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ORIGINAL REPORT

Revised Tumor and Node Categorization for Rectal Cancer Based on Surveillance, Epidemiology, and End Results and Rectal Pooled Analysis Outcomes

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ABSTRACT

Purpose
The sixth edition of the American Joint Committee on Cancer (AJCC) rectal cancer staging subdivided stage II into IIA (T3N0) and IIB (T4N0) and stage III into IIIA (T1-2N1M0), IIIB (T3-4N1M0), and IIIC (anyTN2M0). Subsequent analyses supported revised substaging of stage III as a result of improved survival with T1-2N2 versus T3-4N2 and survival of T4N1 more similar to T3-4N2 than T3N1. The AJCC Hindgut Taskforce sought population-based validation that depth of invasion interacts with nodal status to affect survival.

Methods
Surveillance, Epidemiology, and End Results (SEER) population-based data from January 1992 to December 2004 for 35,829 patients with rectal cancer were compared with rectal pooled analysis data (3,791 patients). T4N0 cancers were stratified by tumors that perforate visceral peritoneum (T4a) versus tumors that invade or are adherent to adjacent organs or structures (T4b). N1 and N2 were stratified by number of positive nodes as follows: N1a/N1b (one *v* two to three nodes) and N2a/N2b (four to six *v* ≥ seven nodes). Five-year observed and relative survival rates were obtained for each TN category.

Results
SEER rectal cancer analyses confirm that T1-2N2 cancers have better prognosis than T3-4N2, T4bN1 have similar prognosis to T4N2, T1-2N1 have similar prognosis to T2N0/T3N0, and T1-2N2a have similar prognosis to T2N0/T3N0 (T1N2a) or T4aN0 (T2N2a). Prognosis for T4a lesions is better than T4b by N category. The number of positive nodes affects prognosis.

Conclusion
This SEER population-based rectal cancer analysis validates the rectal pooled analyses and supports the shift of T1-2N2 lesions from IIIC to IIIA or IIIB and T4bN1 from IIIB to IIIC. SEER outcomes support subdividing T4, N1, and N2 and revised substaging of stages II and III. Survival by TN category suggests a complex biologic interaction between depth of invasion and nodal status.

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INTRODUCTION

Survival and disease relapse after surgery alone or combined with adjuvant treatment for rectal cancer are a function of both degree of bowel wall penetration of the primary lesion (T classification) and nodal status (N classification), as suggested for 40 to 50 years.[1-3] Nodal involvement alone is inadequate as the sole pathologic factor to predict survival and relapse rates.[4-13] However, through the fifth edition of the American Joint Committee on Cancer (AJCC) staging manual, marked differences in survival by TN category of disease within stages II and III were not taken into account by appropriate substaging.

In the sixth edition of AJCC staging, stage II was subdivided into IIA (T3N0) and IIB (T4N0), and stage III was subdivided into IIIA (T1-2N1M0), IIIB (T3-4N1M0), and IIIC (anyTN2M0).[14] The addition of substaging for stages II and III was based on existing outcomes for IIA versus IIB and for IIIA and IIIB. The placement of all TN2 patients into IIIC was based on data that patients with N2 cancers (four or more positive nodes) had poorer outcomes than patients with N1 cancers (one to three positive nodes).

Subsequent rectal cancer pooled analyses demonstrated the independent prognostic significance of each TN and NT category of resected rectal cancer (N subcategory within T category and T subcategory within N category).[15,16] The outcomes in the rectal pooled analyses supported revised substaging of stage III as a result of improved survival for patients with T1-2N2 cancers versus T3-4N2 and survival rates with T4N1 lesions that are more similar to rates seen with T3-4N2 than T3N1.

Before making such changes in the seventh edition of AJCC staging, the AJCC Hindgut Taskforce (HTF) sought validation in a population-based data set that depth of invasion interacts with nodal status to impact survival. Data were obtained for patients with both rectal and colon cancers; the colon cancer data in 109,953 evaluable patients with invasive cancer are reported in a separate article.[16a]

METHODS

Surveillance, Epidemiology, and End Results (SEER) population-based data were obtained from January 1, 1992 to December 2004 for 55,011 patients with rectal and rectosigmoid cancer (C19.9 and 20.9); 35,829 patients had invasive rectal cancer and evaluable TN category of disease (T1-4N0-2), 17,302 were categorized as NX, and 1,880 were categorized as Tis or T1 polyp. Data of the 35,829 patients with invasive cancers and evaluable TN category of disease were compared with cooperative group rectal pooled analysis data on 2,551 and 3,791 patients (pooled analyses 1 and 2, respectively).[15,16] Patients who died within 30 days of surgical resection were not included in the current analysis. The effects of different treatment approaches (surgical technique [total mesorectal resection], adjuvant chemoradiotherapy [pre- or postoperative], adjuvant chemotherapy, or other) were not felt to be pertinent to the current analysis; such data were not analyzed in depth. Of the total group of 55,011 patients, only 4,821 (8.8%) were recorded as having received preoperative irradiation as a component of treatment (T1-4N0-2, 3,353 patients [9.4% of 35,829 patients with evaluable TN category of disease]; NX category, 1,400 patients; Tis/T1 polyp N0-2, 68 patients).

Tumors were stratified by SEER's extent of disease and number of positive nodes coding schemes. T4N0 cancers were stratified by tumors that perforate visceral peritoneum (T4a) versus tumors that invade or are adherent to adjacent organs or structures (T4b). N1 (metastasis in one to three regional nodes) and N2 (metastasis in ≥ four regional nodes) were stratified by number of positive lymph nodes, as follows: N1a (one positive node), N1b (two to three positive nodes), N2a (four to six positive nodes), and N2b (≥ seven positive nodes). T1 to T3 categories were defined as per prior AJCC staging (T1 = tumor invades submucosa; T2 = tumor invades muscularis propria; T3 = tumor invades pericolorectal tissues).

Both observed and relative survival data were obtained for each TN category of disease. Observed survival (≃ overall survival [OS]) is the proportion of cancer patients surviving for a specified time interval after diagnosis. Relative survival (survival corrected by age-related morbidity; ≃ disease-specific survival) is a net survival measure representing cancer survival in the absence of other causes of death.

RESULTS

Survival Outcomes: SEER Versus Rectal Pooled Analyses

Observed survival outcomes at 5 years in the current SEER rectal cancer analysis were compared with 5-year OS outcomes in the two rectal cancer pooled analyses for patients with invasive rectal cancer and evaluable TN category of disease (SEER database, 35,829 patients; rectal pooled analysis 1, 2,551 patients; rectal pooled analysis 2, 3,791 patients). As shown in Table 1, SEER analyses confirmed the findings of the two pooled analyses with regard to differential prognosis by NT/TN category of disease for patients with stage II and III cancers. For most TN categories, survival rates in the SEER analysis were 7% to 10% lower than in the rectal pooled analyses.

For patients with stage II cancers, the differential survival outcomes for T3N0 and T4N0 lesions are listed in Table 1. In both pooled analyses, patients with T3N0 lesions had improved 5-year OS relative to patients with T4N0 ($P = .046$ and $P = .02$). In the SEER rectal analysis, large differences in 5-year observed survival were found between T3 versus T4N0 cancers, and SEs were small based on large patient numbers (T3N0, 64.0% ± 0.5%, n = 10,615; T4N0, 50.5% ± 1.4%, n = 1,587).

For stage III cancers, patients with T1-2 lesions (confined to rectal wall) had much better prognoses than patients with T3-4 lesions for both N1 and N2 category of disease. These differences were statistically significant in both the SEER and rectal pooled analyses. In addition, patients with T4N1 lesions had prognoses more akin to

Table 1. Survival Outcomes at 5 Years by NT Category and Series in Rectal Adjuvant Pooled Analyses and SEER Analysis

	Pooled Analysis 1*			Pooled Analysis 2†			SEER Analysis‡		
NT Category	No. of Patients	OS Rate (%)	*P*	No. of Patients	OS Rate (%)	*P*	No. of Patients	Observed Survival Rate (%)	SE (%)
N0T1-2	—	—		—	—		9,961	77.6	0.5
N0T3	668	74	.046	1,060	75	.02	10,615	64.0	0.5
N0T4	95	65		111	65		1,587	50.5	1.4
N1T1-2	225	81	< .001	355	79	< .001	2,008	72.1	1.2
N1T3	544	61		887	60		5,787	52.4	0.8
N1T4	59	33		62	35		903	37.4	1.8
N2T1-2	180	69	< .001	226	67	< .001	508	56.1	2.6
N2T3	663	48		935	44		3,755	37.5	0.9
N2T4	84	38		108	37		705	26.4	1.9
Total	2,551			3,791			35,829‡		

NOTE. See Table 3 for observed survival data expansion.
Abbreviations: SEER, Surveillance, Epidemiology, and End Results; OS, overall survival.
*Modified from Gunderson et al.[15]
†Modified from Gunderson et al.[16]
‡Current series, observed survival data (observed survival ≃ OS); lymph node status unknown, n = 17,302; Tis or T1 polyp, n = 1,880.

Table 2. Rectal SEER Analysis: Relative Survival at 5 Years by NT Category of Disease

NT Category	No. of Patients	5-Year Survival Rate (%)	SE
N0	23,902		
Tis	821	95.9	1.9
T1 polyp	918	97.3	1.7
T1-2	9,961	93.6	0.6
T1	3,348	96.6	0.9
T2	6,613	92.1	0.7
T3	10,615	78.7	0.7
T4	1,587	61.6	1.7
T4a*	818	69.2	2.4
T4b*	769	53.6	2.5
NX	17,302		
Tis	2,718	89.4	1.1
T1 polyp	2,668	91.2	1.1
T1-2	7,585	80.9	0.8
T1	5,688	81.5	0.9
T2	1,897	79.0	1.6
T3	2,834	51.8	1.3
T4	1,497	23.8	1.4
T4a*	238	42.8	4.2
T4b*	1,259	20.2	1.4
N1 (1-3 positive nodes)	8,817		
Tis	60	86.7	6.9
T1 polyp	59	84.8	9.2
T1-2	2,008	85.1	1.4
T1	444	88.1	2.8
T2	1,564	84.3	1.6
T3	5,787	63.1	0.9
T4	903	44.9	2.2
T4a*	480	58.7	3.1
T4b*	423	28.5	2.9
N1a (1 positive node)	4,419		
Tis	34	92.7	7.2
T1 polyp	45	87.7	7.1
T1-2	1,197	86.5	1.8
T1	274	88.4	3.7
T2	923	86.0	2.0
T3	2,758	66.9	1.4
T4	419	48.6	3.3
T4a*	218	65.6	4.6
T4b*	201	28.9	4.3
N1b (2-3 positive nodes)	4,338		
Tis	26	75.4	11.5
T1 polyp	14	57.4	26.2
T1-2	811	83.1	2.2
T1	170	85.9	4.4
T2	641	81.8	2.5
T3	3,029	59.7	1.3
T4	484	41.6	2.9
T4a*	262	52.6	4.1
T4b*	222	27.8	4.0
N2 (≥ 4 positive nodes)	4,990		
Tis	15	71.7	16.1
T1 polyp	7	65.4	21.8
T1-2	508	64.9	3.0
T1	86	77.0	6.4
T2	422	62.4	3.3
T3	3,755	44.1	1.1
T4	705	31.2	2.2
T4a*	397	40.6	3.2
T4b*	308	18.4	3.0
N2a (4-6 positive nodes)	2,683		
Tis	12	64.1	17.9
T1 polyp	2	100	0
T1-2	364	70.7	3.5
T1	62	82.7	7.0
T2	302	67.7	4.0
T3	1,964	49.9	1.5
T4	355	39.5	3.4
T4a*	199	53.1	4.8
T4b*	156	22.1	4.3
N2b (≥ 7 positive nodes)	2,285		
Tis	3	—	—
T1 polyp	5	54.5	25.9
T1-2	144	49.5	5.4
T1	24	59.3	14.6
T2	120	46.2	5.8
T3	1,791	37.5	1.5
T4	350	22.8	2.9
T4a*	198	28.5	4.0
T4b*	152	14.1	4.0

NOTE. Relative survival data (≈ disease-specific survival) were available for 55,011 patients (T1-4N0-2, n = 35,829; NX, n = 17,302; Tis or T1 polyp, n = 1,880).

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

*T4a = tumors that penetrate to the surface of visceral peritoneum; T4b = tumors that invade or are adherent to adjacent organs or structures.

those of patients with T3N2 or T4N2 cancers in both the SEER and rectal pooled analyses.

The 5-year survival of patients with T1-2 lesions was better than expected for both N1 and N2 category of disease in both the SEER and rectal pooled analyses. For patients with T1-2N1 lesions, 5-year survival was similar to that of patients with T3N0 lesions. For patients with T1-2N2 lesions, 5-year survival was more akin to that of patients with T3-4N0 or T3N1 lesions.

Survival Outcomes by TN Category: SEER Analysis

The large patient numbers in the SEER rectal cancer database allowed the evaluation of both observed and relative survival at 5 years for each TN category of disease, including patients with Tis, T1 polyp, and NX lesions (Tables 2 and 3). Analyses of highest pertinence to this article included the 35,829 patients with invasive T1-4N0-2 cancers.

A clear survival difference for patients with stage I versus IIA cancers is seen in the SEER analysis (Tables 1 to 3). For patients with T1-2N0 lesions, 5-year observed survival was 77.6% ± 0.5% *v* 64.0% ± 0.5% for patients with T3N0 lesions.

Subcategories of patients with T1-2N2 cancers had survival rates similar to those in patients with N0 disease. Patients with T1N2a

Table 3. Rectal SEER Analysis: Observed Survival at 5 Years by NT Category of Disease

NT Category	No. of Patients	5-Year Survival Rate (%)	SE
N0	23,902		
Tis	821	80.8	1.6
T1 polyp	918	83.6	1.4
T1-2	9,961	77.6	0.5
T1	3,348	81.4	0.8
T2	6,613	75.7	0.6
T3	10,615	64.0	0.5
T4	1,587	50.5	1.4
T4a*	818	55.7	1.9
T4b*	769	44.7	2.1
NX	17,302		
Tis	2,718	74.5	1.0
T1 polyp	2,668	76.3	1.0
T1-2	7,585	65.3	0.6
T1	5,688	66.4	0.7
T2	1,897	62.1	1.3
T3	2,834	41.4	1.1
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N1 (1-3 positive nodes)	8,817		
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T1 polyp	59	74.3	8.0
T1-2	2,008	72.1	1.2
T1	444	75.8	2.4
T2	1,564	71.1	1.3
T3	5,787	52.4	0.8
T4	903	37.4	1.8
T4a*	480	48.2	2.5
T4b*	423	24.3	2.5
N1a (1 positive node)	4,453		
Tis	34	86.4	6.4
T1 polyp	45	82.1	6.2
T1-2	1,197	73.4	1.5
T1	274	75.7	3.2
T2	923	72.7	1.7
T3	2,758	55.4	1.1
T4	419	40.1	2.7
T4a*	218	53.2	3.7
T4b*	201	24.4	3.6
N1b (2-3 positive nodes)	4,364		
Tis	26	65.6	10.0
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T1	170	75.9	3.8
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T4b*	222	24.0	3.4
N2 (≥ 4 positive nodes)	4,990		
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T4b*	308	15.6	2.5
N2a (4-6 positive nodes)	2,697		
Tis	12	58.6	16.1
T1 polyp	2	100	0
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T1	62	73.8	6.2
T2	302	58.2	3.4
T3	1,964	42.5	1.3
T4	355	32.9	2.8
T4a*	199	44.3	4.0
T4b*	156	18.5	3.6
N2b (≥ 7 positive nodes)	2,293		
Tis	3	—	—
T1 polyp	5	53.3	24.8
T1-2	144	43.4	4.7
T1	24	53.2	13.0
T2	120	41.7	5.0
T3	1,791	32.0	1.3
T4	350	19.6	2.5
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NOTE. Observed survival data (≈ overall survival) were available for 55,011 patients (T1-4N0-2, n = 35,829; NX, n = 17,302; Tis or T1 polyp, n = 1,880).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
*T4a = tumors that penetrate to the surface of visceral peritoneum; T4b = tumors that invade or are adherent to adjacent organs or structures.

lesions had similar 5-year observed survival to patients with T2N0 or T3N0 cancers (T2N0, 75.7% ± 0.6%; T1N2a, 73.8% ± 6.2%; T3N0, 64.0% ± 0.5%). Patients with T2N2a lesions had similar 5-year observed survival to patients with T4aN0 cancers (T2N2a, 58.2% ± 3.4%; T4aN0, 55.7% ± 1.9%).

Prognosis for patients with T4a lesions (tumor penetrates to the surface of visceral peritoneum; revised definition, AJCC seventh edition) is better than the prognosis for patients with T4b lesions (tumor directly invades or is adherent to other organs or structures) for each N category. Relative and observed 5-year survival rates for T4aN0 versus T4bN0 lesions were 69.2% ± 2.4% *v* 53.6% ± 2.5% (relative) and 55.7% ± 1.9% *v* 44.7% ± 2.1% (observed), respectively. For N1 and N2 categories, the survival differences for T4a versus T4b were even more striking, as shown in Tables 2 and 3 (N1: relative, 58.7% ± 3.1% *v* 28.5% ± 2.9%; observed, 48.2% ± 2.5% *v* 24.3% ± 2.5%; N2: relative, 40.6% ± 3.2% *v* 18.4% ± 3.0%; observed, 34.3% ± 2.7% *v* 15.6% ± 2.5%, respectively).

The number of positive nodes affects prognosis for most TN categories of disease (Tables 2 and 3). Patients with only one metastatic regional node (N1a) have a 3% to 10% better 5-year relative and observed survival than patients with two to three positive nodes (N1b)

for most TN categories of disease. Patients with four to six involved nodes (N2a) have a 5% to 20% better 5-year survival than patients with ≥ seven positive nodes (N2b) by TN category (Tables 2 and 3).

The relative survival impact of both the number of positive nodes and number of nodes evaluated by the pathologist is presented in Figure 1. Relative survival improves for some TN categories as the number of nodes examined increases, most obvious in the larger T3 category of disease (Fig 1C). Prognosis as a function of percentage of nodes involved was not evaluated in the current analysis.

DISCUSSION

Survival and disease relapse after surgery alone[1-9,13] or combined with adjuvant treatment[10-12,14-16,18-44] for rectal cancer patients are a function of both degree of bowel wall penetration of the primary lesion and nodal status. However, nodal involvement alone does not determine survival and relapse rates. Invasion through the bowel wall and number of involved lymph nodes are independent high-risk factors for both relapse and survival.

For patients with a single high-risk factor of either direct tumor extension beyond the wall, nodes negative (T3N0), or positive nodes but primary tumor confined to the wall (T1-2N1-2), local relapse rates published in older surgical series have ranged from 20% to 40%.[2-7] For patients with both positive nodes and extension beyond the wall (T3-4N1-2), the risk of pelvic relapse was nearly additive (40% to 65% in clinical series and 70% in a reoperative series).[2-7]

The rate of systemic metastases is significantly higher for patients with both high-risk pathologic factors (extension beyond rectal wall and positive nodes; T3-4N1-2), as opposed to patients with only a single risk factor (T3-4N0, T1-2N1). In published data from adjuvant rectal cancer patients irradiated at either Massachusetts General Hospital[10,11] or Mayo Clinic,[12] the incidence of subsequent

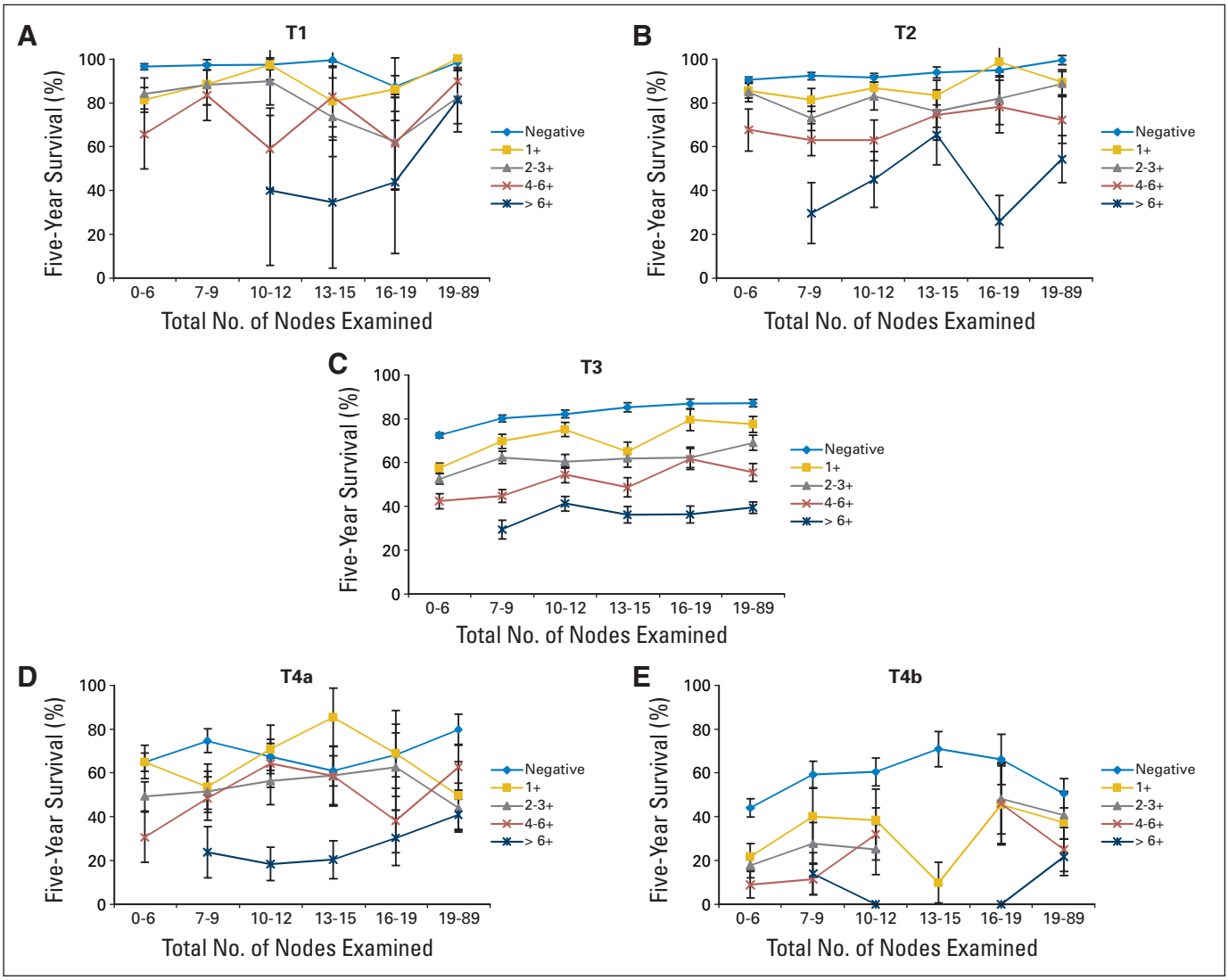

Fig 1. Interaction among tumor and node classifications and total nodes examined on 5-year survival in rectal cancer Surveillance, Epidemiology, and End Results (SEER) analysis. (A-E) Relative survival for pT1-4 by N1a (one positive node), N1b (two to three positive nodes), N2a (four to six positive nodes), and N2b (≥ seven positive nodes) on 35,829 patients (SEER analysis). The effect of the total number of nodes examined is categorized along the abscissa. Relative survival improves for some TN categories as number of lymph nodes examined increases, which is most obvious with (C) T3 category. Reprinted with permission.[17]

systemic relapse was approximately 20% for patients with T3-4N0 and T1-2N+ lesions versus 40% to 60% for patients with T3-4N+ lesions.

Single-institution analyses from Massachusetts General Hospital[10] and Mayo Clinic[12] had previously suggested that patients with T1-2N1-2 lesions who were treated with postoperative irradiation alone or combined with chemotherapy had outcomes similar to T3N0 and T4N0 patients, but patient numbers in each stage subset were small. In the rectal pooled analyses with larger numbers of patients, the 5-year OS rate observed for the T1-2N1 patients was similar to that for T3N0 patients, and the 5-year survival for T1-2N2 patients was similar to that for patients with T4N0 or T3N1 lesions (Table 1).[15,16] Results by N2 category were rarely available before the first pooled analysis,[15] and results by T subcategory for patients with N2 disease (ie, T1-2N2, T3N2, T4N2) were nonexistent.

Data from the rectal cancer pooled analyses (Table 1)[15,16] strongly supported substaging of TNM stages II and III, as accomplished in the sixth edition (2002) of TNM staging.[14,18] As shown in Table 1, for TNM stage III patients, three separate prognostic subgroups of lesions exist (intermediate risk, T1-2N1; moderately high risk, T1-2N2 and T3N1; and high risk, T3N2 and T4N1-2). To combine or merge all of these patients into TNM stage III (Dukes C) does not provide full prognostic information for patients or physicians. However, patients with T1-2N1-2 disease had a more favorable prognosis than previously thought, and patients with T4N1 lesions (stage IIIB, AJCC sixth edition, along with T3N1 lesions) had prognoses more akin to those of patients with T3-4N2 lesions (stage IIIC, sixth edition).

For patients with N2 disease, data from the rectal pooled analyses demonstrated that N2 disease does not by itself confer poor prognosis.[15,16] Substaging by T category influenced both 5-year OS (N2T1-2, 67%; N2T3, 44%; and N2T4, 37%; $P < .001$; Table 1) and 5-year disease-free survival (N2T1-2, 58%; N2T3, 36%; and N2T4, 30%; $P < .001$). Placement of all N2 patients in AJCC IIIC substage in the sixth edition[16a] did not reflect the markedly different prognosis of N2 patients observed in the rectal pooled analyses.

As shown in Table 1, data in the current large SEER population-based rectal cancer analysis validates the rectal pooled analyses with regard to the more favorable prognosis of patients with T1-2N1-2 lesions (stage IIIC, AJCC sixth edition) and less favorable prognosis of patients with T4N1 cancers (stage IIIB, sixth edition). Both SEER and rectal pooled analyses data support the shift of T1-2N2 lesions from stage IIIC to an earlier stage of disease (IIIA/IIIB) and T4N1 lesions from stage IIIB to IIIC (Tables 4 and 5).

Expanded SEER rectal cancer outcomes data (Tables 2 to 5) also support subdividing T4, N1, and N2 categories of disease. Patients with T4a lesions (penetrates to the surface of visceral peritoneum [revised definition, AJCC seventh edition]) have a better prognosis than patients with T4b lesions (directly invades or is adherent to other organs or structures) for each N category of disease (N0, N1, and N2). For patients with N0T4a versus N0T4b lesions, there is an approximately 10% improvement in absolute 5-year relative survival and OS, and for patients with N1T4a versus N1T4b and N2T4a versus N2T4b disease, there is a nearly 20% improvement in 5-year survival. Patients with one positive node (N1a) have a better prognosis than patients with two to three positive nodes (N1b), and patients with four to five positive nodes (N2a) have a better prognosis than patients with ≥ seven positive nodes (N2b) by T category.

Table 4. Rectal SEER Analysis: 5-Year Relative and Observed Survival by TN Category of Disease in Patients With Invasive Cancer and Evaluable TN Category

TN Category	No. Patients	SEER: 5-Year Relative Survival Rate (%)	SE (%)	TNM Stage (sixth edition)	Proposed TNM Stage (seventh edition)	SEER: Observed Survival Rate (%)	SE (%)
T1N0	3,348	96.6	0.9	I	I	81.4	0.8
T2N0	6,613	92.1	0.7	I	I	75.7	0.6
T3N0	10,615	78.7	0.7	IIA	IIA	64.0	0.5
T4aN0	818	69.2	2.4	IIB	IIB	55.7	1.9
T4bN0	769	53.6	2.5	IIB	IIC*	44.7	2.1
T1-2N1	2,008	85.1	1.4	IIIA	IIIA	72.1	1.2
T1N2a	62	82.7	7.0	IIIC	IIIA*	73.8	6.2
T2N2a†	302	67.7	4.0	IIIC	IIIB*	58.2	3.4
T3N1a	2,758	66.9	1.4	IIIB	IIIB	55.4	1.1
T4aN1a	218	65.6	4.6	IIIB	IIIB	53.2	3.7
T3N1b	3,029	59.7	1.3	IIIB	IIIB	49.7	1.1
T1N2b	24	59.3	14.6	IIIC	IIIB*	53.2	13.0
T4aN2a‡	199	53.1	4.8	IIIC	IIIC	44.3	4.0
T4aN1b	262	52.6	4.1	IIIB	IIIB	43.9	3.4
T3N2a	1,964	49.9	1.5	IIIC	IIIB*	42.5	1.3
T2N2b	120	46.2	5.8	IIIC	IIIB*	41.7	5.0
T3N2b	1,791	37.5	1.5	IIIC	IIIC	32.0	1.3
T4aN2b	198	28.5	4.0	IIIC	IIIC	24.5	3.4
T4bN1	423	28.5	2.9	IIIB	IIIC*	24.3	2.5
T4bN2a	156	22.1	4.3	IIIB	IIIC	18.5	3.6
T4bN2b	152	14.1	4.0	IIIC	IIIC	12.3	3.5

NOTE. Survival outcomes of 35,829 patients with invasive T1-4N0-2 rectal cancer are shown.
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
*Changes in substaging of stages II and III are based on expanded outcomes in SEER rectal/colon analyses.
†T2N2a rectal lesions did worse than colon T2N2a lesions; both categories are placed in stage IIIB.
‡T4aN2a rectal lesions did better than colon T4aN2a lesions; both categories are placed in stage IIIC.

Table 5. Rectal Cancer: Proposed Changes in Substaging of AJCC Stages II and III Based on Rectal Pooled and SEER Analyses

	Rectal Pooled Analysis 1		Rectal Pooled Analysis 2				SEER Rectal Cancer		
TN Category	No. of Patients	5-Year Overall Survival Rate (%)	No. of Patients	5-Year Overall Survival Rate (%)	AJCC TNM Stage (sixth edition)	Proposed TNM Stage (seventh edition)	No. of Patients	5-Year Observed Survival Rate (%)	SE (%)
T1-2N0	—	—	—	—	I	I	9,961	77.6	0.5
T1N0	—	—	—	—	I	I	3,348	81.4	0.8
T2N0	—	—	—	—	I	I	6,613	75.7	0.6
T3N0	668	74	1,060	75	IIA	IIA	10,615	64.0	0.5
T4N0*	95	65	111	65	IIB	T4a, IIB	818	55.7	1.9
						T4b, IIC*	769	44.7	2.1
T1-2N1	225	81	355	79	IIIA	IIIA	2,008	72.1	1.2
T1-2N2*	180	69	226	67	IIIC	IIIA/IIIB*†	508	56.1	2.6
T3N1	544	61	887	60	IIIB	IIIB	5,787	52.4	0.8
T4N1*	59	33	62	35	IIIB	T4a, IIIB	480	48.2	2.5
						T4b, IIIC*	423	24.3	2.5
T3N2*	663	48	935	44	IIIC	T3N2a, IIIB*	1,964	42.5	1.3
						T3N2b, IIIC	1,791	32.0	1.3
T4N2	84	38	108	37	IIIC	T4a, IIIC	397	34.3	2.7
						T4b, IIIC	308	15.6	2.5

Abbreviations: AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.
*Proposed changes in substaging.
†IIIA = T1N2a; IIIB = T2N2a, T1-2N2b.

Previous analyses with much smaller data sets had suggested that patients with perforated T4 lesions may have a worse prognosis than patients with invasion of or adherence to other organs or structures.[45,46] However, as shown in the current SEER analysis with large data sets for each TN category of disease, patients with T4 lesions that penetrate to the surface of visceral peritoneum (T4a in AJCC seventh edition) have a more favorable prognosis than patients with invasion of or adherence to other organs or structures (T4b in AJCC seventh edition).

Data in the current SEER analyses combined with rectal pooled analyses data support revised substaging of stages II and III (Tables 4 and 5). The AJCC seventh edition HTF recommended the following changes (Table 5): subdivide IIB into IIB (T4aN0) and IIC (T4bN0); shift more favorable TN2 categories to either IIIA (T1N2a) or IIIB (T2N2a, T1-2N2b, T3N2a); and shift less favorable T4N1 lesions from IIIB to IIIC (T4bN1).

Survival outcomes by TN/NT category in the rectal pooled analyses[15,16] and the current SEER rectal cancer analysis suggest a complex biologic interaction between depth of invasion and nodal status. As shown in Tables 1 to 5, some TN categories of patients with positive nodes (T1-2N1 and T1-2N2) have a similar or better prognosis than patients with negative nodes with regard to both relapse (rectal pooled) and survival (SEER, rectal pooled). Patients with T1-2N1 lesions have better 5-year OS (rectal pooled), relative survival, and observed survival (SEER) than patients with T3N0 or T4N0 cancers (Tables 1 to 5), with outcomes more akin to patients with T2N0 lesions (Tables 4 to 5). Accordingly, the indications for adjuvant chemoradiotherapy or chemotherapy in patients with T1-2N1 disease should continue to be evaluated. Patients with N2a category (four to six involved nodes) but limited invasion have 5-year survival outcomes similar to those of patients with T2N0 and T3N0 cancers (T1N2a) or T4aN0 cancers (T2N2a) in the current analysis.

Survival outcomes by TN category of disease in the SEER rectal cancer analysis are more similar to SEER colon cancer outcomes than expected.[16a] Because of the similarities, the AJCC seventh edition HTF recommended continuance of a common staging system for patients with rectal and colon cancers. These similarities may be the result of common tumor biology, the impact of adjuvant chemoradiotherapy (preoperative or postoperative), and/or adjuvant chemotherapy or other factors.

This revision of TNM classification for rectal cancer demonstrates the critical role of formulating postulates and then assessing them in data sets that are larger than single-institution series. As the AJCC proceeds to the next edition, it will be important to collect data on other points of consideration that include, but are not limited to, the number of peritumoral deposits, the number of positive and total nodes examined, and the magnitude of the circumferential radial margin. Only through prospective data collection will usable data exist that can guide decisions relative to the next edition of the staging manual, when hopefully several molecular markers can be incorporated as an adjunct or modifier to the TNM categories of disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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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. Chan KW, Boey J, Wong SKC: A method of reporting radial invasion and surgical clearance of rectal carcinoma. Histopathology 9:1319-1327, 1983

9. 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

10. Hoskins RB, Gunderson LL, Dosoretz D, et al: Adjuvant postoperative radiotherapy in carcinoma of the rectum and rectosigmoid. Cancer 55:61-71, 1985

11. Tepper JE, Cohen AM, Wood WC, et al: Postoperative radiation therapy of rectal cancer. Int J Radiat Oncol Biol Phys 13:5-10, 1987

12. Schild SE, Martenson JA, Gunderson LL, et al: Postoperative adjuvant therapy of rectal cancer. Int J Radiat Oncol Biol Phys 17:55-62, 1989

13. 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

14. 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 (ed 6). New York, NY, Springer, 2002, pp 113-124

15. 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

16. 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

16a. Gunderson LL, Jessup JM, Sargent DJ, et al: Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 28: 264-271, 2010

17. Edge SB, Byrd DR, Compton CC, et al (eds): Colon and rectal, in AJCC Cancer Staging Manual (ed 7). Springer, New York, NY, 2009, pp 143-164

18. Greene FL, Stewart A, Norton HJ: New tumor-node-metastasis staging strategy for node-positive (stage III) rectal cancer: An analysis. J Clin Oncol 22:1778-1784, 2004

19. 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

20. National Institutes of Health Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444-1450, 1990

21. 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

22. 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 331:502-507, 1994

23. 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

24. Gunderson LL: Indications for and results of combined modality treatment of colorectal cancer. Acta Oncol 38:7-21, 1999

25. 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

26. 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

27. 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

28. 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

29. 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

30. 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

31. 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

32. 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 Radiat Oncol Biol Phys 48:1075-1080, 2000

33. 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

34. 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

35. 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

36. 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

37. 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

38. Crane CH, 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

39. Gérard JP, Chapet O, Nemoz C, et al: Preoperative concurrent chemotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimen: The Lyon R0-04 phase II trial. J Clin Oncol 21:1119-1124, 2003

40. 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

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. Gérard 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. Rodel C, Valentini V, Minsky B: Rectal cancer, in Gunderson LL, Tepper JE (eds): Clinical Radiation Oncology (ed 2). Philadelphia, PA, Churchill Livingstone/Elsevier, 2007, pp 1113-1143

45. Compton C, Fenoglio-Preiser CM, Pettigrew N, Fielding LP: American Joint Committee on Cancer Prognostic Factors Consensus Conference: Colorectal Working Group. Cancer. 88:1739-1757, 2000

46. Compton CC, Greene FL: The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin 54:295-308, 2004

