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ORIGINAL REPORT

Postoperative Adjuvant Chemotherapy Use in Patients With Stage II/III Rectal Cancer Treated With Neoadjuvant Therapy: A National Comprehensive Cancer Network Analysis

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ABSTRACT

Purpose
Practice guidelines recommend that patients who receive neoadjuvant chemotherapy and radiation for locally advanced rectal cancer complete postoperative adjuvant systemic chemotherapy, irrespective of tumor downstaging.

Patients and Methods
The National Comprehensive Cancer Network (NCCN) Colorectal Cancer Database tracks longitudinal care for patients treated at eight specialty cancer centers across the United States and was used to evaluate how frequently patients with rectal cancer who were treated with neoadjuvant chemotherapy also received postoperative systemic chemotherapy. Patient and tumor characteristics were examined in a multivariable logistic regression model.

Results
Between September 2005 and December 2010, 2,073 patients with stage II/III rectal cancer were enrolled in the database. Of these, 1,193 patients receiving neoadjuvant chemoradiotherapy were in the analysis, including 203 patients not receiving any adjuvant chemotherapy. For those seen by a medical oncologist, the most frequent reason chemotherapy was not recommended was comorbid illness (25 of 50, 50%); the most frequent reason chemotherapy was not received even though it was recommended or discussed was patient refusal (54 of 74, 73%). After controlling for NCCN Cancer Center and clinical TNM stage in a multivariable logistic model, factors significantly associated with not receiving adjuvant chemotherapy were age, Eastern Cooperative Oncology Group performance status ≥ 1, on Medicaid or indigent compared with private insurance, complete pathologic response, presence of re-operation/wound infection, and no closure of ileostomy/colostomy.

Conclusion
Even at specialty cancer centers, a sizeable minority of patients with rectal cancer treated with curative-intent neoadjuvant chemoradiotherapy do not complete postoperative chemotherapy. Strategies to facilitate the ability to complete this third and final component of curative intent treatment are necessary.

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INTRODUCTION

In 2009, an estimated 40,870 new cases of rectal cancer were diagnosed in the United States.[1] Treatment strategies for patients with stage II/III rectal cancer have evolved over the past two decades to include neoadjuvant chemoradiotherapy followed by surgery and postoperative adjuvant chemotherapy. There are limited data to define an optimal adjuvant chemotherapy regimen, although select reports have suggested a trend toward improved disease-free survival and overall survival with fluorouracil-based adjuvant chemotherapy.[2-6]

Practically, however, this therapeutic approach can be challenging. After 6 weeks of arduous combined modality treatment and then a major operation, there are some patients who are reluctant to proceed to complete the final phase of treatment (ie, systemic adjuvant chemotherapy). Patients and physicians may be reluctant to proceed to complete therapy when tolerance of neoadjuvant treatment was poor, when there were surgical complications, or, alternatively, when surgical pathology has already demonstrated a dramatic response to the neoadjuvant therapy.[7-13] For example, approximately 20% of patients have a

complete pathologic response to induction neoadjuvant chemoradiotherapy.[7,14-17] In this situation, patients and physicians may forego further systemic therapy.

The National Comprehensive Cancer Network (NCCN) Colorectal Cancer Outcomes (CRC) Database project was initiated in 2005 to evaluate the outcomes of cancer care, practice patterns, and adherence to evidence-based guidelines as a continuum in collaboration among eight of the 21 NCCN cancer centers. A recent analysis evaluating concordance with NCCN CRC Guidelines and the American Society of Clinical Oncology quality measures demonstrated relatively low mean concordance rates (81%) for adjuvant chemotherapy in patients with clinical stage II/III rectal cancer within 9 months of diagnosis.[18] This article reports an analysis of multiple variables from the NCCN CRC database to determine the significant factors that would predict the omission of adjuvant therapy after standard neoadjuvant chemoradiotherapy and surgery.

PATIENTS AND METHODS

Study Cohort

Patients with locally advanced rectal cancer presenting to the eight participating NCCN institutions between September 1, 2005, and December 31, 2010, were selected. Participating institutions included City of Hope Comprehensive Cancer Center, Dana-Farber Cancer Institute, Fox Chase Cancer Center, Memorial Sloan-Kettering Cancer Center, The Ohio State University Comprehensive Cancer Center Arthur G. James Cancer Hospital and Solove Research Institute, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Roswell Park Cancer Institute, and The University of Texas MD Anderson Cancer Center.

Data Collection

Data were abstracted from the medical records of eligible patients with rectal cancer longitudinally from the time of diagnosis. Eligibility criteria included patients ≥ 18 years old with a clinical diagnosis of locally advanced rectal cancer as per the American Joint Committee on Cancer (seventh edition) who received adjuvant chemotherapy within 9 months of diagnosis as well as those who did not. Patients were excluded if they had single or multiple diagnoses of colon cancer, stage I and IV rectal cancer, recurrent disease, incomplete study accession, only a baseline assessment available without further follow-up, lack of final staging, less than 9 months of follow-up, or lack of documentation of administration of neoadjuvant therapy and/or surgery.

Medical records were systematically reviewed at 4, 8, and 12 months and then yearly to document treatment and recurrence information. Baseline patient information included sociodemographic characteristics, insurance status, comorbidities (using Charlson index[19]), performance status, and household income. At the 4-month assessment, data were entered for clinical and pathologic TNM staging, histology, tumor location, distance from the anal verge, number of lymph nodes examined, number of lymph nodes involved with tumor, grade at diagnosis and primary surgery, presence/absence of lymphovascular invasion, perineural invasion, margin involvement (proximal, distal, radial), carcinoembryonic antigen level before and after surgery, and surgical procedures.

All cancer-directed treatments were collected during the follow-up assessments, including documented treatments delivered both at NCCN and outside institutions. The reasons for not receiving adjuvant chemotherapy were recorded, when available. Quality assurance included initial and follow-up training for the study personnel, online edit checking during web-based data entry, programmed logic checks against the pooled data repository, routine quality assurance reports to each institution, and onsite audits of a random sample of source documents against submitted data within the first few months of data collection (repeated annually).[18] Informed consent or waiver of consent was approved by each center's institutional review board.

Statistical Analysis

Baseline characteristics were summarized as descriptive statistics (median and range for continuous variables, number and percentage for categorical variables), stratified by adjuvant versus no adjuvant therapy. Guideline concordance was defined as receipt of adjuvant chemotherapy within 9 months of diagnosis. The association between receipt of guideline-concordant adjuvant therapy and each parameter was assessed independently in a univariate logistic regression model. An independent variable was created for whether a patient had a complete response, was upstaged or downstaged, or had no change in stage; 63 patients (5%) were excluded from the logistic regression model because they were "unable to stage." Pathologic TNM was excluded from the multivariable model because of its colinearity with the clinical to pathologic downstaging variable, as was "lymph nodes positive," which correlated with the pathologic TNM stage. Parameters found to be potentially associated with adjuvant therapy ($P < .20$) were included in the multivariable model, along with variables known to be associated with adjuvant therapy, clinical TNM stage and NCCN cancer center, as defined a priori. The final multivariable model included those predictors with a two-sided P value less than .05, along with the control variables defined a priori. Odds ratios (ORs) and associated 95% CIs were reported. To determine the reasons for not receiving adjuvant chemotherapy in accordance with American Society of Clinical Oncology/NCCN quality measures, the proportions of the patients who did not receive adjuvant therapy were calculated by reasons related to the patient (eg, patient declined treatment), physician (eg, physician recommended against treatment), and system level (eg, delayed treatment).

RESULTS

Description of the Study Cohort

The charts of 8,366 patients with colorectal cancer, enrolled in the NCCN CRC Database at the eight NCCN institutions from September 1, 2005, through December 31, 2010, were reviewed (Fig 1). There were 2,073 patients with locally advanced rectal cancer, and of these, 1,647 patients had a minimum of 9 months of follow-up and primary

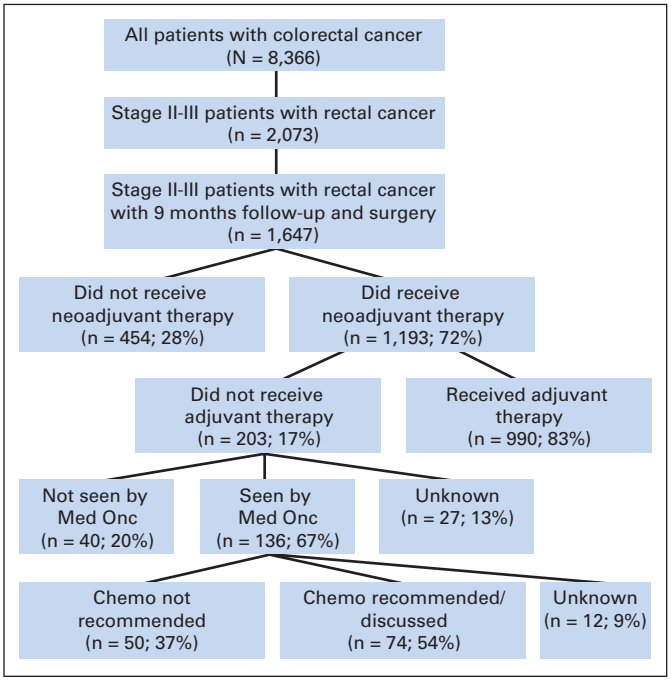

Fig 1. CONSORT diagram of patients with clinical stage II/III rectal cancer and administration of adjuvant chemotherapy. Chemo, chemotherapy; Med Onc, medical oncologist.

surgery. Neoadjuvant therapy was administered to 1,193 patients, of whom 203 patients (17%) did not receive adjuvant chemotherapy.

Table 1 describes the clinical and socioeconomic characteristics of the 1,193 patients who received neoadjuvant chemotherapy and radiation stratified by outcome.

Univariate Analyses

Table 2 summarizes the association with adjuvant therapy for available clinical and socioeconomic variables. It includes only the variables that were significantly associated with administration of adjuvant therapy from the univariate logistic regression and remained significant in the multivariable logistic regression model ($P < .05$).

Multivariable Analyses

Table 2 also summarizes the multivariable association with adjuvant therapy, with the following factors found to be statistically significant: age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), NCCN cancer center, insurance, clinical to pathologic downstaging, re-operation of a wound infection, and closure of an ileostomy/colostomy. Clinical TNM stage was not significant in the multivariable model, but was forced in the final model as a control variable.

Patients $\geq$ 50 years of age ($v <$ 50 years) at diagnosis were less likely to receive adjuvant chemotherapy: age 50 to 64 years (adjusted OR = 0.55, 95% CI, 0.32 to 0.94), age 65 to 74 years (adjusted OR = 0.22, 95% CI, 0.10 to 0.47), age $\geq$ 75 years (adjusted OR = 0.04, 95% CI, 0.02 to 0.10). Those with ECOG PS $\geq$ 1 (v ECOG PS = 0) were less likely to receive adjuvant chemotherapy (adjusted OR = 0.40, 95% CI, 0.24 to 0.68). Patients at Center A (OR = 0.35, 95% CI, 0.17 to 0.73) and Center F (OR = 0.27, 95% CI, 0.15 to 0.48) were less likely to receive adjuvant chemotherapy than patients at Center G, which was chosen as the referent group because it had the largest number of patients. Compared with private insurance, Medicaid and indigent patients were less likely to receive adjuvant chemotherapy (adjusted OR = 0.35, 95% CI, 0.19 to 0.67). Patients with a complete response were less likely to receive adjuvant chemotherapy (adjusted OR = 0.62, 95% CI, 0.37 to 0.99) compared with those with no change in cTNM to pTNM. Patients who had a re-operation of a wound infection were less likely to receive adjuvant chemotherapy (adjusted OR = 0.25, 95% CI, 0.13 to 0.48) compared with those who had no re-operation, as were patients without closure of an ileostomy/colostomy (adjusted OR = 0.60, 95% CI, 0.40 to 0.89) compared with those with closure.

Among the 203 patients who did not receive adjuvant chemotherapy, 67% were seen by a medical oncologist postoperatively, 20% were not seen by a medical oncologist, and for 13%, it was unknown whether they were seen by a medical oncologist (Fig 1). Within the patient cohort seen by a medical oncologist (n = 136), 54% had a discussion with their physician regarding further recommendations about adjuvant chemotherapy, 37% had documentation that adjuvant chemotherapy was not recommended, and 9% had no chart documentation regarding whether or not treatment was recommended. For these patients, reasons cited for not receiving adjuvant therapy recommendation included presence of comorbid illnesses alone (n = 22), therapy not indicated (n = 20), comorbid illnesses/older age (n = 3), disease recurrence (n = 2), death (n = 1), and unknown reasons (n = 2). The reasons chemotherapy was not administered despite physician recommendations included patients declined treatment (n = 54), recurrence before treatment administration (n = 8), no treatment documented at 12-month assessment (n = 3), patient death (n = 2), patient transferred to other center (n = 2), and reason unknown (n = 5). The database does not include the specific reasons why patients declined treatment. Table 3 summarizes the 990 patients who started adjuvant chemotherapy and the frequency and the reason the adjuvant therapy was discontinued (n = 290, 29%).

DISCUSSION

Although decreased local recurrence rates for patients with stage II/III rectal cancer have been achieved with the use of combination chemotherapy and radiation therapy, 35% of patients nevertheless develop metastatic disease.[2,20] Current NCCN CRC Guidelines recommend completion of a 6-month course of adjuvant chemotherapy for patients with stage II/III rectal cancer; however, the rate of administration of adjuvant chemotherapy at NCCN institutions has been variable.[18,21] The goals of the current study were both to evaluate the reasons why adjuvant chemotherapy is not delivered and explore the relationship between patient characteristics and administration of adjuvant chemotherapy.

Our analysis found that the most common reasons adjuvant chemotherapy was not recommended by a medical oncologist was secondary to comorbid illness (25 of 50, 50%) and recommended but not received was patient refusal (54 of 74, 73%). Similar findings have been noted in other colorectal cancer studies in which decreased administration of adjuvant chemotherapy was due to patient refusal, presence of comorbid conditions, and lack of clinical indication by the physician.[8-10] A population-based cohort of patients with both stage II/III rectal cancer and stage III colon cancer from the California Cancer Registry demonstrated that the principal reasons for not receiving adjuvant chemotherapy differed by patient age.[9] Among patients $\geq$ 85 years of age, comorbidities and advanced age were cited as primary reasons. For those offered postoperative therapy, age remained the strongest predictor of patient refusal, with lower rates for younger patients and reaching almost 50% in the group $\geq$ 85 years of age. Despite the increasing number of people older than 75 years, the use of colorectal cancer adjuvant therapy in this age group is declining[11,12] and is an underrepresented population in clinical trials.[13] Some have noted worse outcomes in an aged population with comorbid conditions.[22-25] Other studies have demonstrated that elderly individuals with a good performance status tolerate chemotherapy just as well as the younger population,[26,27] with no significant interactions between age and treatment efficacy.[27-29]

In contrast to the NCCN study in which 83% of patients received recommended adjuvant therapy, a cross-sectional study from the Veteran's Medical Center in Houston found that only 42.5% of patients with stage II/III rectal cancer received recommended therapy (defined as pre- or postoperative radiation therapy, surgical resection, and postoperative chemotherapy).[8] Among 57.5% of the eligible patients who did not receive recommended therapy, 36% had comorbidities, 18% were believed not to require therapy by the physicians, 31% died before follow-up or had postoperative complications, and 15% declined therapy despite physician recommendations.

Table 1. Characteristics of Patients With Clinical Stage II/III and Locally Advanced Rectal Cancer and Received Neoadjuvant Therapy

Characteristic	Adjuvant Therapy: Yes (n = 990) No.	Yes (n = 990) %	Adjuvant Therapy: No (n = 203) No.	No (n = 203) %	All Patients (N = 1,193) No.	All Patients (N = 1,193) %
Age at diagnosis, years						
Median	55		65		57	
Range	22-93		21-89		21-93	
< 50	300	30	29	14	329	27
50-64	451	46	69	34	520	44
65-74	197	20	53	26	250	21
75+	42	4	52	26	94	8
Sex						
Male	602	61	114	56	716	60
Female	388	39	89	44	477	40
Racial/ethnic background						
White Non-Hispanic	789	80	166	82	955	80
African American Non-Hispanic	57	6	14	7	71	6
Asian Non-Hispanic	63	6	4	2	67	6
Other Non-Hispanic	7	< 1	1	< 1	8	< 1
Hispanic	71	7	17	8	88	7
Unknown	3	< 1	1	< 1	4	< 1
Charlson comorbidity index						
0	760	77	123	61	883	74
1	154	15	50	25	204	17
2	55	6	16	8	71	6
3+	21	2	14	7	35	3
ECOG performance status						
0	843	85	141	69	984	82
1	71	7	34	17	105	9
2+	15	2	7	3	22	2
Unknown	61	6	21	10	82	7
Center						
A	45	5	17	8	62	5
B	85	9	12	6	97	8
C	48	5	9	4	57	5
D	298	30	30	15	328	27
E	43	4	17	8	60	5
F	69	7	50	25	119	10
G	338	34	56	28	394	33
H	64	6	12	6	76	6
Insurance						
Private	652	66	74	36	726	61
Medicare	236	24	92	45	328	27
Medicaid/Indigent	59	6	27	13	86	7
Other	31	3	5	2	36	3
Unknown	12	1	5	2	17	1
Household income						
< 40K	355	36	84	41	439	37
40 to < 60K	304	31	63	31	367	31
60 to < 80K	187	19	30	15	217	18
≥ 80K	102	10	16	8	118	10
Unknown	42	4	10	5	52	4
Primary site						
Rectosigmoid junction*	72	7	12	6	84	7
Rectum, NOS	918	93	191	94	1109	93
Clinical TNM stage						
Locally advanced†	37	4	11	5	48	4
II	290	29	76	37	366	31
III	663	67	116	57	779	65
Pathologic TNM stage						
Locally advanced‡	12	1	8	4	20	2
0	190	19	51	25	241	20
I	254	26	52	26	306	26
II	232	23	47	23	279	23
III	302	31	45	22	347	29

(continued on following page)

Table 1. Characteristics of Patients With Clinical Stage II/III and Locally Advanced Rectal Cancer and Received Neoadjuvant Therapy (continued)

Characteristic	Adjuvant Therapy: Yes (n = 990) No.	%	Adjuvant Therapy: No (n = 203) No.	%	All Patients (N = 1,193) No.	%
Clinical to pathologic stage: Was patient downstaged/upstaged?‡						
Complete responders (stage 0)	190	19	51	25	241	20
Downstaged (from stage II to I or from stage III to II)	211	21	56	28	267	22
Downstaged (from stage III to I)	175	18	21	10	196	16
Upstaged (from stage II to III)	64	6	7	3	71	6
No change in stage	303	31	52	26	355	30
Grade at diagnosis						
1	44	4	15	7	59	5
2	745	75	142	70	887	74
3	71	7	9	5	80	7
Unknown	110	11	34	17	144	12
NA	20	2	3	1	23	1
Lymphovascular invasion at primary surgery						
No	642	65	119	59	761	64
Yes	140	14	28	14	168	14
Unknown	130	13	27	13	157	13
NA	78	8	29	14	107	9
Perineural invasion at primary surgery						
No	518	52	109	54	627	53
Yes	107	11	18	9	125	10
Unknown	286	29	46	23	331	28
NA	80	8	30	15	110	9
Any margins (proximal, distal or radial)						
Negative	714	72	125	62	839	70
Positive/close	69	7	21	10	90	8
NA	207	21	57	28	264	22
Distance of tumor from anal verge, cm						
< 6	356	36	87	43	443	37
6-8	304	31	42	21	346	29
>8	275	28	56	28	331	28
Unknown	55	5	18	8	73	6
CEA after surgery for patients with abnormal CEA at baseline§						
Normal	167	17	31	15	198	17
Abnormal	32	3	10	5	42	4
No CEA test after surgery	24	2	15	7	39	3
NA	767	77	147	72	914	76
Surgical procedure						
LAR	670	68	116	57	786	66
APR	209	21	65	32	274	23
Total proctocolectomy	24	2	8	4	32	3
Total pelvic exenteration	9	1	3	1	12	1
Partial pelvic exenteration	2	< 1	1	< 1	3	< 1
Proctectomy	61	6	3	1	64	5
Surgical complications						
Anastomosis leak/peritonitis	4	< 1	6	3	10	< 1
Postoperative bleeding	1	< 1	0	0	1	< 1
Re-operation bowel obstruction	3	< 3	0	0	3	< 1
Re-operation wound infection	35	4	24	12	59	5
Other surgical procedures‖						
Ileostomy	32	3	9	4	41	3
Colostomy	59	6	20	10	79	7
Closure of ileostomy/colostomy	587	59	76	37	663	56
Endoscopic stenting	9	1	6	3	15	1
Surgical drainage of abscess	9	1	6	3	15	1

NOTE. Patients presented to NCCN institutions between September 2005 and December 2010 and received neoadjuvant chemotherapy and pelvic radiation.

Abbreviations: APR, abdominoperineal resection; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; LAR, low anterior resection; NA, not applicable; NOS, not otherwise specified.

*Seventy-six (90%) treated as rectal, four (5%) treated as colon, four treated as indeterminate.

†Locally advanced means no evidence of metastatic disease, but staging was not available. Patients who were not able to be staged clinically and pathologically were not included in this study.

‡Sixty-three of the patients were excluded from the downstaged/upstaged analyses, as these patients either had clinical TNM stage or a pathologic TNM stage of locally advanced, but stage of disease not further specified.

§Baseline was defined as a CEA test before neoadjuvant therapy. NA (not applicable) represents patients who did not have abnormal CEA at baseline (n = 913 with normal CEA at baseline; n = 1 unknown if CEA test was done).

‖Represents procedures that were performed after the primary rectal surgery.

Table 2. Factors Associated With Receiving Adjuvant Therapy for Patients With Stage II/III and Locally Advanced Rectal Cancer

Variable	Patients With Adjuvant Therapy		Unadjusted OR*	95% CI	P*	Adjusted OR†	95% CI	P†
	No.	%						
Age at diagnosis, years								
< 50	300	91	Referent		< .001	Referent		< .001
50-64	451	87	0.63	0.40 to 0.99		0.55	0.32 to 0.94	
65-74	197	79	0.36	0.22 to 0.59		0.22	0.10 to 0.47	
75+	42	45	0.08	0.05 to 0.14		0.04	0.02 to 0.10	
ECOG performance status								
0	843	86	Referent		< .001	Referent		.002
1+	86	68	0.35	0.23 to 0.53		0.40	0.24 to 0.68	
Unknown	61	74	0.49	0.29 to 0.82		0.59	0.29 to 1.16	
Center								
A	45	73	0.44	0.24 to 0.82	< .001	0.35	0.17 to 0.73	< .001
B	85	88	1.17	0.60 to 2.29		1.35	0.61 to 2.98	
C	48	84	0.88	0.41 to 1.90		2.19	0.79 to 6.06	
D	298	91	1.65	1.03 to 2.63		1.38	0.81 to 2.36	
E	43	72	0.42	0.22 to 0.79		0.65	0.30 to 1.41	
F	69	58	0.23	0.14 to 0.36		0.27	0.15 to 0.48	
G	338	86	Referent			Referent		
H	64	84	0.88	0.45 to 1.74		0.86	0.39 to 1.89	
Insurance								
Private	652	90	Referent		< .001	Referent		.009
Medicare	236	72	0.29	0.21 to 0.41		1.42	0.72 to 2.80	
Medicaid/indigent	59	69	0.25	0.15 to 0.42		0.35	0.19 to 0.67	
Other	31	86	0.70	0.27 to 1.87		0.74	0.26 to 2.14	
Unknown	12	71	0.27	0.09 to 0.80		0.90	0.24 to 3.43	
Clinical TNM stage								
Locally advanced	37	77	0.59	0.29 to 1.19	.03	0.30	0.04 to 2.45	.26
II	290	79	0.67	0.49 to 0.92		0.77	0.51 to 1.14	
III	663	85	Referent			Referent		
Clinical to pathologic TNM stage: was the patient downstaged or upstaged?‡								
Complete responders§	190	79	0.64	0.42 to 0.98	.08	0.62	0.37 to 0.99	.03
Downstaged	386	83	0.86	0.59 to 1.26		0.84	0.54 to 1.31	
Upstaged	64	90	1.57	0.68 to 3.61		2.54	0.95 to 6.80	
No Change in stage	303	31	Referent			Referent		
Re-operation wound infection								
No	955	84	Referent		< .001	Referent		< .001
Yes	35	59	0.27	0.16 to 0.47		0.25	0.13 to 0.48	
Closure of ileostomy/colostomy								
No	403	76	0.41	0.30 to 0.56	< .001	0.60	0.40 to 0.89	.01
Yes	587	89	Referent			Referent		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; OR, odds ratio.

*Unadjusted OR = univariate logistic regression.

†Adjusted OR = multivariable logistic regression. The final multivariable logistic regression model has the following factors: age at diagnosis, ECOG performance status, center, insurance, clinical TNM stage, downstaged/upstaged, re-operation of wound infection, and closure of ileostomy/colostomy. Factors that were not significant in the univariate and/or multivariable model were not reported (sex, race/ethnic background, income, histology, grade, Charlson comorbidity score, pathologic TNM stage, lymphovascular invasion, perineural invasion, margin status, distance from and verge, carcinoembryonic antigen, lower anterior resection, abdominoperineal resection, proctectomy, and colostomy).

‡Sixty-three of the patients were excluded from the downstaged/upstaged analyses, as these patients either had clinical TNM stage or a pathologic TNM stage of locally advanced, but stage of disease not further specified.

§Complete responders are patients with pathologic TNM stage 0.

Physicians are concerned with increased therapy-induced toxicity rates and inferior survival for those with comorbidities.[30] A retrospective review of the medical records from the National Institute on Aging, National Cancer Institute, and National Cancer Institute Surveillance, Epidemiology, and End Results tumor registry documented preexisting conditions in the elderly with colon cancer and evaluated the effects of comorbidity on early mortality, stratified by various degrees of Life Threat Risk (High Impact, Moderate, Low, and Negligible).[25] Early mortality was significantly associated with higher stage of disease and the total number of comorbid and chronic conditions in the High Impact Life Threat category. Although this correlation is important, the patients in the NCCN study were well enough to receive neoadjuvant chemoradiotherapy and surgery and had an ECOG PS of 0 or 1 (82% and 9%, respectively). Tolerance of previous

Table 3. Reasons Adjuvant Chemotherapy Ended

Reason	No. of Patients	%
Completed adjuvant treatment	700	70.71
Toxicity	160	16.16
Patient/family preference	40	4.04
Unknown reason	39	3.94
Reason not entered	29	2.93
Other reason	8	0.81
Cancer progression	8	0.81
Patient died	3	0.30
Insurance issues	2	0.20
Transferred care	1	0.10

preoperative therapy and surgery questions the role of comorbidity and failure to treat with adjuvant chemotherapy.

Of those patients who did not receive adjuvant therapy, it was unknown whether 27 patients (13%) were seen by a medical oncologist. Of those seen by a medical oncologist, 12 patients (9%) did not have documentation regarding whether chemotherapy was or was not recommended. Several studies attribute missing data because of lack of available information, data entry errors, and working under time pressure paired with low physician job satisfaction.[31-34] Difficulty with documentation in the NCCN study may be related to the variability in the numbers of patients who receive all medical care at the same institution. The current NCCN database only contains therapy that occurs outside the NCCN institution if the information is noted in the NCCN chart, thus limiting an accurate assessment of whether postoperative treatment was given or not.

Various studies have assessed the association between cancer care and insurance, but few have investigated this relationship in colorectal cancer. Limited reports have shown that medical practices and patient outcomes were not affected by an insurance plan, although patients with low incomes fared worse when enrolled in a health maintenance organization (HMO) compared with a fee-for-service (FFS) plan.[35-37] In the colorectal cancer population, there was no difference in the rates of definitive surgery, chemotherapy, and radiation therapy as well as survival in patients with HMO plans versus FFS plans.[38,39] In contrast, Roetzheim et al[40] found that colorectal cancer treatments in the state of Florida varied considerably based on the insurance coverage, including those with commercial HMO, who were less likely to receive chemotherapy and had greater mortality than those with FFS insurance. Our data showed that patients with Medicaid and indigent patients are less likely to receive adjuvant chemotherapy.

Clinical to pathologic downstaging after neoadjuvant chemoradiotherapy was associated with decreased administration of adjuvant chemotherapy. Although the addition of chemotherapy to radiation has demonstrated improved locoregional control and increased likelihood of pathologic complete response, this benefit has not been translated to improved overall survival.[2,20,41,42] In contrast, a subgroup analysis from the European Organisation for Research and Treatment of Cancer 22921 study has shown that patients downstaged to ypT0-2 disease benefited from adjuvant chemotherapy, whereas those with residual ypT3-4 disease did not.[4-6] Other retrospective reviews also have shown that patients who respond to neoadjuvant therapy are the most likely to achieve enhanced efficacy from adjuvant chemotherapy.[5,6] Currently, there are no data from prospective randomized clinical trials to define the optimal use of postoperative chemotherapy, including the degree of improved outcome for those with tumor downstaging or a pCR after neoadjuvant treatment.[3-6,43-50] Although not definitive, the data demonstrating the correlation between neoadjuvant therapy response and benefit from adjuvant chemotherapy warrants routine postoperative discussion among the surgeon, medical oncologist, and patient.

Re-operation, wound infection, and lack of closure of ileostomy/colostomy sites were also associated with decreased administration of adjuvant chemotherapy. In stage III colon cancer patients, Hershman et al[51] demonstrated that delayed adjuvant chemotherapy administration greater than 3 months was associated with higher mortality rates.[51] Factors associated with delays included older age, increased comorbidities, tumor grade, and marital status. Cheung et al[52] conducted a study to determine the rates and causes of adjuvant chemotherapy delays and the effects of delay on the outcome in patients with stage II/III rectal cancer. They found that patients discharged from the hospital more than 4 weeks postoperatively or readmitted to the hospital more than once waited 3 or more months before receiving their first cycle of therapy, resulting in a significantly worse median survival.

Although this large NCCN database provides the characteristics of patients who do and do not receive recommended adjuvant chemotherapy for rectal cancer and reasons why patients do not receive adjuvant chemotherapy or do not complete the recommended/planned therapy, this analysis does have limitations. These data represent patients who were seen at academic comprehensive cancer centers and thus may not reflect the true percentage of patients with rectal cancer across the United States who do not receive adjuvant therapy, or the full variability of reasons why therapy was not administered or reasons why patients who initiated adjuvant therapy did not complete the treatment course. In addition, some of the individuals received a component of their care at a non-NCCN institution, resulting in under-reporting of information in the medical charts, thus potentially limiting the overall assessment of what occurred in the postoperative period. In addition, 20% of those who did not receive adjuvant therapy were not seen by a medical oncologist, an observation that warrants further investigation but cannot be elucidated from information available in the database. Furthermore, this analysis did not include recurrence or survival data, which will be important for future assessment to measure the true outcome effect for patients who do not receive adjuvant therapy or receive incomplete adjuvant treatment. In addition, the benefit of adjuvant chemotherapy after neoadjuvant chemoradiotherapy and surgery in locally advanced rectal cancer is not definitive and, therefore, may be a reason for the variability in patient selection for adjuvant chemotherapy among institutions. There is no conclusive evidence to define the optimal adjuvant chemotherapy regimen or the most optimal subgroups of patients to be treated, which may lead to variability in physician recommendations. Prospective clinical trials will be required to provide the evidence that defines systemic treatment strategies, including a focus on tumor biology, to enhance patient selection for treatment and to improve survival for patients with stage II/III rectal cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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