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ORIGINAL ARTICLE

The Role of Adjuvant Chemotherapy in ypT0N0 Rectal Adenocarcinoma

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Abstract

Background In patients who develop a complete pathologic response (ypT0N0) following neoadjuvant chemoradiation, the benefits of postoperative chemotherapy remain uncertain. This study aims to determine whether treatment with adjuvant chemotherapy in ypT0N0 patients affects short- and long-term outcomes.

Methods From January 2000 to December 2015, 992 patients at our institution underwent surgery for rectal adenocarcinoma following treatment with neoadjuvant chemoradiation. A complete pathologic response was noted in 96 (9.7%) patients. Adjuvant chemotherapy was administered to 60 (62.5%) patients. We reviewed clinical and pathological records and compared outcomes in ypT0N0 patients who received adjuvant chemotherapy to those who did not.

Results The mean age of patients who received adjuvant chemotherapy was 55.6 ± 11.5 years, compared to 62.1 ± 11.7 years for those who did not ($p = 0.008$). Among the two groups, mean follow-up time after surgery was 5.3 ± 4.1 years for the adjuvant group and 8.3 ± 5.5 years for the non-adjuvant cohort ($p = 0.003$). The 1, 3, and 5-year survival rates were 100.0%, 97.7%, and 92.1% for patients who received adjuvant chemotherapy and 97.2%, 94.1%, and 90.7% for those who did not ($p = 0.382$). In a subanalysis of patients with available follow-up information, we observed 3/53 (5.7%) disease recurrences in patients who received adjuvant chemotherapy, compared to 2/18 (11.1%) in those who were not treated postoperatively ($p = 0.456$).

Conclusion In patients with ypT0N0 rectal adenocarcinoma, we found equivalent survival and recurrence outcomes. Further study will be necessary to determine the importance of adjuvant chemotherapy following ypT0N0 resection.

Keywords Rectal adenocarcinoma · Pathologic complete response

Introduction

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the USA. In 2018, an estimated 43,030 new cases of rectal cancer will occur in the USA (25,920 cases in men; 17,110 cases in women).[1] Patients with locally advanced low- and mid-rectal cancer (American Joint Committee on Cancer [AJCC] stage II or stage III) are treated with neoadjuvant chemoradiation (nCRT) followed by surgical resection and adjuvant chemotherapy.[2,3] Preoperative chemoradiation reduces the risk of local recurrence, decreases tumor size, and thus facilitates resection with negative margins (R0 resection).[4] The recommended nCRT regimens are based on fluorouracil (5-FU) and external beam radiation with a dose of 45 Gy.[4]

Approximately 15–25% of patients who receive nCRT will develop a complete pathologic response (ypT0N0), which is associated with improved overall and disease-free survival.[5–7] In patients who develop a complete pathologic response following nCRT, optimal therapy following surgical treatment remains unclear, and there is no consensus on whether these patients will benefit from adjuvant chemotherapy. While some clinicians advocate adjuvant chemotherapy in all patients, others may be reluctant to subject patients to further cycles of cytotoxic medications due to morbidity associated with additional chemotherapy. In this study, we aimed to investigate whether adjuvant chemotherapy provides any short- or long-term benefits to patients with ypT0N0 rectal cancers by

Synopsis In this study of 96 patients with ypT0N0 rectal adenocarcinoma, we found equivalent survival and recurrence outcomes. Further study will be necessary to determine the importance of adjuvant chemotherapy following ypT0N0 resection.

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comparing patients with pathologic complete response who received adjuvant chemotherapy to those who did not.

Methods

Study Population

This study was approved by the Institutional Review Board. A total of 1929 patients at our institution underwent surgery for rectal adenocarcinoma between January 2000 and December 2015 (Fig. 1). We excluded patients who did not receive chemoradiation prior to surgery ($n = 937$). One-hundred nineteen patients had a complete pathologic T stage response, but we excluded those who were node positive ($n = 15$) and those with distant metastases at diagnosis ($n = 6$). Thus, our study population consisted of 96 patients, of whom 60 (62.5%) received adjuvant chemotherapy and 36 (37.5%) did not. We compared baseline characteristics and early and late outcomes between ypT0N0 patients receiving adjuvant chemotherapy to those who did not.

Many patients did not receive preoperative chemoradiation at Mayo Clinic, and some may not have tolerated the full treatment regimen; this may explain the lower rate of complete pathologic response (9.7%) in the present series. It is also important to note that adjuvant chemotherapy is discussed with all patients who have a ypT0N0 resection, but decisions on postoperative treatment are made by the patient.

Data Collection

Information was retrospectively reviewed utilizing our prospectively maintained colorectal database. This dataset includes information on patient demographics, tumor characteristics, and surgical and follow-up details.

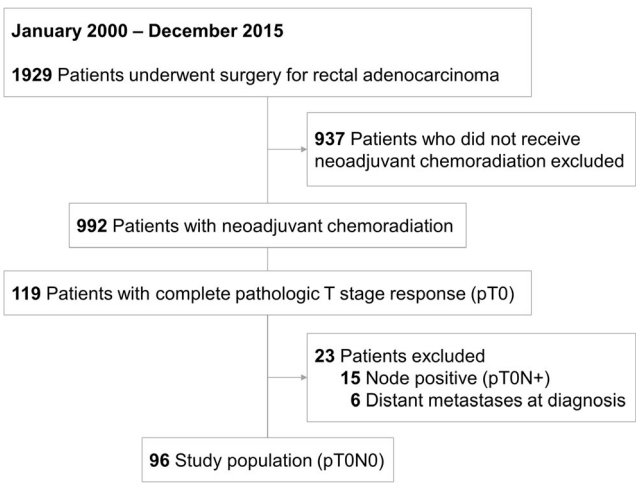

Fig. 1 Study population

Statistical Analysis

Categorical data are presented as frequencies and percentages, and continuous variables are expressed as medians and interquartile range (IQR). Comparison of pre- and postoperative measurements was conducted using chi-square and the Wilcoxon signed rank test. Analysis of survival and recurrence was carried out using the Kaplan–Meier methods, and survival differences were determined with the log-rank test. All statistical analyses were carried out using JMP Pro 13 (Cary, NC, USA).

Results

Baseline Characteristics

Ninety-six patients met the study inclusion criteria. All of these patients had a complete pathologic response (ypT0N0) on final pathology following neoadjuvant chemotherapy. Preoperatively, 53 (55.2%) patients received 5-FU, 23 (24.0%) capecitabine, and in the remaining patients, detailed information on neoadjuvant treatment was not available. Sixty-five (67.7%) patients had preoperative treatment at Mayo Clinic. Overall, the majority of patients ($n = 94$, 97.9%) were able to complete preoperative chemotherapy.

Following surgery, 60 patients (62.5%) received adjuvant chemotherapy and the remaining 36 (37.5%) did not. Those who received adjuvant chemotherapy were younger at diagnosis ($p = 0.008$) and at surgery ($p = 0.008$) (Table 1). There were no significant differences between the two groups in regard to sex or race ($p = 0.175$ and $p = 0.404$, respectively). Patients who received adjuvant chemotherapy had a lower tumor grade than those who did not ($p = 0.015$). Tumor size and preoperative AJCC stage were similar among the two groups ($p = 0.546$ and $p = 0.247$, respectively) (Table 1).

Operative Details

Following nCRT, all patients underwent surgical resection. Time from last chemoradiation treatment to surgery was 48.9 ± 14.0 days for patients who received adjuvant therapy and 48.0 ± 23.4 for those who did not ($p = 0.828$) (Table 2). Laparoscopic or robotic procedures were performed in 23 (38.3%) and nine (25.0%) ($p = 0.175$), and the remainder were performed with an open approach.

Survival and Recurrence

There were 11 mortalities in our study cohort. Detailed information on causes of death was available in five patients; in these patients, recurrence of rectal cancer was the cause of

Table 1 Baseline characteristics and histologic details

	Adjuvant chemotherapy ($n = 60$)	No adjuvant chemotherapy ($n = 36$)	p value
Age at diagnosis, year	55.6 ± 11.5	62.1 ± 11.7	0.008
Age at surgery, year	56.4 ± 11.4	63.0 ± 11.6	0.008
Male	37 (61.7%)	27 (75%)	0.175
Race			0.404
White	56 (93.3%)	33 (91.7%)	
Black	1 (1.7%)	0 (0.0%)	
Asian	0 (0.0%)	1 (2.8%)	
Other	3 (5.0%)	2 (5.6%)	
Tumor size, mm	46.6 ± 17.7	43.1 ± 23.6	0.546
Tumor grade			0.015
Undetermined (GX)	7 (11.7%)	1 (2.8%)	
Low (G1)	2 (3.3%)	0 (0.0%)	
Intermediate (G2)	33 (55.0%)	13 (36.1%)	
High, poorly differentiated (G3)	18 (30.0%)	32 (58.3%)	
High, undifferentiated (G4)	0 (0.0%)	1 (2.8%)	
AJCC stage			0.247
II	18 (30.0%)	7 (19.4%)	
III	42 (70.0%)	29 (80.6%)	
Operation			0.323
Low anterior resection	41 (68.3%)	21 (58.3%)	
Abdominoperineal resection	19 (31.7%)	15 (41.7%)	
Approach			0.175
Open	37 (61.7%)	27 (75.0%)	
Laparoscopic/robotic	23 (38.3%)	9 (25.0%)	

Table 2 Follow-up details

	Adjuvant chemotherapy ($n = 60$)	No adjuvant chemotherapy ($n = 36$)	p value
Time from last chemoradiation to surgery, d	48.9 ± 14.0	48.0 ± 23.4	0.828
Recurrence	3/53 (5.7%)	2/18 (11.1%)	0.456
Local recurrence	1 (33.3%)	2 (100.0%)	
Distal recurrence	2 (66.7%)	0 (0.0%)	
Stoma closure	38/40 (95.0%)	15/20 (75.0%)	0.028
Time to closure, day	189.0 ± 48.9	143.9 ± 61.7	0.019
Mortality	4 (6.7%)	7 (19.4%)	0.062
Follow-up time, year	5.3 ± 4.1	8.3 ± 5.5	0.003
Chemotherapy regimen		–	–
FOLFOX	43 (71.7%)		
Capecitabine	6 (10.0%)		
Other/unknown	11 (18.3%)		
Completion of chemotherapy		–	–
Completed	54 (90.0%)		
Aborted due to side effects	4 (6.7%)		
Unknown	2 (3.3%)		
No. of chemotherapy cycles	6.9 ± 2.4	–	–

death in one patient; the remaining patients died of renal failure (two patients), metastatic melanoma, and liver cirrhosis.

As seen in Fig. 2, time-to-event analysis showed similar survival in those who received adjuvant chemotherapy and those who did not ($p = 0.382$). When comparing survival in patients with preoperative stage II vs. stage III cancer, survival was also similar in both groups ($p = 0.283$) (Fig. 2). Younger patients (< 59 years old) had better survival than those who were older ($p = 0.002$).

In patients with follow-up information ($n = 71$), recurrence of cancer was seen in 3/53 (5.7%) of those who received adjuvant chemotherapy and 2/18 (11.1%) of those who did not ($p = 0.456$). There were no distant recurrences in patients who did not receive adjuvant chemotherapy. There were no recurrences in patients with stage II cancer, and all five recurrences occurred in patients with stage III cancer. As seen in Fig. 3, disease-free survival appeared to be slightly improved in patients who received adjuvant chemotherapy, and those with lower stage tumors, but not statistically significant ($p = 0.155$ and $p = 0.079$, respectively). Disease-free survival was similar in those < 59 compared to ≥ 59 years of age ($p = 0.222$).

Details on Adjuvant Chemotherapy

In our study cohort, 60 (62.5%) patients received adjuvant chemotherapy. Most patients (64.2%) received a FOLFOX regimen (Table 2). Ninety percent of patients completed adjuvant chemotherapy, with an average number of 6.9 ± 2.4 cycles. Out of the six patients who did not complete their postoperative chemotherapy regimen, four (6.7%) could not tolerate the side effects, and in two (3.3%), reasons for stopping could not be determined.

Stoma Closure

In patients with available follow-up data, temporary diverting stoma closure was achieved in 38/40 (95.0%) of those who received adjuvant chemotherapy versus only 15/20 (75.0%) of those who did not ($p = 0.028$) (Table 2). Time to stoma closure was significantly longer in patients receiving adjuvant therapy (189.0 ± 48.9 days vs. 143.9 ± 61.7 days, $p = 0.019$).

Discussion

Our study of 96 patients with rectal cancer who developed a complete pathologic response following neoadjuvant chemoradiation did not show a clear survival benefit associated with postoperative chemotherapy. Overall and disease-free survival are similar between patients with adjuvant chemotherapy and those without, and our results add to the growing evidence that adjuvant chemotherapy may not be necessary for patients who have developed a complete pathologic response following nCRT.

Patients who received adjuvant chemotherapy in our cohort were younger and more likely to have a lower tumor grade than those who did. This result is consistent with outcomes reported by Shahab and colleagues using the National Cancer Database (NCDB).[8] These authors observed 5-year overall survival rates of 94% in nCRT plus adjuvant therapy patients, compared to 84% in the nCRT-alone groups. Furthermore, other single-center studies have also reported a higher likelihood of adjuvant therapy being administered to younger patients.[9,10] This suggests that physicians may be more likely to treat younger patients aggressively using adjuvant chemotherapy. In their analysis of NCDB data, Shahab et al. also found significant sex-based differences, Charlson Comorbidity Index, clinical T stage, and elevated carcinoembryonic antigen levels prior to surgery.[8]

All patients included in the present study underwent surgical resection, and operative details did not differ among the two treatment groups. Time from the last dose of chemoradiation to surgery was approximately 7 weeks in both groups and is within the 6–8-week interval advocated at most US institutions.[4]

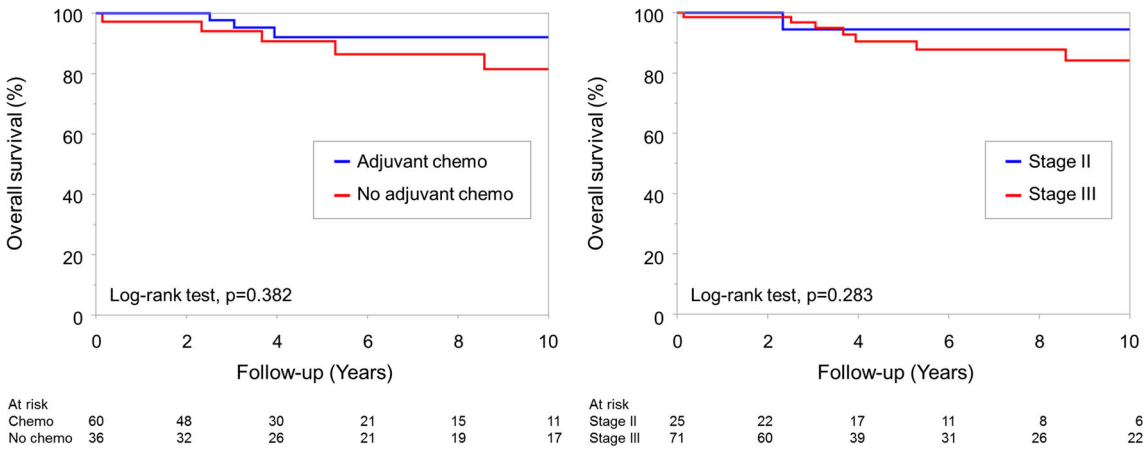

Fig. 2 Overall survival by adjuvant chemotherapy and stage

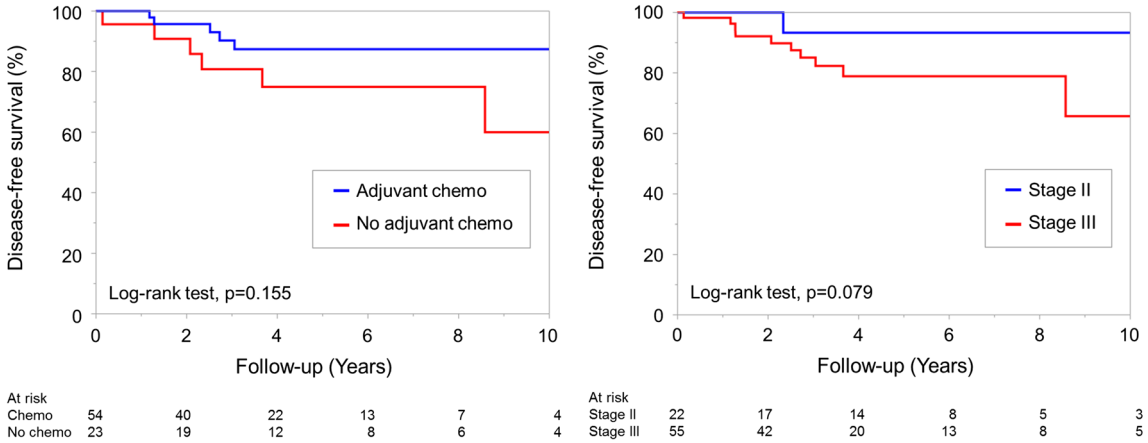

Fig. 3 Disease-free survival by adjuvant chemotherapy and stage

Following surgery, some clinicians may be reluctant to treat patients with adjuvant chemotherapy due to side effects and unknown benefits of adjuvant chemotherapy in this setting. Previous studies have suggested that completion of adjuvant chemotherapy is low, and rates of < 70% have been reported in patients with stage III colon cancer.[11] In our cohort, however, completion of adjuvant chemotherapy was achieved in 90% of patients, and less than 7% aborted adjuvant treatment due to side effects. Thus, postoperative chemotherapy was well-tolerated in our patients.

However, another emerging treatment option in patients with rectal cancer is total neoadjuvant chemotherapy (TNT),[12,13] whereby the full chemotherapy regimen is given alongside radiation prior to surgery. Clinical trials investigating the use of total neoadjuvant chemotherapy are ongoing, but initial results appear to be promising, and high complete pathologic response rates may be achievable following TNT. In a retrospective cohort analysis, Cercek and colleagues reported pathologic response rates of 36% in patients who underwent TNT, which was defined as induction 5–8 cycles of chemotherapy in the form of mFOLFOX6, CAPOX, or FLOX prior to chemoradiation.[14] If TNT becomes the standard of care, this may eliminate the decision regarding the need for adjuvant chemotherapy after a pathologic complete response.

Our survival analysis showed no significant differences between patients treated with and without adjuvant chemotherapy (Fig. 2). Disease-free survival was also similar among the two groups (Fig. 3). Most single-center experiences have reported no significant survival differences between patients receiving adjuvant chemotherapy and those who do not.[9,10,15,16] However, in contrast to these single-center studies and our findings, Shahab and colleagues observed better overall survival rates in patients who were treated with postoperative chemotherapy.[8] The authors used a large cohort identified through NCDB and likely had higher power to detect small differences in survival that could not be determined in single-center studies.

In the present study, recurrence rates were similar among the two groups. There was no distant recurrence observed in patients who did not receive postoperative treatment. However, recurrence following pathologic complete response is low,[7,17] and we only observed five recurrences in the entire cohort. The time-to-event analysis did not show any differences in disease-free survival among patients who received adjuvant chemotherapy and those who did not. Therefore, in patients with the ypT0N0 response, adjuvant chemotherapy does not appear to improve overall or disease-free survival, and thus may not be necessary for patients with a complete pathologic response.

Most patients who are treated with surgical resection for rectal carcinoma will eventually undergo reversal of a temporary stoma, although some studies suggest that risk of stoma reversal failure may be as high as 6–32%.[18] In our cohort, stoma closure was achieved in 95.0% of patients who received adjuvant chemotherapy and 75.0% of those who did not. The higher rates of stoma closure in the adjuvant therapy group are somewhat surprising, but may be confounded by other factors, such as younger age; it is possible that comorbidities due to older age and overall worse health resulted in lower stoma closure rates for patients who did not receive adjuvant chemotherapy. As expected, time to stoma reversal was delayed in patients who received adjuvant chemotherapy, and this delay in stoma closure may be an important factor affecting on quality of life in these patients.

Study Limitations

This is a retrospective study from a single institution and is prone to selection bias. Our study is also limited by the small sample size inherent to most single-center reviews, and these results may not be replicable in other centers. Follow-up information was not available on all patients, impacting analysis on recurrence and survival.

Conclusions

In this study of patients who had a complete pathological response following nCRT, overall and disease-free survival were similar among patients who received adjuvant chemotherapy versus those who did not. Further prospective studies should focus on potential survival benefits and impact on quality of life associated with adjuvant chemotherapy.

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