Stratification of Rectal Cancer Stage for Selection of Postoperative Chemoradiotherapy: Current Status

Leonard L. Gunderson, Matthew Callister, Robert Marschke, Tonia Young-Fadok, Jacques Heppell, Jonathan Efron

ABSTRACT

Disease relapse (local, distant) and survival rates (overall [OS], disease-free [DFS]) are dependent on disease stage at time of diagnosis. In rectal cancer pooled analyses of phase III North American trials, OS and DFS were dependent on TN stage (N substage within T stage), NT stage (T substage within N stage), and treatment method. Three risk groups of patients were defined: (1) intermediate T1-2N1, T3N0; (2) moderately high T1-2N2, T3N1, T4N0; and (3) high T3N2, T4N1, T4N2. Patients with a single high-risk factor (T1-2N1, T3N0) were shown to have better OS, DFS, and disease control than patients with both high-risk factors. Although adjuvant chemoradiotherapy (CRT) is indicated for patients with moderately high-risk and high-risk stage of disease, many of these patients are currently treated preoperatively if stage of disease can be defined. If surgery precedes adjuvant treatment, however, postoperative CRT is certainly indicated for these risk groups. For patients with intermediate-risk stage of disease (T1-2N1, T3N0), use of trimodality treatment (surgery plus radiotherapy and chemotherapy) in all patients may be excessive. The challenge is in determining which patients can be spared adjuvant CRT and whether it is worth the exercise.

Gastrointest Cancer Res 2:25–33.

L.L. Gunderson, MD, MS; M. Callister, MD: Department of Radiation Oncology

R. Marschke, MD: Division of Medical Oncology

T. Young-Fadok, MD; J. Heppell, MD; J. Efron, MD: Division of Colorectal Surgery

Mayo Clinic Cancer Center–Arizona
Scottsdale, AZ

Submitted December 21, 2006
Accepted March 1, 2007

As has been suggested for more than 50 years,[1–3] survival and disease relapse rates for resected rectal cancer patients are related to stage of disease with regard to both degree of bowel wall penetration by the primary cancer and nodal status.[4–10] Rectal cancer pooled analyses[11,12] demonstrated the independent prognostic significance of both TN and NT stage (N substage within T stage and T substage within N stage).[11,12]

For several decades, it has been noted that some patients have relatively low risk of local and distant relapse when treated with surgery alone.[13–15] The intent of this article is to discuss the rates of survival and relapse by stage of disease and treatment method in an attempt to define a subset of patients who may have less benefit from adjuvant chemoradiotherapy (CRT).

DISEASE OUTCOMES BY DISEASE STAGE

The TNM staging system defines the extent of the primary tumor relative to the layers of the rectal wall (confined to vs. extending beyond), and defines nodal involvement by the number of involved nodes (N1 ≤ 3, N2 ≥ 4). The updated 2002 AJCC/UICC TNM classification (6th edition) was refined and improved by the addition of substaging for TNM stage II and III lesions based on differential survival and relapse rates and should be used as the standard staging system.[16]

Subsequent pooled analyses of phase III North American rectal cancer postoperative adjuvant studies[11,12] demonstrated the independent prognostic significance of each TN category of resected rectal cancer (TN stage based on surgical and pathologic findings) and supported the value of substaging (see subsequent sections). Use of TNM stage I, II, or III[16] without the benefit of substaging is insufficient for presentation of data in either oral or manuscript formats, since patient prognosis is not accurately reflected, and should be discouraged.

First Rectal Cancer Pooled Analysis

The intent of the initial rectal cancer pooled analysis[11] was to determine if the trends for improved survival and disease control seen in single-institution analyses from Massachusetts General Hospital[6,8,9] and the Mayo Clinic[10] for patients with intermediate- vs. high-risk lesions could be confirmed in multi-institution phase III trials. Rates of survival and disease control by TN, NT, and modified Astler-Coller (MAC) stage were determined in 2,551 eligible patients from three randomized North American rectal cancer adjuvant studies.[17–21] Data were merged from the NCCTG (North Central Cancer Treatment Group) 79-47-51 (N = 200), NCCTG 86-47-51 (N = 656), and US GI Intergroup 0114 (N = 1,695) trials. All patients received postoperative radiotherapy, and 96% were randomized to receive concurrent and maintenance chemotherapy.

Address correspondence to: Leonard L. Gunderson, MD, MS, Getz Family Professor and Chair, Department of Radiation Oncology, Mayo Clinic Arizona, Deputy Director of Clinical Affairs, Mayo Clinic Cancer Center–Arizona, 13400 East Shea Blvd, Scottsdale, AZ 85259. E-mail: gunderson.leonard@mayo.edu.

Table 1. Rectal cancer pooled analysis: Effect of NT stage on survival and relapse.

	Overall survival*			Disease-free survival*			Local recurrence†		Distant metastasis†	
Stage	**No. pts**	**5-yr(%)**	***P* value**	**No. pts**	**5-yr(%)**	***P* value**	**5-yr(%)**	***P* value**	**5-yr(%)**	***P* value**
N0T3	668	74	.046	664	66	.05†	8	.04	19	.04
T4	95	65		95	54		15		28	
N1T1-2	225	81	< .001	225	74	< .001	6	.002	15	< .001
T3	544	61		536	50		11		34	
T4	59	33		59	30		22		39	
N2T1-2	180	69	< .001	180	62	< .001	8	.14	26	< .001
T3	663	48		659	39		15		45	
T4	84	38		84	30		19		50	

Modified from Gunderson et al.[11]
*Unadjusted Kaplan-Meier survival estimates
†Cumulative incidence rates

Table 2. Rectal cancer pooled analysis: Survival and relapse rates by stage of disease.*

	Stage*		5-yr survival†		Relapse		Stage	
Risk of relapse	**TN**	**MAC**	**OS(%)**	**DFS(%)**	**Local(%)**	**Distant(%)**	**Dukes**	**TNM**
Low‡	T1N0	A	~90	~90	≤ 5	~10	A	I
	T2N0	B1	~90	~90	≤ 5	~10	A	I
Intermediate	T1-2N1	C1	81	74	6	15	C	IIIA
	T3N0	B2	74	66	8	19	B	IIA
Moderately high	T1-2N2	C1	69	62	8	26	C	IIIC
	T4N0	B3	65	54	15	28	B	IIB
	T3N1	C2	61	50	11	34	C	IIIB
High	T3N2	C2	48	39	15	45	C	IIIC
	T4N1	C3	33	30	22	39	C	IIIB
	T4N2	C3	38	30	19	50	C	IIIC

Modified from Gunderson et al.[11]
*Stage of disease based on surgical and pathologic findings at the time of resection
†Survival: Unadjusted Kaplan-Meier estimates
‡Data derived from prior publications, as low-risk patients were not eligible for the three phase III trials in the pooled analysis
Abbreviations: DFS = disease-free survival; MAC = modified Aster-Coller; OS = overall survival; TNM = tumor, node, metastasis.

Survival and Relapse by NT Stage of Disease

Within N0 stage, an increase in T substage (T3, T4) resulted in a decrease in long-term survival and an increase in disease relapse, as shown in Table 1. For patients with T3N0 vs. T4N0 lesions, 5-year overall survival (OS) was 74% vs. 65% ($P = .046$), and disease-free survival (DFS) was 66% vs. 54% ($P = .05$). An increase in T substage (N0T3 vs. N0T4) was associated with an increase in both local and distant relapse (local relapse 8% vs. 15%; distant relapse 19% vs. 28%; $P = .04$ for each).

For patients with N1 stage, an increase in T substage also resulted in a decrease in survival and an increase in disease relapse ($P < .001$; Table 1). For patients with N1T3 and N1T4 lesions, 5-year OS was markedly decreased at 61% and 33%, respectively, when compared with the 81% OS achieved in patients with N1T1-2 lesions ($P < .001$). Disease-free survival at 5 years was also markedly different (N1T1-2 74%, N1T3 50%, N1T4 30%; $P < .001$). Of interest, for the subset of 225 patients with N1T1-2 disease, 5-year OS and DFS were similar to or exceeded that observed in N0T3 and N0T4 patients (5-year OS: N1T1-2 81%, N0T3 74%, N0T4 65%; 5-year DFS; 74%, 66%, and 54%, respectively).

Patients with N2 disease had differential prognosis by T substage for OS, DFS, and distant metastasis. Even within N2 stage, a subset of patients (N2T1-2) had higher than expected 5-year OS (N2T1-2 69%, N2T3 48%, N2T4 38%; $P < .001$) and 5-yr DFS (62%, 39%, and 30%, respectively; $P < .001$). The N2T1-2 patients also had a lower rate of distant metastasis than those with T3 or T4 substage (26%, 45%, and 50%, respectively; $P < .001$). The current placement of all N2 patients within AJCC IIIC substage[19] does not reflect the markedly different prognosis of N2 patients; however, the rectal pooled analysis data were not available at the time that such decisions were made. In a subsequent AJCC/UICC staging classification, N2T1-2 should probably be shifted to stage IIB and N2T3-4 should be kept in stage IIIC in view of the marked difference in prognosis.

Risk Analysis by TN Stage of Disease

In the initial pooled analysis,[11] patients were separated into four risk groups based on survival and relapse rates by TN stage of disease (low, intermediate, moderately high, and high risk; Table 2). Outcomes data

for low-risk patients (T1-2N0) were taken from single-institution[4–10] or "patterns of care" analyses.[22] For the intermediate-risk (T1-2N1, T3N0), moderately high-risk (T4N0, T1-2N2, T3N1), and high-risk patients (T3N2, T4N1-2), the 5-year OS, DFS, and relapse rates are data from the first pooled analysis (Table 1).[11]

Patients with the best survival are those with the primary cancer confined to the rectal wall and negative nodes (T1-2N0M0, TNM stage I), with an expected 5-year survival of approximately 90%.[4–10,22] With this stage of disease, distant relapse rates are approximately 10% and local recurrence rates are ≤ 5%.

Intermediate but still excellent results exist in patients with one high-risk feature (confined to the wall but with positive nodes [T1-2N1, TNM IIIA] or primary tumor extension beyond the rectal wall with no adherence to or invasion of surrounding organs or structures [T3N0, TNM IIA]; see Table 2). Five-year survival rates range from 75% to 80%. It is of interest that patients with both limited primary tumor and lymph node involvement (T1-2N1) have an equivalent or slightly improved prognosis relative to patients with T3N0 disease reflecting the independent prognostic importance of each TN substage of disease.

A moderately high risk of relapse is found in patients with more advanced local or nodal stage of disease (T4N0, TNM IIB; T3N1, IIIB; T1-2N2, IIIC; see Table 2). For those with negative nodes but adherence to or invasion of surrounding organs or structures (T4N0), a higher number of involved nodes (T1-2N2) or extension beyond the rectal wall and 1 to 3 involved nodes (T3N1), 5-year survival ranges from 60% to 70%. Local relapse rates were 8% to 15% and distant relapse rates were 26% to 34% with adjuvant postoperative treatment in the initial rectal pooled analysis.

The poorest survival and highest relapse rates are in patients with more advanced local and nodal stage of disease (T3N2, T4N1-2, TNM IIIC).[11] Five-year survival ranges from 30% to 50%. The local relapse rate was 15% to 22% in the first pooled analysis, and the distant metastasis rate was 39% to 50% (approximately double that of patients with a single risk factor).

These data demonstrate that the stage of disease related to the extent of both the primary tumor and nodal disease are independent prognostic factors. Each prognostic factor must be taken into consideration in determining appropriate adjuvant therapy (whether to deliver, how aggressive).

DISEASE OUTCOMES BY DISEASE STAGE AND TREATMENT

Second Rectal Cancer Pooled Analysis

The objective of the second rectal cancer pooled analysis was to determine disease outcomes (survival, relapse) by TN stage and treatment method in 3,791 eligible patients from five phase-III North American rectal cancer postoperative adjuvant trials.[12] Data from NSABP R01[23] and NSABP R02[24] were combined with data from the three North American randomized phase III rectal adjuvant trials that were included in the first pooled analysis.[11,17–21] Surgery alone was the treatment arm in only 179 patients; most patients received adjuvant treatment with either radiotherapy alone (n = 281), chemoradiotherapy (n = 2,799), or chemotherapy alone (n = 532). The second pooled analysis confirmed findings in the initial analysis regarding the relationship of stage of disease (TN, NT) to both OS and DFS.

For the second pooled analysis,[12] descriptive data were presented regarding the effect of treatment method on survival and relapse by TN stage (Tables 3 and 4). The decision to use descriptive rather than

Table 3. Rectal cancer pooled analysis: 5-year survival rates by treatment method for intermediate-risk, moderately high-risk, and high-risk patients.

Risk group/ TN stage	S + CT(%)	RT + bolus CT*(%)	RT + PVI CT(%)	RT + bolus CT† (%)
Overall survival				
Intermediate risk				
T1-2N1 (n = 355)	85	83	78	82
T3N0 (n = 1,060)	84	76	80	74
Moderately high risk				
T1-2N2 (n = 226)	43	55	44	77
T3N1 (n = 887)	52	61	73	63
T4N0 (n = 111)	70 (10)‡	58	80	67
High risk				
T3N2 (n = 935)	45	42	46	50
T4N1 (n = 62)	29 (7)‡	57	0 (1)‡	31
T4N2 (n = 108)	25 (4)‡	29	53	44
Disease-free survival				
Intermediate risk				
T1-2N1 (n = 355)	78	78	76	75
T3N0 (n = 1,058)	69	63	75	66
Moderately high risk				
T1-2N2 (n = 226)	36	48	39	66
T3N1 (n = 881)	43	51	63	51
T4N0 (n = 111)	50 (10)‡	55	70	55
High risk‡				
T3N2 (n = 929)	36	34	30	42
T4N1 (n = 62)	14 (7)‡	57	0 (1)‡	26
T4N2 (n = 108)	25 (4)‡	26	47	31

Modified from Gunderson et al[12]
*NCCTG and NSABP trials
†INT 0114
‡Number of patients at risk
Abbreviations: CT = chemotherapy; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; PVI = protracted venous infusion; RT = radiotherapy; S = surgery; TN = tumor, node.

Table 4. Rectal cancer pooled analysis: 5-year relapse rates by treatment method for intermediate-risk, moderately high-risk, and high-risk patients.

Risk group/ TN stage	S + CT(%)	RT + bolus CT*(%)	RT + PVI CT(%)	RT + bolus CT†(%)
Local relapse				
Intermediate risk				
T1-2N1 (n = 355)	5	6	5	6
T3N0 (n = 1,058)	11	10	5	8
Moderately high risk				
T1-2N2 (n = 226)	0	13	11	9
T3N1 (n = 881)	17	12	9	10
T4N0 (n = 111)	20 (10)‡	18	10	11
High risk				
T3N2 (n = 929)	15	17	11	15
T4N1 (n = 62)	43 (7)‡	0	18	22
T4N2 (n = 108)	0 (4)	22	33	16
Distant relapse				
Intermediate risk				
T1-2N1 (n = 355)	16	14	15	14
T3N0 (n = 1,058)	18	20	13	18
Moderately high risk				
T1-2N2 (n = 226)	57	40	61	28
T3N1 (n = 881)	37	35	30	33
T4N0 (n = 111)	20 (10)‡	27	59	25
High risk				
T3N2 (n = 929)	46	53	30	41
T4N1 (n = 62)	43 (7)‡	40	36	34
T4N2 (n = 108)	75 (4)‡	78	22	53

Modified from Gunderson et al[12]
*NCCTG and NSABP trials
†INT 0114
‡Number of patients at risk
Abbreviations: CT = chemotherapy; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; PVI = protracted venous infusion; RT = radiotherapy; S = surgery; TN = N substage within T stage.

comparative data was based on several factors, including the evolution of surgical technique, treatment method, and sequencing of treatment over a 13-year accrual period. In addition, significant between-trial heterogeneity was observed when the same treatment arm was used in two trials (ie, the results of external beam radiation + 5-fluorouracil [5-FU]–based arms in NCCTG 86-47-51, INT 0114, and R02 differed significantly, as did the results of semustine-based chemotherapy in R01 and R02).

For each of the six treatment methods, survival and relapse rates at 5 years were analyzed as a function of both TN and NT stage. Surgery alone and adjuvant radiotherapy alone were associated with inferior survival when compared with the other four treatment methods ($P < .001$); therefore, those data are not included in Tables 3 and 4. For some of the treatment methods, there was a steady decrease in OS with a progressive increase in both TN and NT stage (Table 3).

Intermediate-Risk Lesions (T3N0, T1-2N1)

Patients with intermediate-risk lesions had similar 5-year OS with either surgery followed by adjuvant chemotherapy or with trimodality treatment arms (radiotherapy + bolus chemotherapy, radiotherapy + protracted venous infusion chemotherapy, radiotherapy + bolus chemotherapy; Table 3). For surgery + chemotherapy, 5-year OS was 85% and 84%, and for the trimodality treatment arms ranged from 74% to 83%. Five-year DFS with surgery + chemotherapy was 78% with T1-2N1 lesions, but for T3N0 lesions, 5-year DFS fell to 69% (Table 3). For the trimodality arms, 5-year DFS ranged from 75% to 78% for patients with T1-2N1 lesions and from 63% to 75% for those with T3N0 lesions. Local relapse rates with T1-2N1 lesions ranged from 5% to 6% with adjuvant treatment; for T3N0 lesions, local relapse was 11% with surgery + chemotherapy vs. a range of 5% to 10% with trimodality methods (Table 4). Distant relapse rates for treatment arms without chemotherapy ranged from 25% to 41% vs. a range of 13% to 20% for chemotherapy arms (Table 4).[12]

Moderately High-Risk Lesions (T1-2N2, T3N1, T4N0)

For patients with moderately high-risk lesions (T1-2N2, T3N1, T4N0), 5-year OS ranged from 43% to 70% with surgery (S) + chemotherapy (CT) and 44% to 80% with S + radiotherapy (RT) + CT (Table 3); 5-year DFS ranged from 36% to 50% with S + CT and from 30% to 70% with S + RT + CT (Table 3). Local relapse rates ranged from 0% to 20% with S + CT and from 9% to 18% with S + RT + CT. Distant relapse rates varied between 20% to 57% for S + CT and between 25% to 61% for S + RT + CT.

High-Risk Lesions (T3N2, T4N1-2)

For patients with high-risk lesions (T3N2, T4N1-2), the 5-year OS range was 25% to 45% with S + CT and 29% to 57% with S + RT + CT (Table 3); 5-year DFS ranged from 14% to 36% with S + CT and from 26% to 57% for S + RT + CT. Local relapse rates were 15% and 43% with S + CT for the two subsets with ≥ 5 patients at risk and varied from 0% to 33% with S + RT + CT. Distant relapse rates were 43% to 75% with S + CT and 22% to 78% with S + RT + CT.

Outcomes vs. Depth of Perirectal Invasion, Radial Margins, Number of Nodes

For several decades, it has been suggested that properly selected patients with T3N0 and T1-2N1 lesions may have relatively low risks of local and distant relapse when treated with surgery alone.[13,14] Low-risk T3N0 lesions were felt to be those with minimal extension beyond the muscularis propria into perirectal fat and adequate radial/

circumferential resection margins.[13,14,25–27] Low-risk T1-2N1 lesions were defined as upper rectal cancers with only one or two nodes involved.[13]

The challenges in identifying low-risk lesions include adequate pathologic evaluation of specimens to provide the necessary information to discern patient prognosis and determination of what constitutes an adequate radial/circumferential resection margin and an adequate number of nodes to be examined. Although collection of both the depth of perirectal invasion and radial margin data was encouraged in NCCTG 86-47-51[18] and INT 0114,[19–21] the percentage of patients with that information recorded was so low that it could not be evaluated relative to outcomes.

Massachusetts General Hospital Series, T3N0 Cancers

In an attempt to better define indications for adjuvant radiotherapy and chemotherapy in patients with T3N0 lesions, investigators at Massachusetts General Hospital performed an analysis of the influence of various pathologic findings on outcomes for 117 patients treated with surgery alone for T3N0 rectal cancers from 1968 to 1985.[14] Histology slides of the surgical specimens were retrospectively assessed for maximum depth of tumor invasion beyond the muscularis propria into perirectal fat (in mm), lymphatic or venous vessel involvement, and tumor grade (well, moderate, poorly differentiated), without knowledge of clinical outcomes. Radial resection margins were evaluated; however, because of the retrospective nature of the analysis and the method of specimen-processing during the time period, such data were not felt to be reliable. Depth of perirectal invasion was therefore characterized as minimal (less than 2 mm), moderate (2–7.9 mm) or extensive (≥ 8 mm).

Clinical outcomes were evaluated including disease control (local, distant) and relapse-free survival (RFS). Patients with favorable histologic features (well- or moderately well-differentiated tumors, invasion less than 2 mm into perirectal fat, no evidence of lymphatic or venous involvement) had significantly better disease control and RFS ($P < .05$) than those with unfavorable features (Table 5). In patients with favorable features, 10-year actuarial rates of local control and RFS were 95% and 87%, respectively, vs. 71% and 55% for patients with unfavorable features. The authors suggested that for patients who had surgically resected T3N0 lesions with favorable histologic features and a negative radial resection margin, there may be little benefit to adjuvant therapy (radiotherapy, chemotherapy).

Dutch TME ± Preoperative EBRT Trial: Effect of Radial Margins on Outcomes

In a Dutch phase III study in resectable rectal cancer (no clinical fixation), 1,861 patients were randomly assigned to total mesorectal excision (TME) alone or preceded by short-course preoperative external beam radiation (EBRT) (25 Gy in 5 fractions over 1 week).[28] Standardization and quality control measures existed for the surgery, pathology, and EBRT techniques. Of the 1,861 randomized patients, 1,805 were eligible for analysis and 1,653 had a curative resection.

In the 1,748 patients with a complete local resection (R0 or R1 resection), the 2-year local relapse rate was 5.3%. For patients randomized to TME alone, the 2-year local relapse rate was 8.2% compared to 2.4% in those randomized to receive preoperative EBRT ($P < .001$; Table 6). Significant predictors of local relapse, in both univariate and Cox regression analyses, included treatment-group assigned ($P < .001$), tumor location (distance of tumor from anal verge; $P = .003$, univariate analysis; $P = .03$, multivariate) and TNM stage ($P < .001$). The benefit of preoperative EBRT was seen for patients with both stage II and III disease (stage II, 2-year local relapse rate of 5.7% with TME alone vs. 1% with preoperative EBRT, $P < .01$; stage III, 15 % vs. 4.3%, $P < .001$; Table 6). In a subsequent analysis by Nagtegaal et al,[29] the rate of local relapse in the TME alone patients was shown to be higher in those with a circumferential resection margin (CRM) of ≤ 2 mm vs. > 2 mm (16% vs. 5.8%, $P < .0001$).

The effect of CRM on outcomes was subsequently analyzed in the 1,530 patients who had treatment in the Netherlands (the remaining 331 were from Sweden, other parts of Europe, or Canada).[30] Only 1,318 patients were eligible for the CRM analysis

Table 5. Outcomes by histologic feature in patients with T3N0 lesions treated with surgery alone at Massachusetts General Hospital (1968–1985).

		Relapse-free survival		Local control		Distant control	
Histologic feature	**No. pts**	**10-yr (%)**	***P* value**	**10-yr (%)**	***P* value**	**10-yr (%)**	***P* value**
Depth of invasion*							
< 2 mm	33	87	.0007	93	.01	90	.0007
2–7.9 mm	62	57		75		65	
≥ 8 mm	18	36		49		41	
Vessel invasion							
Absent	93	71	.0001	81	.029	79	.0001
Present	24	29		58		30	
Grade							
Well or moderate	79	70	.0005	82	.01	76	.0005
Poor	38	45		65		51	

Modified from Willett et al[14]
Kaplan-Meier statistics and statistical significance determined by log-rank test
*Unable to evaluate depth of invasion beyond muscularis propria into perirectal fat in 4 of 117 patients

(656 TME alone and 662 preoperative EBRT). Local relapse was analyzed on the basis of amount of CRM margin, as defined previously by Nagtegaal et al[29] (≤ 1 mm [positive], > 1 mm and ≤ 2 mm [narrow], > 2 mm [wide]), in addition to the prior factors of treatment method (TME alone or plus preoperative EBRT), TNM stage, and tumor location (Table 7). The relationship between amount of CRM and 2-year local relapse rate by treatment method was as follows: CRM > 2 mm, 5.8% local relapse with TME alone (n = 483 patients) vs. 0.9% with preoperative EBRT (n = 504), $P < .0001$; CRM > 1 to ≤ 2 mm, local relapse rate 14.9% (TME, n = 53) vs. 0% (preoperative EBRT, n = 47), $P = .02$; CRM ≤ 1 mm, local relapse rate 16.4% (TME, n = 120) vs. 9.3% (preoperative EBRT, n = 107), $P = .08$. Even for patients with a CRM ≥ 1 cm, there was still an advantage in 2-year local relapse by adding preoperative EBRT to TME (3.3% vs. 0%; $P < .0002$).

Outcomes vs. Number of Nodes (Involved, Examined)

Recent evaluations have determined the prognostic significance of both number of nodes involved and number of nodes examined for patients with resected rectal cancer.[20] If an adequate number of nodes are not evaluated, an N1 patient could be denoted as N0 or an N2 patient as N1.

DISCUSSION

Most rectal cancer patients with low-risk disease (T1-2N0) are appropriately treated with surgery alone. These patients are usually not referred for adjuvant treatment unless surgical resection margins are compromised or local excision is used as the method of surgical removal. Select patients with T1-2N0 lesions may be amenable to nonsurgical treatment (ie, endocavitary radiation).

More controversy exists for patients with intermediate-risk disease (T1-2N1, T3N0). These patients were candidates for the postoperative adjuvant chemoradiotherapy trials included in the rectal cancer pooled analyses.[11,12] They were also included in the mandate for postoperative chemoradiotherapy in the 1990 National Institutes of Health consensus statement.[31]

In the second rectal cancer pooled analysis, an evaluation of 5-year OS data by treatment method suggests that use of trimodality postoperative adjuvant treatment (surgery plus CRT) for all patients with intermediate-risk T1-2N1 and T3N0 cancers may be excessive treatment (Tables 3 and 4). When treated with surgery + chemotherapy as a single adjuvant, 5-year OS was 85% and 84% vs. a 5-year OS range of 74% to 83% with trimodality treatment. Since this was a descriptive analysis of results across different trials and eras, however, definitive conclusions could not be made regarding the necessity of adjuvant radiotherapy. When 5-year DFS and relapse rates were evaluated for patients with T3N0 lesions, 5-year DFS decreased to 69% with surgery + chemotherapy and local relapse increased to 11%. For trimodality treatment, the 5-year DFS range was 63% to 75% with T3N0 lesions and local relapse ranged from 5% to 10%. For patients with T1-2N1 lesions, there were similar changes in 5-year DFS with either surgery + chemotherapy or trimodality treatment (surgery + chemotherapy, 78%; trimodality, range of 75% to 78%). The DFS and relapse data suggest that further improvements in outcome should be feasible, even for patients with T3N0 and T1-2N1 rectal cancers. Such improvements might be achieved with the use of preoperative chemoradiotherapy in properly selected patients (T3 or node positive on the basis of EUS or coil magnetic resonance imagining [MRI]) by the addition of new agents to current "standard regimens" or with the evaluation

Table 6. Local relapse: TME alone vs. preoperative RT plus TME: Dutch phase III trial.

	TME alone		Preop RT + TME		
		Local relapse		Local relapse	
Type of resection	**No. pts**	**2-yr (%)**	**No. pts**	**2-yr (%)**	***P* Value**
Low anterior	603	7.3	577	1.2	< .001
Abdominoperineal	232	10.1	248	4.9	.02
Hartmann	39	10.7	47	3.2	.18
TNM stage†					
I	244	0.7	265	.5	.15
II	241	5.7	251	1.0	.01
III	324	15.0	298	4.3	< .001
IV*	48	23.8	47	10.1	.25
Total†	874	8.2	872	2.4	< .001

Modified from Katipeijn et al[18]
*Distant metastases but complete local resection
†Additional cases of unknown stage
Abbreviations: RT = radiotherapy; TME = total mesorectal excision; TNM = tumor, node, metastasis.

Table 7. Local relapse by radial margin, TME alone vs. RT plus TME: Dutch phase III trial.

	TME alone		Preop RT + TME		
		Local relapse		Local relapse	
Radial margin	**No. pts**	**2-yr (%)**	**No. pts**	**2-yr (%)**	***P* Value**
≥ 1 cm*	264*	3.3	286*	0.0	.0002
> 2 mm	483	5.8	504	0.9	< .0001
> 1 to ≤ 2 mm	53	14.9	47	0.0	.02
≤ 1 mm	120	16.4	107	9.3	.08
Total	656	8.4	658	2.1	< .0001

Modified from Marijnen et al[30]
*Subset of patients with > 2 mm radial margin
Abbreviations: RT = radiotherapy; TME = total mesorectal excision.

Table 8. Treatment algorithm: Rectal cancer, Mayo Clinic Cancer Center–Arizona.

Disease extent (stage grouping)	Surgery	Irradiation (alone or with CT)	Chemotherapy
T1-2N0M0 (I)	Low anterior or abdominoperineal resection (LAR, CAPR) and regional nodes; local excision of select lesions	Endocavitary RT, select lesions*; EBRT-CT before local excision or LAR of distal T2N0 lesions	NR as systemic treatment; CCRT: 5-FU–based with local excision of T2N0 lesions
T3N0M0 (IIA) T4N0M0 (IIB)	LAR or CAPR/regional nodes Resect after preop CCRT (or before for T3N0 lesions)	T3N0, Pre- or postop EBRT-CT 45–54 Gy† T4N0, Preop EBRT-CT 45–54 Gy IOERT	CCRT: 5-FU–based, PVI 5-FU 5–7 d/wk or as bolus with leucovorin wk 1,5; consider postop MACT
T1-2N1M0 (IIIA) T1-2N2M0 (IIIC) T3N1-2M0 (IIIB/C)	LAR or CAPR/ regional nodes; Resect after CCRT (or before)	Preop EBRT-CT 45–54 Gy, preferred if TN stage known† Postop EBRT-CT, 45–54 Gy	CCRT: 5-FU–based, PVI 5-FU 5–7 d/wk or as bolus with leucovorin wk 1,5; postop MACT
T4N1M0 (IIIB) T4N2M0 (IIIC)	LAR or CAPR/regional nodes Resect after preop CCRT; IOERT‡	Preop EBRT-CT, 45–54 Gy IOERT	CCRT: 5-FU–based, PVI 5-FU 5–7 d/wk or as bolus with leucovorin wk 1,5; postop MACT

*30 Gy × 3-4 surface dose; available at Mayo Clinic Cancer Center–Rochester
† Prefer preop CCRT for T4N0-2M0 cancers (based on physical exam and computed tomography) and for T3N0-2 or T1-2N1-2 cancers (based on endoscopic ultrasound or pelvic MRI staging)
‡ IOERT dose-dependent on amount of residual disease after maximal surgical resection: R0, 10–12.5 Gy; R1, 12.5–15 Gy; R2, 15–20 Gy
Abbreviations: CAPR = combined abdominoperineal resection; CCRT = concurrent chemoradiotherapy; EBRT = external beam radiation; EBRT-CT = external beam radiation + chemotherapy; ICT = investigational chemotherapy clinical trials; IOERT = intraoperative electron radiation; LAR = low anterior resection; MACT = multiagent chemotherapy; NR = not recommended; postop = postoperative; preop = preoperative; PVI = protracted venous infusion.

of targeted therapy.

For patients with moderately high-risk and high-risk stage of disease, the second rectal cancer pooled analysis of results by treatment method showed definite room for improvement in disease outcomes of survival and relapse (Tables 3 and 4). With moderately high-risk lesions, 5-year OS ranged from 43% to 70% with surgery + chemotherapy and 44% to 80% with trimodality treatment; DFS ≥ 60% was uncommon and both local and distant relapse were common (local, 9% to 18%; distant, 20% to 60%). For patients with high-risk lesions, 5-year OS and DFS were < 50% for most combinations of TN stage and treatment method (5-year OS range: 25% to 45% with surgery + chemotherapy and 29% to 57% with trimodality treatment); local and distant relapse were both common (local, 0% to 33% with trimodality treatment; distant, 22% to 78% even with chemotherapy arms).

Current and Future Treatment Implications

At the Mayo Clinic Cancer Center and many other institutions, there has been a paradigm shift in the sequencing of chemoradiotherapy relative to surgical resection over the past decade. Previously, patients with mobile mid and upper rectal cancers underwent surgical removal of their cancer followed by postoperative chemoradiotherapy if pathology evaluation indicated a moderate to high risk of local or distant relapse if treated by surgery alone (T3N0, T1-2N1-2). The only patients referred for preoperative chemoradiotherapy were those with decreased mobility (tethered T3 or T4), disease fixation (T4) or patients with distal cancers in whom downstaging would likely increase the probability of achieving sphincter preservation. With the advent of endoscopic ultrasound staging, a majority of rectal cancer patients with indications for adjuvant treatment are now being treated with preoperative chemoradiotherapy in our institution (Table 8). The results of the German phase III trial[32] testing preoperative vs. postoperative chemoradiotherapy demonstrated an advantage to preoperative trimodality treatment for patients with T3-4 or node-positive cancers (Table 9) and confirmed our transition to the preoperative adjuvant strategy.[32,35–45]

Different treatment strategies are indicated for rectal cancer patients with intermediate-risk disease (T1-2N1, T3N0) vs. moderately high-risk or high-risk patients in view of variable rates of survival and relapse (Tables 3, 4, and 9). For carefully selected patients with T3N0 or T1-2N1 cancers (TNM stages IIA, IIIA), it may be appropriate to evaluate surgery alone or plus postoperative chemotherapy if careful pathology evaluation suggests a low risk of local relapse after a confirmed total mesorectal excision by an experienced surgeon.[17,28–30,33,34] Initiation of new trials that evaluate radiotherapy as a component of treatment for select T3N0 and T1-2N1 patients, however, should be done with caution, using stringent surgical and pathologic guidelines,[25–30] since preoperative EBRT reduced local response rates for patients with both stage II and III cancers when combined with TME (8% vs. 2%, $P < .0001$) in a Dutch phase III trial.[28] In the German phase III trial testing pre- vs. postoperative chemoradiotherapy,[34] the local relapse rate with TME plus adjuvant CRT was 6% with the preoperative approach and 13% with postoperative treatment, again demonstrating that TME alone does not prevent local relapse (Table 9).

Patients with T1-2N1 and T3N0 lesions are still appropriate candidates for adjuvant chemoradiotherapy. Trials evaluating adjuvant preoperative chemoradiotherapy[34–45] would be reasonable for patients with distal lesions in whom downstaging would improve the chance for rectal preservation and reanastamosis. Postoperative chemoradiotherapy trials should include patients

without indications for preoperative treatment who have an inadequate evaluation of nodes (< 10–15 examined by pathology)[20] and those at higher risk for local relapse based on amount of primary tumor extension beyond the muscularis propria (≥ 2 mm) or a narrow radial margin (≤ 4mm).[14] As noted in the Dutch phase III trial,[28–30] even for patients with circumferential resection margin ≥ 1 cm, preoperative EBRT improved 2-year local relapse when added to TME.[30]

For patients with moderately high-risk and high-risk disease, the high rates of both local and distant relapse and decreased rates of OS and DFS support continuing use of both concurrent chemoradiotherapy and adjuvant chemotherapy or other systemic therapy. A majority of patients with moderately high-risk or high-risk cancers are currently treated with preoperative chemoradiotherapy when the high-risk features can be defined by preoperative EUS or imaging (computed tomography of the abdomen and pelvis, MRI of the pelvis) or when lesions are tethered or fixed on the basis of physical examination and these findings are confirmed with imaging and EUS.

The preferred preoperative sequencing of adjuvant chemoradiotherapy for moderately high-risk and high-risk patients is supported by the results of the German phase III trial,[32] which demonstrated an improvement in sphincter preservation, local control (Table 9), and treatment tolerance for patients randomized to receive preoperative chemoradiotherapy. In our institution and others, the use of intraoperative radiation (electron beam or high-dose-rate brachytherapy) to deliver additional radiation to sites of narrow or microscopically positive resection margins after preoperative chemoradiotherapy is also felt to be appropriate for patients with T4 lesions.[46–48] Evaluation of preoperative chemoradiotherapy combined with more aggressive chemotherapy (ie, irinotecan or oxaliplatin)[40,43–45] or targeted therapy (vascular endothelial growth factor [VEGF] or epidermal growth factor receptor [EGFR] inhibitors)[49–52] is also indicated in patients with moderately high-risk and high-risk cancers.

If disease extent is not defined preoperatively, however, patients found to have moderately high-risk or high-risk stage of disease (T1-2N2, T3N1-2, T4N0-2) after surgical resection are appropriate candidates for adjuvant postoperative chemoradiotherapy. The results of the latest US GI Intergroup postoperative chemoradiotherapy trial INT 0144[53] are shown in Table 9 along with outcome results from other adjuvant chemoradiotherapy phase III trials including the German pre- vs. postoperative trial, and INT 0114. The data from INT 0144 show that postoperative chemoradiotherapy is still a very reasonable treatment option with regard to OS, DFS, and local relapse.

As with preoperative chemoradiotherapy strategies, evaluation of more aggressive chemotherapy regimens and targeted therapies will be necessary strategies to pursue in order to improve disease outcomes.

Table 9. Disease outcomes by series in phase III adjuvant chemoradiotherapy trials in rectal cancer.

	German trial*			US GI Intergroup postop	
Disease outcomes (5-yr)	**Preop CRT**	**Postop CRT**	***P* value**	**INT 0114†**	**INT 0144‡**
No. patients/series	397	384		1,695	1,917
Overall survival	76%	74%	.80	64%	68%–71%
Disease-free survival	68%	65%	.32	54%	57%–62%
Local relapse					
Total group	6%	13%	.006	14%	4.6%–8%‡
T1-2N1-2; T3N0-2‡	–	–		–	3%–5%‡
Intermediate risk†	–	–		–	–
T1-2N1				6%	
T3N0				8%	
Distant metastasis	36%	38%	.84	NA	NA

* Modified from Sauer et al[34]
† Modified from Tepper et al[21] and Gunderson et al[12]
‡ Modified from Smalley et al[53]
Local relapse data are absolute not 5-year actuarial; the T1-2N1-2 plus T3N0-2 data are only for patients with low anterior resection.
Abbreviations: CRT = chemoradiotherapy; NA = not available; Postop = postoperative; Preop = preoperative.

REFERENCES

1. Dukes CE: Cancer of the rectum: an analysis of 1000 cases. *J Pathol Bacteriol* 50:527–539, 1940
2. Astler VB, Coller FA: The prognostic significance of direct extension of carcinoma of the colon and rectum. *Ann Surg* 139:846–852, 1954
3. Copeland EM, Miller LD, Jones RS: Prognostic factors in carcinoma of the colon and rectum. *Am J Surg* 116:875–881, 1968
4. Gunderson LL, Sosin H: Adenocarcinoma of the rectum: areas of failure found at reoperation (second or symptomatic look) following curative surgery for adenocarcinoma of the rectum: clinicopathologic correlation and implications for adjuvant therapy. *Cancer* 34:1278–1292, 1974
5. Gilbert SB: The significance of symptomatic local tumor failure following abdominoperineal resection. *Int J Radiat Oncol Biol Phys* 4:801–807, 1978
6. Rich T, Gunderson LL, Galdabini J, et al: Clinical and pathologic factors influencing local failure after curative resection of carcinoma of the rectum and rectosigmoid. *Cancer* 52: 1317–1329, 1983
7. Cass AW, Million RR, Pfaff WW: Patterns of recurrence following surgery alone for adenocarcinoma of the colon and rectum. *Cancer* 37:2861–2865, 1976
8. Hoskins RB, Gunderson LL, Dosoretz D, et al: Adjuvant postoperative radiotherapy in carcinoma of the rectum and rectosigmoid. *Cancer* 55:61–71, 1985
9. Tepper JE, Cohen AM, Wood WC, et al: Postoperative radiation therapy of rectal cancer. *Int J Radiat Oncol Biol Phys* 13:5–10, 1987
10. Schild SE, Martenson JA, Gunderson LL, et al: Postoperative adjuvant therapy of rectal cancer. *Int J Radiat Oncol Biol Phys* 17:55–62, 1989
11. Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: a pooled analysis. *Int J Radiat Oncol Biol Phys* 54:386–396, 2002
12. Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 22:1785–1796, 2004
13. Gunderson LL, Dosoretz D, Blitzer PH, et al: Low dose preoperative irradiation, surgery and elective postoperative irradiation for resectable rectal and rectosigmoid carcinoma. *Cancer* 52:446–451, 1983
14. Willett CG, Badizadegan K, Ancukiewicz M, et

al: Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? *Dis Colon Rectum* 42:167–173, 1999

15. Gunderson LL: Indications for and results of combined modality treatment of colorectal cancer. *Acta Oncol* 38:7–21, 1999
16. Jessup JM, Gunderson LL, Greene FL, et al: Colon and rectum, in Greene FL, Page AL, Fleming ID, et al (eds): AJCC Cancer Staging Manual (6th ed). New York, Springer, pp 113–124, 2002
17. Krook J, Moertel C, Gunderson LL, et al: Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 324:709–715, 1991
18. O'Connell MJ, Martenson JA, Wieand HS, et al: Improving adjuvant therapy for rectal cancer by combining protracted infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 33:502–507, 1994
19. Tepper JE, O'Connell MJ, Petroni G, et al: Adjuvant postoperative 5-FU-modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: initial results of Intergroup 0114. *J Clin Oncol* 15:2030–2039, 1997
20. Tepper JE, O'Connell MJ, Niedzwiecki D, et al: Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 19:157–163, 2001
21. Tepper JE, O'Connell MJ, Niedzwiecki D, et al: Adjuvant therapy in rectal cancer: analysis of stage, sex and local control—final report of Intergroup 0114. *J Clin Oncol* 20:1744–1750, 2002
22. Coia LR, Gunderson LL, Haller D, et al: Outcomes of patients receiving radiation for carcinoma of the rectum. Results of the 1988-1989 patterns of care study. *Cancer* 86:1952–1958, 1999
23. Fisher B, Wolmark N, Rockette H, et al: Postoperative adjuvant chemotherapy or radiation therapy or rectal cancer: results from NSABP R-01. *J Natl Cancer Inst* 80:21–29, 1988
24. Wolmark N, Wieand HS, Hyams DM, et al: Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 92:388–396, 2000
25. Chan KW, Boey J, Wong SKC: A method of reporting radial invasion and surgical clearance of rectal carcinoma. *Histopathology* 9:1319–1327, 1983
26. Quirke P, Durdey P, Dixon MF, et al: Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumor spread and surgical excision. *Lancet* 2:996–999, 1986
27. Adam IJ, Mohamdee MO, Martin JG, et al: Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 344: 707–711, 1994
28. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 345:638–646, 2001
29. Nagtegaal ID, Marijnen CAM, Kranenbarg EKM, et al: Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 26: 350–357, 2002
30. Marijnen CAM, Nagtegaal ID, Kapiteijn E, et al: Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 55:1311–1320, 2003
31. NIH Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 264:1444–1450, 1990
32. Sauer R, Becker H, Hohenberger W, et al, for the German Rectal Cancer Group: Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351:1731–1740, 2004
33. MacFarlane JK, Ryall RD, Heald RJ: Mesorectal excision for rectal cancer. *Lancet* 341:457–460, 1993
34. Enker WE, Thaler HT, Cranor ML, et al: Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 181: 335–346, 1995
35. Rich TA, Skibber JM, Ajani JA, et al: Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. *Int J Radiat Oncol Biol Phys* 32:1025–1029, 1995
36. Mohiuddin M, Hayne M, Regine WF, et al: Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. *Int J Rad Oncol Biol Phys* 48:1075–1080, 1997
37. Grann A, Feng C, Wong D, et al: Preoperative combined modality therapy for clinically resectable UT3 rectal cancer. *Int J Radiat Oncol Biol Phys* 49:987–995, 2001
38. Valentini V, Coco C, Cellini N, et al: Ten years of preoperative chemoradiation for extraperitoneal T3 rectal cancer: acute toxicity, tumor response and sphincter preservation in three consecutive studies. *Int J Radiat Oncol Biol Phys* 51:371–383, 2001
39. Crane DH, Skibber JM, Feig BW, et al: Response to preoperative chemoradiation increases the use of sphincter-preserving surgery in patients with locally advanced low rectal carcinoma. *Cancer* 97:517–524, 2003
40. Gerard JP, Chapet O, Nemoz C, et al: Preoperative concurrent chemotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimem: the Lyon R0-04 phase II trial. *J Clin Oncol* 21: 1119–1124, 2003
41. Bosset JF, Collette L, Calais G, et al: Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 355:1114–1123, 2006
42. Gerard JP, Conroy T, Bonnetain F, et al: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 24:4620–4625, 2006
43. Mohiuddin M, Winter K, Mitchell E, et al: Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group trial 0012. *J Clin Oncol* 24:650–655, 2006
44. Chau I, Brown G, Cunningham D, et al: Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol* 24: 668–674, 2006
45. Rodel C, Valentini V, Minsky B: Rectal cancer, in Gunderson LL, Tepper JE (eds): Clinical Radiation Oncology (2nd ed). Churchill Livingstone/Elsevier, Philadelphia, pp 1113–1143, 2007
46. Willett CG, Shelito PC, Gunderson LL: Primary colorectal EBRT and IOERT, in Gunderson LL, Willett CG, Harrison LB, et al (eds): Intraoperative Irradiation, Techniques and Results. Totowa, New Jersey, Humana Press, pp 249–272, 1999
47. Willett CG, Shellito PC, Tepper JE, et al: Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. *J Clin Oncol* 9:843–849, 1991
48. Gunderson LL, Nelson H, Martenson JA, et al: Locally advanced primary colorectal cancer: intra-operative electron and external beam irradiation +/- 5FU. *Int J Radiat Oncol Biol Phys* 37:601–614, 1997
49. Goldberg RM, Morton RF, Sargent DJ, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22: 23–30, 2004
50. Andre T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350:2343–2351, 2004
51. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluourouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350:2335–2342, 2004
52. Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory CRC. *N Engl J Med* 351:337–345, 2004
53. Smalley SR, Benedetti J, Williamson SK, et al: Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol* 24:3542–3547, 2006

Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.