

Rectal Cancer

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Rectal Cancer - Redefining Clinical Stage Based on Outcomes Data

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Background: The sixth edition (ed) of the American Joint Committee on Cancer (AJCC) staging subdivided stage II into IIA (T3N0)/IIB(T4N0), and stage III into IIIA (T1-2N1M0), IIIB(T3-4N1M0), IIIC (anyTN2M0). Subsequent analyses supported revised substaging of stage III due to improved survival with T1-2N2 vs. T3-4N2 cancers, and survival in T4N1 lesions more similar to T3-4N2 than T3N1 (Rectal Cancer Pooled Analysis, Tables 1-2). Before making such changes in the AJCC seventh edition, the AJCC Hindgut Taskforce (HTF) sought validation in a population-based dataset that depth of invasion interacts with nodal status to affect survival.

Table 1. Impact of NT Category on Survival and Relapse, Rectal Cancer Pooled Analysis #1

| Category | Overall Survival* | | | Disease-Free Survival* | | | Local Recurrence [†] | | Distant Metastasis [†] | |
|---------------|-------------------|----------|---------|------------------------|----------|---------|-------------------------------|---------|---------------------------------|---------|
| | No. | 5-yr (%) | p-value | No. | 5-yr (%) | p-value | 5-yr (%) | p-value | 5-yr (%) | p-value |
| N0T3 | 668 | 74 | 0.046 | 664 | 66 | 0.05 | 8 | 0.04 | 19 | .04 |
| T4 | 95 | 65 | | 95 | 54 | | 15 | | 28 | |
| N1T1-2 | 225 | 81 | <0.001 | 225 | 74 | <0.001 | 6 | 0.002 | 15 | <.001 |
| T3 | 544 | 61 | | 536 | 50 | | 11 | | 34 | |
| T4 | 59 | 33 | | 59 | 30 | | 22 | | 39 | |
| N2T1-2 | 180 | 69 | <0.001 | 180 | 62 | <0.001 | 8 | 0.14 | 26 | <.001 |
| T3 | 663 | 48 | | 659 | 39 | | 15 | | 45 | |
| T4 | 84 | 38 | | 84 | 30 | | 19 | | 50 | |

From Gunderson LL, Sargent DJ, Tepper JE, et al. *Int J Rad Onc Biol Phys* 54:386-396, 2002.

* = Unadjusted Kaplan-Meier estimates; [†] = cumulative incidence rates.

Table 2. Rectal Pooled Analysis - Survival and Relapse Rates by Risk for Relapse

| Risk for Relapse | Stage | | Survival, 5yr* | | Relapse [†] | | TNM 6 th Ed. |
|------------------|-------|-----|----------------|-----|----------------------|---------|-------------------------|
| | TN | MAC | OS | DFS | Local | Distant | |
| Low | T1N0 | A | ~90 | ~90 | ≤ 5 | ~10 | I |

| | | | | | | | |
|------------------------|--------|----|-----|-----|-----|-----|------|
| | T2N0 | B1 | ~90 | ~90 | ≤ 5 | ~10 | - |
| Intermediate | T1-2N1 | C1 | 81 | 74 | 6 | 15 | IIIA |
| | T3N0 | B2 | 74 | 66 | 8 | 19 | IIA |
| Moderately High | T1-2N2 | C1 | 69 | 62 | 8 | 26 | IIIC |
| | T4N0 | B3 | 65 | 54 | 15 | 28 | IIB |
| | T3N1 | C2 | 61 | 50 | 11 | 34 | IIIB |
| High | T3N2 | C2 | 48 | 39 | 15 | 45 | IIIC |
| | T4N1 | C3 | 33 | 30 | 22 | 39 | IIIB |
| | T4N2 | C3 | 38 | 30 | 19 | 50 | IIIC |

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* = Unadjusted Kaplan-Meier estimates; † = cumulative incidence rates.

Methods: Surveillance, Epidemiology, and End Results (SEER) population-based data from January 1, 1992, to December 2004 for 35,829 rectal and 109,953 colon cancer patients were compared with Cooperative Group rectal data on 2,551 patients (Rectal Pooled Analysis). 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) vs. "tumors that invade or are adherent to adjacent organs or structures" (T4b). N1 and N2 were stratified by number of N+: N1a/N1b (1 vs. 2-3), N2a/N2b (4-6 vs. ≥7). Five-year observed survival (≈ overall survival, OS) and relative survival (survival corrected by age-related morbidity) were obtained for each TN category.

Results: Survival outcomes for rectal and colon cancer were very similar by TN category of disease (Tables 3-4). T1-2N2 cancers have better prognosis than T3-4N2, and T4bN1 lesions have prognosis more akin to T4N2 in both rectal and colon datasets. Prognosis for T4a lesions (tumor penetrates visceral peritoneum) is better than T4b (tumor directly invades or is adherent to other organs or structures) by N category (shown in Table 4 for N0-N2). The number of N+ affects prognosis (Table 3). N1a(1N+) has a 5% -10% better 5-year OS than N1b(2-3N+); N2a(4-6N+) ~12% better 5-year OS than N2b(≥7N+) by T category.

Table 3. Rectal SEER Analysis: 5-yr Observed Survival (OS) by TN Category

| Category TN | Pt. No. | 5-yr OS (%) | SE | TNM Stg 6th Ed. | Proposed TNM Stg 7th Ed. |
|------------------------------|----------------|------------------------------|-----------|---|--|
| T1N0 | 3,348 | 81.4 | 0.8 | I | I |
| T2N0 | 6,613 | 75.7 | 0.6 | I | I |
| T3N0 | 10,615 | 64.0 | 0.5 | IIA | IIA |
| T4aN0 | 818 | 55.7 | 1.9 | IIB | IIB |

| | | | | | |
|---------------|-------|------|------|------|-------------|
| T4bN0 | 769 | 44.7 | 2.1 | IIB | IIC |
| T1-2N1 | 2,008 | 72.1 | 1.2 | IIIA | IIIA |
| T1N2a | 62 | 73.8 | 6.2 | IIIC | IIIA |
| T2N2a^ | 302 | 58.2 | 3.4 | IIIC | IIIB |
| T3N1a | 2,758 | 55.4 | 1.1 | IIIB | IIIB |
| T4aN1a | 218 | 53.2 | 3.7 | IIIB | IIIB |
| T3N1b | 3,029 | 49.7 | 1.1 | IIIB | IIIB |
| T1N2b | 24 | 53.2 | 13.0 | IIIC | IIIB |
| T4aN2a* | 199 | 44.3 | 4.0 | IIIC | IIIC |
| T4aN1b | 262 | 43.9 | 3.4 | IIIB | IIIB |
| T3N2a | 1,964 | 42.5 | 1.3 | IIIC | IIIB |
| T2N2b | 120 | 41.7 | 5.0 | IIIC | IIIB |
| T3N2b | 1,791 | 32.0 | 1.3 | IIIC | IIIC |
| T4aN2b | 198 | 24.5 | 3.4 | IIIC | IIIC |
| T4bN1 | 423 | 24.3 | 2.5 | IIIB | IIIC |
| T4bN2a | 156 | 18.5 | 3.6 | IIIC | IIIC |
| T4bN2b | 152 | 12.3 | 3.5 | IIIC | IIIC |

^ T2N2a rectal lesions did worse than colon T2N2a lesions, both categories placed in stage IIIB.

*T4aN2a rectal lesions did better than colon T4aN2a lesions, both categories placed in stage IIIC.

** Proposed change in sub-staging (**bold**) based on expanded outcomes in SEER data analyses.

Table 4. Impact of TN Category on Survival, Rectal Cancer Pooled Analysis/SEER Rectal and Colon Cancer Analyses

| TN Category | Rectal Pooled 5-yr OS | | TNM 6 th Ed. | Proposed TNM 7 th Ed. | SEER, Rectal 5-yr Observed SR | | | SEER, Colon 5-yr Observed SR | | |
|-----------------|-----------------------|----|-------------------------|----------------------------------|-------------------------------|------|------|------------------------------|------|------|
| | Pt No. | % | | | Pt No. | % | SE | Pt No. | % | SE |
| T1-2N0 | -- | -- | I | I | 9,961 | 77.6 | 0.5% | 23,861 | 76.3 | 0.3% |
| T3N0 | 668 | 74 | IIA | IIA | 10,615 | 64.0 | 0.5 | 40,338 | 66.7 | 0.3 |
| T4N0** | 95 | 65 | IIB | T4a, IIB | 818 | 55.7 | 1.9 | 5,020 | 60.6 | 0.8 |
| | | | | T4b, IIC | 769 | 44.7 | 2.1 | 3,088 | 45.7 | 1.0 |
| T1-2N1 | 225 | 81 | IIIA | IIIA | 2,008 | 72.1 | 1.2 | 3,134 | 71.1 | 1.0 |
| T1-2N2** | 180 | 69 | IIIC | IIIA/IIIB* | 508 | 56.1 | 2.6 | 499 | 61.5 | 2.6 |
| T3N1 | 544 | 61 | IIIB | IIIB | 5,787 | 52.4 | 0.8 | 17,866 | 54.9 | 0.4 |
| T4N1** | 59 | 33 | IIIB | T4a, IIIB | 480 | 48.2 | 2.5 | 2,771 | 47.0 | 1.1 |
| | | | | T4b, IIIC | 423 | 24.3 | 2.5 | 1,774 | 27.9 | 1.2 |
| T3N2** | 663 | 48 | IIIC | IIIB/IIIC^ | 3,755 | 37.5 | 0.9 | 8,566 | 38.1 | 0.6 |
| T4N2 | 84 | 38 | IIIC | T4a, IIIC | 397 | 34.3 | 2.7 | 1,653 | 26.6 | 1.2 |
| | | | | T4b, IIIC | 308 | 15.6 | 2.5 | 1,383 | 15.8 | 1.1 |

*IIIA-T1N2a; IIIB-T2N2a, T1-2N2b. ^IIIB-T3N2a; IIIC-T3N2b. ** Proposed change in sub-staging (**bold**) based on outcomes.

Conclusions: The SEER population-based outcomes analysis validates the Rectal Cancer Pooled Analysis data and supports the shift of T1-2N2 cancers from IIIC to IIIA/IIIB and T4bN1 from IIIB to IIIC (Tables 3-4). It also supports subdividing IIB into IIB(T4aN0) or IIC(T4bN0) and shifting more favorable TN2 categories from IIIC to IIIA(T1N2a) or IIIB (T1N2b, T2N2a-b, T3N2a, T4aN2a). Outcomes by TN category suggest a complex biologic interaction between depth of primary invasion and nodal metastases. Survival

outcomes for rectal and colon cancer by TN category of disease were more similar than expected.