AJCC 8th edition update*: Colorectal cancer

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* and other prognostic controversies
Chapter 20

- Colorectal adenocarcinoma
- High grade neuroendocrine carcinoma
- SCC colon and rectum
8th edition updates and corrections

- https://cancerstaging.org/references-tools/deskreferences/Pages/8EUpdates.aspx

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**8th Edition Updates and Corrections**

When the AJCC embarked on updating the AJCC Cancer Staging Manual, we knew that we would have to think beyond the book, with an eye toward continuously improving content throughout the life of the edition.

The *delay of implementation to January 1, 2018* has given AJCC an opportunity to work with the surveillance community, the pathology community, and clinical decision support software developers in ways we never have before. In the era of electronic decision making, the level of scrutiny is higher, we are learning more about how the content is applied in different use cases beyond the human reader. Collaborating with these groups in real time has allowed us to take an extra critical look at our content and make improvements and clarifications that will help all audiences.

This highly analytical effort has resulted in a greater number of updates and errata than in past editions, and we are committed to communicating them transparently.

This site contains important updates and errata identified in the first printing of the AJCC Cancer Staging Manual, 8th Edition, and are effective for hard copy manuals purchased from September 2016 to present. This list does not include typographical errors. Updates and errata are tracked by staff and updated weekly. If you have identified any issues not listed here, please email laurameyer@facs.org.

To make this list more useful, we have divided the updates and errata into four levels of significance:

1. **Critical Changes.** Change is critical for accurate staging. Includes changes to TNM categories, criteria, or prognostic stage groups.
2. **Histology/Topography.** Corrections and additions made to histology or topography codes.
3. **Clarification.** Clarification of concepts in text or definitions that does not affect staging.
4. **Omission.** Error of omission that does not affect staging.
Summary of changes

- pT4a – definition clarified
- Definition of tumour deposit
- Definition of distant metastasis
- Additional factors for clinical care
  - LVI – reintroduced L and V
  - MSI – clarified importance as predictive and prognostic factor
  - *KRAS, NRAS* and *BRAF* mutations – identified importance as predictive and prognostic factors
pT4

• Tumours involving serosal surface (visceral peritoneum) (pT4a)
• Tumours directly invading adjacent organs or structures (pT4b)

• Not applicable to portions of the colorectum that are not peritonealised
  – posterior ascending colon
  – posterior descending colon
  – lower portion of rectum
pT4a – definition clarified

- Involvement of serosal surface by direct tumour extension
pT4a

- Tumours with perforation with tumour cells continuous with serosal surface through inflammation
pT4a - controversies

• Tumours <1mm from serosal surface with a serosal reaction
  – unclear? Higher risk of peritoneal relapse
  – Levels, further blocks → if serosa not involved then pT3

• Use of elastin stain?
Orcein = Incomplete elastic lamina
pT4a – controversies

- Acellular mucin at or close to serosal surface
  - Not considered pT4a
pT4a – clinical significance

• Prognosis

• Peritoneal recurrence

• Choice of therapy
  – NCCN guidelines – high risk features in stage II
    • Likely chemotherapy
    • Possible HIPEC (hyperthermic intraperitoneal chemotherapy)
pN: Isolated tumour cells/micrometastasis – definition clarified

• Are they significant? - depends on definition – conflicting data on outcome of ITC

• ITC: individual tumour cells in subcapsular or marginal sinus <0.2mm = pN0

• Micrometastasis: 0.2-2mm = pN1

• Do not need to use N0 (i+) or N1 (mic)
Deposit = 0.1mm = pN0
Tumour deposits – criteria redefined

- discrete tumour nodules within lymph drainage area of primary carcinoma, without identifiable lymph node, vascular or neural structure
- Use pT1c if negative regional lymph nodes
- Shape, contour and size not considered
- No minimum size or distance from invasive front
- Location: subserosa, mesentery, nonperitonealised pericolic, perirectal/ mesorectal tissue
Tumour deposits changes

• If vessel wall or remnant identified = LVI
  – small vessel
  – venous invasion (tumour within endothelial lined space containing red cells or surrounded by smooth muscle) (elastic stain may be helpful)
    • Intramural = submucosa or m. propria
    • Extramural = beyond m. propria

• If nerve identifiable = PNI
Extramural venous invasion
Extramural artery

Extramural vein occluded by tumour
TD- due to perineural spread
Tumour deposits - controversies

• TD can show small focus of LVI or PNI? What to do

• If neoadjuvant therapy – “important for the pathologist to assess whether tumour nodules represent tumour deposits...or discontinuous eradication of the original tumour....” (pg 261)
pM

- Addition of pM1c - peritoneal carcinomatosis
- 1-4% of cases
- Prognosis worse than visceral metastasis
Molecular

- MSI
- \textit{KRAS, NRAS}
- \textit{BRAF}
*and other prognostic controversies

• Tumour grading
• Grading mucinous adenocarcinomas
• Tumour budding
• Acellular mucin in lymph nodes (and elsewhere)- non-neoadjuvant setting
• Circumferential resection margin
• Post neoadjuvant Rx – ypT
Serosal surfaces, mucin pools, and deposits, Oh my: challenges in staging colorectal carcinoma

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Colorectal carcinoma is the third most common cancer in the United States. Proper and standardized pathologic staging is vital for prognostic assessment and impacts therapeutic decisions. The TNM staging system was developed by the American Joint Committee on Cancer (AJCC) to be a data-driven, evidence-based staging system providing an accurate prediction of outcome. The AJCC 7th edition (2010) included several changes clarifying some issues and leading to new controversies. We aim to address selected challenging issues in tumor staging, neoadjuvant treatment effects in rectal cancer, and definition of lymph node vs tumor deposit. Serosal involvement in colorectal cancer is staged as T4, which is associated with decreased survival and may impact additional therapy decisions. Although careful sampling and sectioning are helpful, challenges remain in interpretation of tumor within 1 mm of serosal surface with a reaction. Elastic in situ as a surrogate marker for serosal invasion has been studied, but its usefulness remains unclear. Some unique issues in rectal cancer include the presence of seroma in proximal but not in distal tumors and post neoadjuvant effects. Tumor should be staged based on tumor cells rather than cellular mucin pools. Additionally, tumor response should be graded only in primary tumor but not in lymph nodes or metastatic sites. The distinction between tumor deposits and lymph nodes has been modified in AJCC TNM from using size in the 5th edition, to only features of residual lymph node architecture in the 7th edition. Interobserver variability remains but tumor deposits should be documented when present. The number of deposits should not be added to the total number of positive lymph nodes, and the T4c designation should only be used in cases without any positive lymph nodes. Future clarification will likely evolve as more data become available.


Colorectal carcinoma (CRC) is the third most common cancer in the United States. According to National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) Fact Sheets, it is estimated that there will be ~132,000 new cases and greater than 50,000 deaths in 2014 in the United States. Pathologic assessment is the gold standard for determining local extent of disease, and is vital for prognosis and decisions regarding need for adjuvant therapy and resection to clinical trials. The strongest predictor of survival is pathologic staging. Other important morphologic prognostic factors include tumor type and margin assessment. Stage-independent factors include lymphovascular and perineural invasion, tumor border configuration, tumor budding, host lymphoid response, and morphologic features suggestive of micrometastatic instability.

A number of challenges and caveats exist in the pathologic staging and reporting of CRC. In this article, we focus on selected issues in tumor T staging, neoadjuvant treatment effects in rectal cancer, and the definition of lymph node vs tumor deposits. The TNM staging system was developed by the American Joint Committee on Cancer (AJCC) to be a data-driven, evidence-based staging system providing an accurate prediction of outcome. As new evidence is acquired, frequent updating of staging is essential. The AJCC Cancer Staging Manual 7th edition, released in 2010, included several changes clarifying some issues and leading to new controversies.

The College of American Pathologists (CAP)
Tumour grade – how much is enough?? ﾅ_(_ツ)_/¬

- Important prognostic parameter
- No consensus on grading system
  - 2, 3 or 4 tiered
  - Significant interobserver variability
WHO histological classification

• **Well differentiated** adenocarcinoma shows glandular structures in >95% of the tumour.

• **Moderately differentiated** adenocarcinoma show 50–95% glandular structures.

• **Poorly differentiated** adenocarcinoma show 0-49% glandular structures.

• Low grade= well + moderate

• High grade = poor/ undifferentiated
TNM

- Grade 1 = well
- Grade 2 = moderate
- Grade 3 = poor
- Grade 4 = undifferentiated
How to grade?

• Difference in grade between superficial and invasive front
  – ? % gland formation
  – ? Worst pattern (regardless of amount)
Should the grading of colorectal adenocarcinoma include microsatellite instability status?

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Summary: Adenocarcinomas of the colon and rectum are graded using a 3-tiered system into histologic low-grade and high-grade tumors based on the proportion of gland formation. The current grading system does not apply to subsets of carcinoma associated with a high frequency of microsatellite instability (MSI), such as mucinous and metastatic carcinomas. We investigated the combined effect of histologic grade and MSI status on survival for 716 patients with colorectal carcinomas (49% female; mean age at diagnosis 61.2 years). The proportion of high-grade adenocarcinoma was 15%, MSI was observed in 29 adenocarcinomas (9%), with higher frequency in high-grade tumors compared with low-grade tumors (29% versus 6%, P < 0.01). Using Cox regression models, adjusting for sex and age at diagnosis and stratifying by the American Joint Committee on Cancer stage, microsatellite stable (MSS) high-grade tumors were associated with a hazard ratio of 2.08 (95% confidence interval [CI], 1.36-3.17) and 2.54 (95% CI, 1.56-4.17), respectively, both P < 0.01. A new grading system separating microsatellites into low grade (all histologic low grade and

YES! (for high grade)
Grading mucinous adenocarcinomas
Should it involve MSI?

MISMATCH REPAIR DEFICIENCY AS A PROGNOSTIC FACTOR IN MUCINOUS COLORECTAL CANCER

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There is some controversy about pathological grading of mucinous gastrointestinal adenocarcinoma, defined as colorectal cancer demonstrating at least 50% mucinous differentiation. Under the WHO 2010 classification mucinous colorectal cancer was considered high grade. However, under the current WHO 2010 classification mucinous colorectal cancer is considered low grade, whereas intestinal-type adenocarcinomas are still graded. This could lead to under staging of patients with mucinous colorectal cancer in a large unselected cohort of patients undergoing surgery in our institute from 2000 to 2011. There were 2009 patients in the cohort, of which 264 (13.1%) were mucinous (MSH1/MSH6) and 1745 (86.9%) were intestinal (MSH2/MSH6). The proportion of high-grade mucinous colorectal cancer was similar to that of non-mucinous low-grade colorectal cancer (75 vs 67%, P = 0.001) and mucinous colorectal cancer was slightly better than that of non-mucinous high-grade patients (78 vs 57%, P = 0.007), but significantly more than that of non-mucinous low-grade colorectal cancer (57 vs 47%, P = 0.046), in contrast to the current WHO 2010 classification. Some expression analysis and conventional histological grading based on a grade of differentiation may result in misclassification of gastrointestinal adenocarcinoma. Interestingly, patients with mucinous colorectal cancer are currently overclassifying, however, grading based exclusively on MSH1/MSH6 status may be overly simplistic as mucinous colorectal cancer is a heterogeneous group of mucinous colorectal cancers.

Mucinous colorectal carcinoma is usually defined as colorectal carcinoma in which extracellular mucin accounts for greater than 50% of the tumour volume. Mucinous colorectal carcinomas are frequently associated with extracellular mucinous differentiation and an MMR-D phenotype was described in 1988. In fact, between 10% (5) and 30% (7) of mucinous colorectal carcinomas have been reported. In our study, MMR-D was observed in 30% of cases.

MUCIN EXPRESSION IN GASTROINTESTINAL TRACT CARCINOMA: A PROGNOSTIC FACTOR IN MUCINOUS COLONIC CANCER

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Tumour budding in CRC

- Independent prognostic factor
  - High risk in stage II
- Not included in AJCC 8\textsuperscript{th} ed, NCCN guidelines
- Recommended in some structured reports inc RCPA, UK
Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

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Tumour budding: recommendations

- Assess on H&E
- Single cell or cell cluster \(\leq 4\) tumour cells
- Assess in one hotspot at the invasive tumour front
- Budding count + 3 tier system (bud count/0.785 mm\(^2\) field)
  - Bd1 (low) 0-4 buds
  - Bd2 (intermediate) 5-9 buds
  - Bd3 (high) \(\geq 10\) buds
Acellular mucin in lymph nodes – what does it mean? 

• Post neoadjuvant – no influence on local recurrence

• Controversial in the non-neoadjuvant setting
  – LN with mucin categorised as pN1 when malignant cells identified
  – How does mucin reach LN without neoplastic epithelium?
  – Does it reflect overwhelming host response?
  – Is it “mucin spillage” into lymphatics?
• Multiple levels

• Shepherd N *Histopathol* 2016; 69: 522-8 regard this as metastatic disease with designation pN1 (acellular mucin)

• Rare, may not be able to gather enough data to provide information on staging
Acellular mucin elsewhere......?
Circumferential resection margins (CRM)

- Distance from deepest point of **tumour invasion** and retroperitoneal or mesenteric resection margin
- One of most important determinants of local control in colon and rectal cancer
- 0-1mm= high risk of recurrence and decreased survival
- What about lymph nodes near the CRM?
• “Any lymph nodes lying close to the non-peritonealised resection margin need to be sampled in continuity with that margin. If there is tumour in any of the lymph nodes then it is the measurement from the involved lymph node to the nonperitonealised resection margin, if it is closer, rather than from the primary tumour, that is important. This is also true for any isolated tumour deposit in the perirectal or pericolic fat.”
• Example of TD near CRM
• What if a positive lymph node is transected at the CRM but the location of the tumour deposit in the node is >1mm from the margin?
Post neoadjuvant treatment ypT

- How to define “viable tumour cells”
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- Large mucin pool containing few viable tumour cells at one edge? Is the entire mucin pool regarded as viable tumour?
- How to stage when abundant mucin and few viable tumour cells- and mucin crosses boundaries for T staging?
Post CT/RT with one gland in a LN 1mm from the CRM - ? Is the gland viable ? what does this mean?
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