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AJCC-7TH Edition Staging Criteria for Colon Cancer: Do the Complex Modifications Improve Prognostic Assessment?

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Abstract

Background—The seventh edition of the American Joint Committee on Cancer staging system (AJCC-7) includes significant changes for colon cancer (CC), which are particularly complex in patients with stage II and III disease. We used a national cancer database to determine if these changes improved prediction of survival.

Study Design—The database of the Surveillance, Epidemiology, and End Results (SEER) Program was queried to identify patients with pathologically confirmed stage I–III CC diagnosed between 1988 and 2008. CC was staged by sixth edition AJCC criteria (AJCC-6) and then restaged by AJCC-7. Five-year disease-specific survival (DSS) and overall survival (OS) were compared.

Results—After all exclusion criteria were applied, AJCC-6 and AJCC-7 staging was possible in 157,588 patients (68.9%). Bowker's test of symmetry showed that the number of patients per substage was different for AJCC-6 and AJCC-7 ($p < 0.001$). The Akaike information criteria comparison showed superior fit with the AJCC-7 model ($p < 0.001$). However, although AJCC-7 staging yielded a progressive decrease in DSS and OS of patients with stage IIA (86.3% and 72.4%, respectively), IIB (79.4% and 63.2%, respectively), and IIC (64.9% and 54.6%, respectively) disease, DSS and OS of patients with stage IIIA disease increased (89% and 79%, respectively). Subset analysis of patients with > 12 lymph nodes examined did not affect this observation.

Conclusion—AJCC-7 staging of CC does not address all survival discrepancies, regardless of the number of lymph nodes examined. Consideration of other prognostic factors is critical for decisions regarding therapy, particularly for patients with stage II CC.

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Keywords

colon cancer; TNM staging; quality measures

INTRODUCTION

In the United States, colon cancer (CC) is the third most common malignancy diagnosed in both men and women and the second leading cause of cancer deaths¹. Surgical resection remains the mainstay of treatment for local and regional disease². Adjuvant chemotherapy is frequently used in advanced CC, but remains controversial for stage II disease³.

Understanding the pathologic staging in conjunction with prognostic values is essential to making therapeutic decisions. The American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging model has provided this universal modality since its first edition in 1959⁴. Since that time, extent of primary tumor and nodal status remain the foundation of the staging and continue to drive therapeutic decisions.

In 2002, the sixth edition of the AJCC staging guidelines (AJCC-6) expanded stage II and stage III CC into two and three substages, respectively. However, as O'Connell et al and others have shown⁵⁻⁷, the survival of patients with stage IIIA CC is superior to that of patients with stage IIB CC. This has been attributed to treatment practice, such as administration of chemotherapy to patients with stage III but not stage II CC, and to understaging because of inadequate sampling and assessment of lymph nodes (LNs).

As a result, significant changes to the AJCC staging model were expected, and the next revision was published. As shown in Table 1, the seventh edition of AJCC staging guidelines (AJCC-7) subdivides stage II CC and reclassifies stage III CC⁴. In addition, AJCC-7 describes seven new prognostic factors: tumor regression grade, circumferential resected margin (CRM), isolated tumor cells (ITC), perineural invasion, microsatellite instability (MSI), KRAS mutation status and 18q loss of heterozygosity (LOH)⁴. However, these factors have not yet been incorporated into AJCC-7.

The increased complexity of the AJCC-7 staging model was intended to improve the prognostic staging of CC, but the impact of these changes remains unclear. In this study, we used data from the Surveillance Epidemiology and End Results (SEER) registries to compare the prognostic accuracy of AJCC-6 and AJCC-7 in patients with stage I, II and III CC through survival models. We also examined the association of a 12-LN quality measure with improvements in the prognostic accuracy of AJCC-7.

METHODS

The SEER Program is a national database that is funded and maintained by the NIH/NCI. Population-based data are collected from 14 regional and three supplemental cancer registries which represent approximately 26% of the population in the United States⁸. SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology and health policy, and thus are exempt from IRB review. A 98% case ascertainment is mandated with annual quality-assurance studies.

The National Cancer Institute's SEER*Stat software was used to identify patients whose microscopically confirmed, invasive CC was diagnosed between 1988 and 2008⁹. Only patients who underwent surgical treatment of stages I, II and III CC were considered. Surgical patients were excluded if they had in situ or stage IV disease as determined by extent of disease codes. Patients were also excluded if LN examination and positivity status were unknown. Age, sex, race, TNM stage, tumor grade, tumor histology, tumor location, cause of death and vital status were assessed. Adjuvant chemotherapy was not considered because this information is not included in the SEER database.

Using the extent of disease codes and LN positivity status, CC was staged based on the AJCC-6 and AJCC-7 (Table 2). Patients were then divided into 2 groups by number of examined LNs (12 or 1-11) and staging comparisons were repeated within each group. In the database, patients were designated into one of three outcome categories: dead from CC, dead from other causes, or alive at the last follow-up.

STATISTICAL ANALYSIS

Survival curves were generated using Kaplan-Meier estimates, and 5-year DSS and OS were compared using the log-rank test. Bowker's test of symmetry was used to assess the agreement between AJCC-6 and AJCC-7 for all stages of CC (7×7 cross-table) and then for all stages except I and IIA (5×5 cross table).

Multivariable Cox proportional hazard (PH) regression models were built using AJCC-6 and AJCC-7; these models incorporated variables with $p < 0.02$ in univariable analyses. The final models were built in a stepwise fashion that involved forward and backward selection. Regression models were built first for all stages of CC and then for all stages except I and IIA.

Goodness of fit for each regression model was evaluated using the Akaike information criterion (AIC)¹⁰. The PH assumption was checked for the final models using Cox-Snell residual plots. All the statistical analyses were done using SAS 9.2 (Cary, NC). P -values less than 0.05 were considered statistically significant.

RESULTS

During the 21-year study period, 228,603 patients with stage I-III CC were identified but only 157,588 (68.9%) met our inclusion criteria (Figure 1). The median age at diagnosis was 71 years (interquartile range [IQR] 61-69) and median follow-up was 44 months (IQR 17-84). Patient demographics and pathological features are summarized in Table 3. This table also compares staging of CC with AJCC-6 versus AJCC-7 criteria; although there was no difference in the total number of patients with stage I and IIA CC, the distribution of patients in all remaining categories was different. Bowker's test of symmetry performed for all stages of CC and then for all stages except I and IIA confirmed the lack of agreement between AJCC-6 and AJCC-7 for stage IIB/C and stage IIIB/C CC ($p < 0.001$).

Both AJCC-6 and AJCC-7 showed that patients with stage I, II and III CC had 5-year DSS rates of 95%, 84.7% and 68.7%, respectively (Figure 2A), and 5-year OS rates of 82.7%,

70.3% and 58.3%, respectively (Figure 2C). Five-year DSS was 73.4% for patients with AJCC-6 stage IIB CC, as compared with 79.4% for those with AJCC-7 stage IIB CC and 64.9% for those with AJCC-7 stage IIC CC (Figure 2B). Similarly, 5-year OS was 59.6% for patients with AJCC-6 stage IIB CC, as compared with 63.2% for those with AJCC-7 stage IIB CC and 54.6% for those with AJCC-7 stage IIC CC (Figure 2D).

For patients with stage IIIA, IIIB, and IIIC CC, AJCC-6 yielded 5-year DSS rates of 89.1%, 73% and 56.4%, respectively (Figure 2B), and 5-year OS rates of 79.1%, 61.6% and 47.5%, respectively (Figure 2D). AJCC-7 also showed progressively decreased survival for patients with stage IIIA, IIIB and IIIC CC: 5-year DSS rates were 89%, 70.4%, and 55.8%, respectively (Figure 2B), and 5-year OS rates were 79%, 59%, and 47.9%, respectively (Figure 2D).

When CC was staged by AJCC-6, 5-year DSS was better for patients with stage IIIA disease (89.1%) than stage IIA (86.9%) or stage IIB (73.2%) disease ($p < 0.001$). When CC was staged by AJCC-7, 5-year DSS was better for patients with stage IIIA disease (89%) than stage IIA (72.4%), stage IIB (79.4%), or stage IIC (64.9%) disease ($p < 0.001$). This was also observed for 5-year OS ($p < 0.001$ for both AJCC-6 and AJCC-7).

Lymph Node Assessment

Of the 157,588 patients, 74,095 (47%) had fewer than 12 LNs examined and 83,493 (53%) had at least 12 LNs examined (Table 2). Corresponding rates of 5-year DSS were 79.4% and 83.4%, respectively ($p < 0.001$, Figure 3A). Corresponding rates of 5-year OS were 64.1% and 73.2%, respectively ($p < 0.001$, Figure 3B).

Staging based on both AJCC-6 and AJCC-7 showed that the number of examined nodes had a significant impact on 5-year OS and DSS ($p < 0.001$). Thus, regardless of the staging system, when fewer than 12 nodes were examined, patients with stage I, II and III CC had 5-year DSS of 94.5%, 80.3% and 64.6%, respectively, and 5-year OS of 80.4%, 62.5% and 51.7%, respectively. However, when at least 12 LNs were examined, patients with stage I, II and III CC had 5-year DSS of 95.7%, 88.4% and 71.6%, respectively, and 5-year OS of 85.8%, 76.9% and 63%, respectively.

When the impact of AJCC-6 versus AJCC-7 substage was examined according to number of nodes (Figure 4), trends mirrored those observed for the entire cohort (Figure 2B/D).

However, patients with stage IIA/B/C and stage IIIA/B/C CC had better DSS (Figure 4A and 4B) and OS (Figure 4C and 4D) if at least 12 LNs were examined. When at least 12 nodes were examined and CC was staged by AJCC-7, 5-year DSS was 90.9% for patients with stage IIIA CC, as compared with 90% for stage IIA ($p = 0.18$), 83.7% for stage IIB ($p < 0.001$) and 73.9% for stage IIC ($p < 0.001$) disease. Similarly, 5-year OS was 82.2% for patients with stage IIIA CC, as compared with 78.4% for stage IIA ($p < 0.001$), 70.7% for stage IIB ($p < 0.001$), and 65.5% for stage IIC ($p < 0.001$) disease.

Multivariable Cox PH survival models were built using a forward and backward, stepwise selection method that incorporated age at diagnosis, sex, race, tumor grade, tumor, size, tumor location, geographic region, radiation therapy, number of LNs examined, LN

positivity and AJCC stage. Age, sex, tumor location, tumor grade, tumor size, number of LNs examined and AJCC stage were significant predictors of DSS and OS ($p < 0.001$) when this analysis included all stages of CC and when it excluded stages I and IIA.

AIC values for AJCC-6 and AJCC-7 were 705,885 and 659,613, respectively, when the analysis was based on all stages of CC, and 655,391 and 654,751, respectively, when the analysis excluded stages I and IIA. In both cases, the model based on AJCC-7 yielded a smaller AIC value and therefore was a better fit.

Statistical analyses were repeated in patients with at least 12 LNs examined and in those with fewer than 12 LNs examined. In the former group, multivariable analysis identified age, sex, primary site, tumor grade, tumor size, and AJCC stage as significant predictors of DSS and OS ($p < 0.001$), both before and after excluding stage I and IIA. AIC analysis favored AJCC-7 over AJCC-6 for patients with at least 12 LNs examined: AIC values for AJCC-7 and AJCC-6 were 295,037 and 313,757, respectively, for all stages, and 292,274 and 292,655, respectively, after excluding stages I and IIA.

DISCUSSION

Since the 1940s, the TNM staging system has defined the extent of a cancer based solely on anatomic pathology. Revisions to the system are made every 6-8 years and until recently it has been regarded as the most comprehensive tool for prognostic and predictive grouping of patients with CC⁴. However, when AJCC-6 was released in 2002¹¹, it elicited criticism because survival of patients with stage IIIA CC was superior to that of patients with stage IIB CC⁵. Our SEER-based study shows that AJCC-7 has not eliminated the survival discrepancies between patients with stage II and stage IIIA CC (Figure 2).

This problem with AJCC staging of CC was initially attributed to inadequate LN assessment. Several studies demonstrated that the number of examined LNs impacted survival¹²⁻¹⁶, and in 2007 the National Quality Forum endorsed examination of at least 12 LNs as a quality measure for CC. Subsequent studies have shown a strong correlation between outcomes and compliance with the 12-LN minimum^{6, 12, 13, 17-20}. Findings of our study confirmed that examination of at least 12 LNs was associated with improved 5-year DSS and OS rates, whether CC was staged by AJCC-6 or AJCC-7 criteria. However, even when at least 12 LNs were examined, outcomes of patients with stage III CC were statistically better than those of patients with stage IIB and IIC CC. This suggests that stage migration due to inadequate LN examination might not be responsible for survival disparities in the AJCC-7 staging system.

In recent years, researchers have recognized the importance of tumorigenesis and the role of non-anatomic markers in establishing the prognosis and anticipated response to therapy²¹⁻²⁶. Of particular interest are the seven non-anatomic factors acknowledged by but not incorporated in the AJCC-7 staging system. Of these factors, the circumferential margin of the resected nonperitonealized surface of the specimen (CRM) is relevant for prognostic assessment of patients with tumors in the ascending and descending colon^{27, 28}. Isolated tumor cells in the LNs may have prognostic relevance in CC, but are still considered

N0.²⁹⁻³¹ Microsatellite instability, reflecting a defect in DNA repair, accounts for 10-15% of all CCs. The KRAS mutation in either codon 12 or 13 is strongly associated with metastatic CC that does not respond to treatment with anti-EGFR antibodies. MSI, KRAS mutation and the 18q LOH have been shown to have clinical prognostic significance^{32, 33}. These factors have not been incorporated into the staging system because it is not clear how they should be used to determine prognosis⁴ or the need for adjuvant chemotherapy. Also, assessment of these non-anatomic factors adds significantly to a pathologist's workload³⁴.

Our study is one of the largest population-based studies to compare the AJCC-6 and AJCC-7 staging systems while incorporating the quality measure of adequate LN examination, but it does have limitations. Although the SEER database maintains a 98% accuracy rate, incorrect coding or erroneous data are possible⁸. Recurrence data is not available. Also, the SEER database lacks chemotherapy data so we were unable to confirm our suspicion that treatment-related differences contributed to the inferior survival for patients with stage II CC. Because of the NCCN guidelines in effect during the study period, we speculate that most patients with stage IIIA CC received adjuvant chemotherapy. We also believe that the use of chemotherapy for patients with high-risk stage IIB and IIC CC likely increased during the study period, although chemotherapy for this group remains controversial.^{3, 7, 35} Whether chemotherapy is responsible for survival differences and whether it should be used for patients with stage IIB and IIC CC require investigation in prospective trials. Finally, identification of our cohort required exclusion of 12,072 patients with insufficient staging data and 56,379 patients with incomplete nodal data. Although these patients represented only 29.9% of CC patients (stages I-III) during the study period, it is possible that their exclusion could have made our cohort less representative of the SEER population.

The AJCC model remains the most used staging system worldwide for all cancer, but its problems in CC may explain why many physicians continue using Dukes' staging system or the Astler-Coller and Kirklin modifications of the Dukes' system³⁶⁻³⁸. Others have ignored the more recent AJCC revisions and still use the AJCC-5th edition criteria for CC diagnosis and treatment planning³⁴. In its favor, AJCC-7 can distinguish different oncologic outcomes for T4 lesions based on lymph node involvement, and it also makes prognostic distinctions for T1 or T2 lesions based on the presence and extent of nodal involvement. However, staging based on AJCC-7 criteria cannot accommodate the impact of adjuvant therapy in patients with stage II and stage III CC⁷.

Regardless of the 12-LN quality measure, AJCC-7 still needs further refinement. Molecular profiling has recently been incorporated in the treatment of stage II and III colon cancer. A clinically validated diagnostic assay based on expression of 12 genes in the primary tumor is now commercially available; results quantify the likelihood of recurrence after resection of stage II or III colon cancer^{39, 40}. A newer 18-gene assay has also become commercially available which has been shown to improve the prognostic accuracy of pathologic factors and MSI in patients with stage II and II CC⁴¹. The incorporation of other prognostic factors, particularly results of these types of molecular profiling assays, requires prospective evaluation to determine any impact on the prognostic utility of the AJCC staging system. However, preliminary data have demonstrated significant potential in redefining the role of

biomarkers in the TNM staging system^{3, 32, 39, 42} and may transform prognostic skills and clinical decision making for patients with CC in the years to come.

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Figure 1.
Flow diagram of patient selection from the 258,552 patients with colon cancer to establish patients with stages I-III who had surgical resection with curative intent within the SEER database from 1988-2008.

Figure 2. Five-year disease-specific survival (DSS) and overall survival (OS) for the 157,588 patients whose colon cancer was staged based on AJCC-6 (orange) and AJCC-7 (black) criteria. (A) DSS for stages I-III. (B) DSS for all substages. (C) OS for stages I-III (D) OS for all substages.

Figure 3. Five-year survival based on number of lymph nodes (LNs) examined: 1-11 LNs (red) and 12 LNs (black). (A) disease-specific survival, and (B) overall survival.

Figure 4.

Five-year disease-specific survival (DSS) and overall survival (OS) for all patients based on substaging and number of LNs examined. AJCC-6 (< 12 lymph nodes [LNs] yellow, 12+ LNs red) and AJCC-7 (<12 LNs green, 12+ LNs blue) criteria. (A) DSS for Stages I-III. (B) OS for Stages I-III.

Table 1AJCC 6th and 7th Edition Staging For Colon Cancer: Tumor-Node-Metastasis Staging Systems

TNM Stage		
Stage	AJCC-6 ⁵	AJCC-7 ⁴
I	T1N0M0	T1N0M0
	T2N0M0	T2N0M0
IIA	T3N0M0	T3N0M0
IIB	T4N0M0	T4aN0M0
IIC	n/a	T4bN0M0 [*]
IIIA	T1N1M0	T1N1/1cM0
	T2N1M0	T2N1/1cM0
	n/a	T1N2aM0 [†]
IIIB	T3N1M0	T3N1M0
	T4N1M0	T4bN1M0
	n/a	T1N2bM0 [†]
	n/a	T2N2a-bM0 [†]
	n/a	T3N2aM0 [†]
IIIC	T1N2M0	T4aN2aM0
	T2N2M0	T3N2bM0
	T3N2M0	T4aN2bM0
	T4N2M0	T4bN2M0
	n/a	T4bN1M0 [*]
IVA	Any T Any N M1	Any T Any N M1a
IVB	n/a	Any T Any N M1b [*]

* Staging upgrades.

[†] Staging downgrades.

Table 2

Two-Way Classification Table of Staging Based on AJCC-6 vs AJCC-7 Staging Systems for Patients with Stages I-III Colon Cancer from 1988-2008 (n = 157,588)

AJCC-6	AJCC-7							
	I	IIA	IIB	IIC	IIIA	IIIB	IIIC	Total
I	36,421	0	0	0	0	0	0	36,421
IIA	0	55,633	0	0	0	0	0	55,633
IIB	0	0	6,276	4,614	0	0	0	10,890
IIC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
IIIA	0	0	0	0	4,995	0	0	4,995
IIIB	0	0	0	0	0	30,465	0	30,465
IIIC	0	0	0	0	60	6,145	12,979	19,184
Total	36,421	55,633	6,276	4,614	5,055	36,610	12,979	157,588

Table 3

Demographic and Clinical Characteristics of Patients with Stages I-III Colon Cancer from 1988-2008 (n = 157,588)

	< 12 LNs Examined		12 LNs Examined		Total	
	n	%	n	%	n	%
Sex						
Female	38,908	52.5%	45,427	54.4%	84,335	53.5%
Male	35,187	47.5%	38,066	45.6%	73,253	46.5%
Age, y						
<= 20	10	< 0.1%	77	< 0.1%	87	0.1%
21-40	1,103	1.5%	2,992	3.6%	4,095	2.6%
41-60	14,511	19.6%	20,487	24.5%	34,998	22.2%
61-80	40,859	55.4%	42,768	51.2%	83,627	53.1%
> 80	17,612	23.8%	17,169	20.6%	34,781	22.1%
Race						
White	61,279	82.7%	68,374	81.9%	129,653	82.3%
Black	6,963	9.4%	8,089	9.7%	15,052	9.6%
Asian/Other	5,675	7.7%	6,807	8.2%	12,482	7.9%
Unknown	178	0.2%	223	0.3%	401	0.3%
Primary site						
Right colon	30,367	41%	48,015	57.51%	78,382	49.7%
Transverse colon	6,958	9.4%	7,285	8.73%	14,243	9%
Left colon	35,772	48.3%	26,887	32.20%	62,659	39.8%
Colon, NOS	998	1.4%	1,306	1.56%	2,304	1.5%
Geographic region						
East	20,788	28.1%	27,297	32.7%	48,085	30.5%
Northern Plains	13,447	18.2%	12,827	15.4%	26,274	16.7%
Pacific Coast/Alaska	35,954	48.5%	38,805	46.5%	74,759	47.4%
Southwest	3,906	5.3%	4,564	5.5%	8,470	5.4%
No. of LNs examined						
1-11	74,095	100%	n/a	n/a	74,095	47%
12	n/a	n/a	83,493	100%	83,493	53%
No. of positive LNs						
0	51,184	69.1%	51,760	62%	102,944	65%
1-3	16,966	22.9%	18,494	22.2%	35,460	22.5%

	< 12 LNs Examined		12 LNs Examined		Total	
	n	%	n	%	n	%
4-6	4,440	6%	6,513	7.8%	10,953	7%
>=7	1,505	2.3%	6,726	8.1%	8,231	5.2%
Grade						
Well-differentiated	7,794	10.5%	6,940	8.3%	14,734	9.4%
Moderately-differentiated	50,175	67.7%	55,405	66.4%	105,580	67%
Poorly-differentiated	11,421	15.4%	16,906	20.3%	28,327	18%
Undifferentiated/anaplastic	520	0.7%	932	1.1%	1,452	0.9%
Unknown	4,185	5.7%	3,310	4%	7,495	4.8%
Tumor size, cm						
< 5	43,002	58%	40,122	48.1%	83,124	52.8%
5-10	20,202	27.3%	34,214	41%	54,416	34.5%
>10	1,137	1.5%	2,560	3.1%	3,697	2.35%
Unknown	9,754	13.2%	6,597	7.90%	16,351	10.4%
Radiation given						
None	41,823	97%	81,103	97.1%	122,926	78%
Given	1,466	2%	1,601	1.9%	3,067	2%
Unknown	806	1.1%	789	0.9%	1,595	1%
AJCC-6						
I	20,829	28.1%	15,592	18.7%	36,421	23.1%
IIA	24,989	33.7%	30,644	36.7%	55,633	35.3%
IIB	5,366	7.2%	5,524	6.6%	10,890	6.9%
IIIA	2,687	3.6%	2,308	2.8%	4,995	3.2%
IIIB	14,279	19.3%	16,186	19.4%	30,465	19.3%
IIIC	5,945	8%	13,239	15.9%	19,184	12.2%
AJCC-7						
I	20,829	28.1%	15,592	18.7%	36,421	23.1%
IIA	24,989	33.7%	30,644	36.7%	55,633	35.3%
IIB	3,204	4.3%	3,072	3.7%	6,276	4%
IIC	2,162	2.9%	2,452	2.9%	4,614	2.9%
IIIA	2,719	3.7%	2,336	2.8%	5,055	3.2%
IIIB	17,087	23%	19,523	23.4%	36,610	23.2%
IIIC	3,105	4.2%	9,874	11.8%	12,979	8.2%

LNs, lymph nodes.