuvant FOLFOX was commonly used as the adjuvant regimen in this study. Thus, it is possible that the study by Maas et al. was unable to detect a survival benefit due to the predominant use of a less effective adjuvant chemotherapy regimen.

There are numbers of important limitations to this study. As a retrospective analysis of a large national database, there is the possibility for unobserved confounding. We performed a cox proportional hazards analysis to account for a number of potentially confounding variables in our adjusted analysis. Clinical factors not captured in the NCDB may influence the decision for adjuvant chemotherapy and be linked to survival, such as whether care was received at a center of excellence, quantification of postoperative performance status, quality of circumferential resection margins, and distal resection margin. Surrogates for these variables included in adjustment are academic hospital designation, Charlson-Deyo score, readmission, and lymph-node

harvest. With regard to oncologic outcomes, we do not have information on local or distant recurrence of disease and therefore cannot comment on impact of adjuvant chemotherapy to assist in locoregional control of disease or preventing distant metastasis. We also lack the ability to censor based on cause of death. Finally, as noted, the NCDB does not contain information on specific aspects of neoadjuvant or adjuvant treatment regimens. Thus, we cannot discern what adjuvant chemotherapy was employed to provide information on what regimens may impart improved survival. Similar to other observational studies, cohorts of receiving adjuvant therapy and not-receiving adjuvant therapy are not set until the patient dies, or is censored, compared to the a priori setting of cohorts as seen in randomized control trials. Additionally, the limitations of the NCDB variables make the precise timing to the initiation of adjuvant therapy is unclear, as included variable is timing to initiation of first chemotherapy/radiation.

Despite these limitations, our analysis of over 5600 LARC patients with pCR following neoadjuvant chemoradiation demonstrated a survival advantage with the receipt of adjuvant chemotherapy. This finding therefore supports current NCCN guidelines that LARC patients with pCR should be recommended to receive adjuvant chemotherapy. Additional research is needed to verify the findings from this large retrospective study and to determine whether LARC patients without pCR may also benefit from adjuvant chemotherapy. Nevertheless, particularly since our findings also demonstrate that a substantial portion of LARC patients with pCR are not receiving adjuvant chemotherapy, we submit that this data suggest improved adherence to the NCCN guidelines for administration of adjuvant chemotherapy in the LARC population may improve outcomes in this population.

Author Contributions All authors have contributed to the ideas, design, analysis of data, interpretation and messaging, and critical revision and given final approval of the manuscript.

MCT: data acquisition, interpretation, drafting and critical revisions, final approval, accountability agreement

JEK: conception, interpretation, drafting and critical revisions, final approval, accountability agreement

CNR: data acquisition, design/conception, analysis of data, interpretation, critical revisions, final approval, accountability agreement

BCG: interpretation, drafting and critical revisions, final approval, accountability agreement

DPN: interpretation, drafting and critical revisions, final approval, accountability agreement

EB: interpretation, drafting and critical revisions, final approval, accountability agreement

TH: data acquisition, design/conception, analysis of data, interpretation, critical revisions, supervision, final approval, accountability agreement

JHS: conception, interpretation, critical revisions, supervision, final approval, accountability agreement

CRM: conception, interpretation, critical revisions, supervision, final approval, accountability agreement

JM: conception, interpretation, critical revisions, supervision, final approval, accountability agreement

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

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