

20. Colon and Rectum

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Emerging Prognostic Factors for Clinical Care

Immunoscore and Immune Response Markers

Galon et al.^{1,2} reported that measuring the lymphoid infiltrate of tumors and comparing the numbers of CD4⁺ and CD8⁺ T cells and other lymphoid subsets in the advancing edge and center of the tumor was strongly prognostic in colon cancers and stronger than TNM staging. Limitations of this provocative work, however, include failure to identify the MSI subset and the use of retrospective case series. Importantly, a consortium is seeking to standardize this immunohistochemical analysis using primary colorectal carcinomas.^{3,4} These results are forthcoming and will be standardized within the next few years; if this method is validated and it outperforms MSI, it has the potential for inclusion in TNM.

Other important immune response markers are the immune checkpoint proteins and inhibitors PD-1 and PD-L1, CTLA4, and IDO. These molecules also are targets for specific therapies. Recent data suggest that blocking these checkpoint inhibitors may enhance endogenous immune responses to cancer, leading to enhanced survival.² Finally, it is unclear what role cytokines and other soluble factors released by host cells as well as tumors have in the tumor–host relationship. Current research may well identify a few as being sufficiently critical to be modifiers of the TNM stage groups.

Gene Expression Alterations

While risk assessment tools may be useful, current medical decision-making is increasingly being placed on the molecular variants that drive cancers, gene expression alterations caused by those variants or the activation of specific pathways within a patient's cancer since all of these may be targets for therapy. It will take time for the utility of these molecular classifiers in colorectal carcinoma to reach the level of evidence necessary for FDA approval or for inclusion within guidelines but healthcare professionals should know that a 12-gene signature is now at least level II evidence as a prognostic factor in stage II-III colon or rectal carcinoma.⁵⁻⁸

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Risk Assessment Models

Prognostic models will continue to play an important role in 21st century medicine for several reasons.⁹ First, by identifying which factors predict outcomes, clinicians gain insight into the biology and natural history of the disease. Second, treatment strategies may be optimized based on the outcome risks of the individual patient. Third, because of the heterogeneity of disease in most cancers, prognostic models will play a critical role in the design, conduct, and analysis of clinical trials in oncology.⁹ If developed and validated appropriately, these models will become part of routine patient care, decision making, and trial design and conduct.

The AJCC Precision Medicine Core (PMC) developed and published criteria for critical evaluation of prognostic tool quality,¹⁰ which are presented and discussed in Chapter 4. Although developed independently by the PMC, the AJCC quality criteria corresponded fully to the recently developed Cochrane CHARMS tool for critical appraisal in systematic reviews of prediction modeling studies.¹¹

Existing prognostic models for colon and rectum cancer meeting all the AJCC inclusion/exclusion criteria and meriting AJCC endorsement are presented in this section. A full list of the evaluated models and their adherence to the quality criteria is available at www.cancerstaging.org.

The PMC performed a systematic search of published literature for prognostic models/tools in colon and rectum cancer from January 2011 to December 2015. The search strategy is provided in Chapter 4. The PMC defined *prognostic model* as a multivariable model in which factors predict a clinical outcome that will occur in the future. Each tool identified was compared against the quality criteria developed by the PMC as guidelines for AJCC recommendation for prognostication models (see Chapter 4).

Twenty-nine prognostication tools¹²⁻⁴⁰ for colon or colorectal cancer were identified: 14 for patients with resected liver metastases,^{16-19,22,25-30,36,40} two for patients with unresectable liver metastases,^{12,34} four in the adjuvant (Stage I/II/III) setting,^{14,32,38,39} seven for patients with metastatic disease,^{13,15,21,23,24,31,33} one for patients with resected pulmonary metastases,²⁰ one for patients with locally advanced rectal cancer,³⁷ and one across all disease stages.³⁵

Of the 14 models for patients with resected liver metastases, none met all the predefined criteria. Most were excluded because their development used single-institution series lacking sufficient external validation,^{17,18,22,26-29} made predictions generated from data not reflecting current clinical standards of treatment,^{16,19,20,25,30,40} or lacked external validation.^{22,36} Both tools for patients with unresectable liver metastases were excluded because they were from single-institution series and were too small to be reliably generalizable.^{12,34} Of the tools for patients with metastatic disease, Elias et al. (2014)¹⁵ lacked external validation; Peng et al. (2014)³¹ and Shitara et al. (2011)³³ were from a single institution or the

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patient set was too small to be generalizable; and Chibaudel et al. (2011),¹³ Kato et al. (2005),²¹ Kobayashi et al. (2013),²³ and Kohne et al. (2002)²⁴ were felt to be based on datasets not reflective of current treatment paradigms for patients with metastatic disease (although the Kohne tool²⁴ was of very high quality).

Among the four models for patients in the adjuvant setting, two met all inclusion criteria.^{32,38} We note that the Numeracy model¹⁴ was excluded because it was replaced by ACCENT.³² Weiser et al. (2008)³⁹ was excluded because it predicted only recurrence, although it met all other criteria. The model in Stojadinovic et al. (2013)³⁵ was considered very promising; however, it lacked sufficient detail for it to be implemented in practice. The final model, which predicted outcomes in patients with locally advanced rectal cancer,²² met all criteria and is endorsed by the committee for this somewhat limited treatment setting.

Twenty-nine models for prognostication in colon or colorectal cancer were identified, but only three models, two for adjuvant disease^{32,38} and one for local advanced rectal cancer,³⁷ met all predefined AJCC inclusion and exclusion criteria and therefore are endorsed by the AJCC.^{32,37,38} Table 20.3 presents the models meeting the AJCC quality criteria. The two models in the adjuvant setting were developed using very different datasets. Renfro et al. (2014)³² was based on a large collection of completed randomized clinical trials, whereas Weiser et al. (2011)³⁸ was built using SEER data. However, both models were externally validated. The third endorsed tool, by Valentini et al. (2011)³⁷ in locally advanced rectal cancer, also was developed using data from completed clinical trials.

In the interest of precision medicine and informed individualized care for patients, the AJCC supports the appropriate use of both high-value patient classifiers (prognostic factors) and prognostication tools (risk calculators). Both are valuable. Prognostication tools (i.e., risk calculators) provide individualized probability estimates, whereas patient classifiers group patients into ordered risk strata (either directly or based on cut-points for individual probability estimates). The TNM staging system is an example of such a classification tool, yielding at the least granular level ordered classes (I, II, III, IV) of increasingly poor prognosis. Strata based on prognostic factors (e.g., a gene signature) are other examples.

While such stratification is useful, it also limited by the number of categories that are manageable, by the complexity of combining information from multiple predictors to form discrete ordered categories in a transparent manner, and by the inherent variability of prognosis of patients in a given risk class. Risk calculators, in contrast, are designed to deliver a more precise estimate of outcome for an individual patient through computational integration of a variety of patient-specific data elements.

TABLE 20.3. Prognostic tools for colon and rectum cancer meeting all AJCC quality criteria

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Approved prognostic tool	Web address	Factors Included in the model
ACCENT-based web calculators to predict recurrence and overall survival in Stage III colon cancer ³²	http://www.mayoclinic.org/medical-professionals/cancer-prediction-tools/colon-cancer	Age, sex, race, BMI, performance status (PS), T category, lymph node ratio, grade, treatment group, location
Predicting survival after curative colectomy for cancer: individualizing colon cancer staging ³⁸	https://www.mskcc.org/nomograms/colorectal/overall-survival-probability	T category, N category, age, sex, tumor differentiation/grade, number of regional lymph nodes evaluated, number of regional lymph nodes positive
Nomograms predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials ³⁷	http://www.predictcancer.org/Main.php?page=RectumFollowUpModel	Age, sex, T category, radiotherapy dose, concomitant chemotherapy, surgical procedure, pT category, pN category, adjuvant chemotherapy

Recommendations for Clinical Trial Stratification

The Colorectal Committee of the Lower GI Expert Panel recommends that all T, N, and M categories, as well as the factors required and recommended for collection, be included as appropriate for clinical trials.

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