Update on staging colorectal carcinoma, the 8th edition AJCC
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General overview of staging

• Reason for uniform staging
• Requirements to use AJCC manual and/or CAP protocols
  – CAP accreditation
  – American college of surgeons program standards
• Differences between AJCC manual and CAP protocols
• Who decides what is in the AJCC manual and CAP protocols

When is staging required?

• Colon/rectal resection (segmental, partial, total, low anterior or AP resection)
  – For all carcinomas including small and large cell high grade NE carcinomas
  – Not for low grade NE tumors, sarcomas or lymphomas
• Not required for
  – Primary resection specimens with no residual cancer (e.g. following neoadjuvant therapy)
  – Polypectomies/excisional biopsies
  – Local submucosal (anal disc) excisions
  – Cytology specimens
Differences between AJCC and CAP protocols

- AJCC revised about every 7 years
- CAP revised more frequently
- Even for the 8th edition, some minor differences exist
  - AJCC list of histopathological type does not include several subtypes including micropapillary and serrated adenocarcinomas
  - Grading of specific subtypes (medullary, signet ring) are not directly addressed
  - Generally the CAP protocols seem more complete

Basic principles of staging

- TMN stages
- Global stage
- Required elements
- Optional elements

Issues with TNM staging

- TNM results in a global “stage” for a tumor but does not include all relevant prognostic information
  - Generally covered under “Additional factors recommended for clinical care”
- This can result in undertreatment (i.e. all Stage II colon carcinoma is not the same)
  - This has resulted in some unusual “staging” decisions, like N1c
Required elements

• Required by AJCC and CAP to be included in every report
  – Which implies general consensus on the clinical significance of these findings

Optional elements

• Used at the discretion or the pathologist or as driven by local clinical requests
• Some elements that most authorities consider prognostically important are not included as “required” elements, most notably tumor budding

pT-categories

Areas of controversy or 8th edition change in red

• pTX – primary tumor cannot be assessed
• pT0 – no evidence of primary tumor
• pTis – intramucosal carcinoma (so why is it still called “is”?)
• pT1 - invasion into submucosa
• pT2 – invasion into muscularis propria
• pT3 – invasion through muscularis propria
• pT4 – invasion into visceral peritoneum (pT4a) or adjacent structures (pT4b)
### pN-categories

- **pNX** – cannot be assessed
- **pN0** – no regional node metastases
- **pN0(i+)** – metastases <0.2 mm
- **pN1a** – one metastasis ≥ 0.2 mm
- **pN1b** – 2-3 metastases
- **pN1c** – non-nodal tumor deposits without identified LN metastases
- **pN2a** – 4 – 6 metastases
- **pN2b** – 7 or more metastases

### pM-categories

- **M0** – No distant metastases by imaging (not assigned by pathologist)
- **M1** – Metastasis to one or more distant site
  - **M1a** – metastasis to one site/organ without peritoneal involvement
  - **M1b** – metastases to two or more sites/organs without peritoneal involvement
  - **M1c** – peritoneal involvement regardless of other organ involvement

### Controversies and 8th edition changes

- **T-stage**
  - What constitutes invasion
  - Definition of pT4a
- **N-stage**
  - What to do with non-nodal tumor deposits
  - What to do with isolated tumor cells
- **Ancillary issues**
  - What to do with tumor budding
  - Grading non-conventional pattern carcinomas
  - Deletion of histological features suggesting microsatellite instability
  - Use of molecular markers
What constitutes invasion

- In the 6th and 7th edition of AJCC, invasion was defined by invasion into the submucosa
  - “Tis” tumor limited to lamina propria above muscularis mucosa (included both non-invasive high grade dysplasia and intramucosal invasion)
  - “T1” tumor invading through muscularis mucosa into submucosa
  - So, what to do with tumors into but not through the muscularis mucosa?

What is the significance of the MM in terms of invasion

- The existing dogma is that tumors that have not invaded through the MM do not have access to lymphatics and do not metastasize
- However, it is clear that lymphatics do exist in the lamina propria, especially in neoplastic polyps and cancers and lymph node metastases can occur

Into the MM
A not uncommon problem in polyps

- In neoplastic polyps, the MM is often splayed and thickened, making determination of invasion “through” the MM difficult
So...

- Tumors invading into the muscularis mucosa do have some capacity for lymph node metastasis
8th edition revision of definition of invasion

- In the 8th edition the definition of invasion and the difference between Tis and T1 has been clarified
  - High grade dysplasia is no longer considered Tis
  - Tis refers to intramucosal invasion and also invasion into but not through the muscularis mucosae
    - So why is it still called “is”????
  - T1 is defined by invasion into the submucosa
  - This distinction is probably more important in polyps with focal invasive carcinoma

T4a vs 4b

What are the issues?

- Which is worse, 4a or 4b?
- What constitutes peritoneal surface involvement
  - Including new definition for 8th edition

Definitions of T4a and T4b

- 6th edition
  - T4a: tumor invading adjacent organs directly
  - T4b: tumor involving the free peritoneal surface
- 7th and 8th edition (as well as the last CAP revision of the 6th edition)
  - T4a: tumor involving free peritoneal surface
  - T4b: tumor invading adjacent organs
Why the change?

• 6th edition decision based study by Shepard et al demonstrating worse prognosis for surface involvement than invasion of adjacent organs
  — Why? Perhaps because invasion of adjacent organs is confined disease and can be resected
• 7th and 8th edition decision based on large analysis of SEER data showing just the opposite
  — But, is SEER data really better just because the study is larger?
  — After all, there is no quality control for pathology in the SEER data, and the data analyzed was from 1992 – 2004, when different criteria were used for peritoneal involvement

What constitutes surface involvement anyway?

• 5th edition
  — Tumor on surface, ulceration of tumor on surface, and desmoplastic reaction to tumor involving surface
• 6th and 7th editions
  — Only tumor on surface or ulceration of tumor on surface
Not T4a but deserves additional sampling or levels

New to the 8th edition

- Surface involvement is considered present if there is perforation of tumor into inflammatory debris on the external surface of the colon
T4a by virtue of tumor cells in the inflammatory cap

Issues involving lymph nodes

- Tumor deposits
  - AKA non-nodal tumor deposits, previously also known as discontinuous extramural extension
- Isolated tumor cells (pN0(i+))
  - Surprisingly, ITCs have been part of the lexicon of colon cancer since the 5th edition, although most pathologists were not aware of ITCs except in breast carcinoma
The history of N1c and non-nodal tumor deposits

- Non-nodal tumor deposits are nodules of tumor in the fat surrounding the colon that are not obviously associated with a lymph node
- They are clearly recognized as having prognostic significance greater than that of lymph node metastases, but have suffered from varying definitions and reporting requirements

The history of N1c and non-nodal tumor deposits

- 5th edition – defined by size
  - ≤ 3mm = discontinous extramural extension
    - considered part of T-category (T3)
  - >3mm = replaced lymph node
    - Counted with lymph nodes
- 6th edition – defined by shape
  - Round contour resembling node = replaced lymph node (pN)
  - Irregular contour = discontinuous extramural extension (i.e. non-nodal tumor deposit)
    - Considered to be vascular invasion (pV)
The history of N1c and non-nodal tumor deposits

- 7th edition – still defined by shape as in 6th
  - However, any non-nodal tumor deposit is included in the "N" category, but only if there are no other positive nodes
  - Otherwise, not part of N but are to be reported separately as a required element
- 8th edition
  - Defined as discreet tumor nodules within the lymph drainage area of the primary carcinoma without identifiable lymph node and without vascular or neural "structure"
    - i.e. shape, contour and size are no longer considered
  - If one can identify clearcut vascular or perineural invasion, they are not considered non-nodal tumor deposits but rather simply as vascular or perineural invasion (at least 40% (AJCP 2010; 133:388-394).
The history of N1c and non-nodal tumor deposits
• So why in the 7th edition were non-nodal deposits moved to the “N” category
  – Not sure, but if not included as N and there were no clear nodes involved, the case would be considered Stage II and may not receive adjuvant chemotherapy (and this really happens)
  – So, cookbooks may be bad for your health, and this is an attempt to “cook” the cookbook
  – As a practical matter, however, with the new definition of tumor deposit, many of these cases will be reverting to N0 with LVI and will be considered Stage II.

Isolated tumor cells in lymph nodes in colon carcinoma
• Surprisingly to many, ITCs in colon are defined and treated like ITCs in breast carcinoma (< 0.2 mm)
• In the 5th edition of AJCC, there was a general statement that ITCs were N0 regardless of the organ system
• In the 6th and 7th editions they were more organ specific but somewhat hidden
• In the 8th edition, questions are arising in regard to colon but they are still considered pN0(i+)

Why might ITCs in colon cancer be of more significance than ITCs in breast?
• In breast, sentinel nodes are very carefully examined with multiple levels, and if a met is <0.2 mm, that is probably the maximum size of the met
• In colon cancer, ITCs are being discovered in single sections of random nodes, and may well be only the tip of the iceberg if additional levels of the nodes were cut
8th edition and ITCs

- Despite mounting evidence that they may have some prognostic significance, ITCs in the 8th edition are still considered N0(i+)
- However, it might be worthwhile doing additional levels of nodes with ITCs if there are no truly positive nodes to avoid understaging

Changes in the M-category

- A new category of M1c, peritoneal involvement, was added to reflect the known poor prognosis of these patients
  - Given that peritoneal surface involvement (e.g. pT4a) is associated with the development of peritoneal carcinomatosis, this is a subtle admission (perhaps) that T4a might be prognostically worse than p4b

Other changes and issues

- Grading of carcinoma
- Tumor budding
Grading of Adenocarcinoma NOS

- In the 6th and 7th editions a simplified grading system was recommended
  - Low grade - ≥ 50% glands
  - High grade - < 50% glands
- In the 8th edition, reversion to a 4 grade system is recommended (without a really good reason)
  - Gx – cannot be assessed
  - G1 – well differentiated (>95% glands)
  - G2 – moderately differentiated (50 – 95% glands)
  - G3 – poorly differentiated (< 50% glands)
  - G4 – undifferentiated (no glands, no mucin, no squamous or NE differentiation)

Grading of colon carcinoma variants

- NOS
  - Graded by gland percentage
- Always low grade
  - Medullary carcinoma
- Always high grade
  - Signet ring carcinoma
  - Undifferentiated carcinoma (G4)
  - Clear cell and sarcomatoid carcinoma
- What to do with mucinous carcinoma?

Mucinous carcinoma grading

- Dependent on MSI status
  - MSS are considered high grade
  - MSI are considered low grade
Other histological subtypes with prognostic significance
• Micropapillary pattern >5% is associated with lymph node metastases
• Serrated adenocarcinoma may have worse prognosis
  – But this is complicated by MSI status and presence or absence of mucinous carcinoma pattern

Illustrate micropapillary and serrated patterns
Optional elements

• At the users discretion
• However, some elements that most authorities consider prognostically important are not included as “required” elements, most notably tumor budding

A brief history of tumor budding and its significance

• Definition of a tumor bud
  – A single cell or collection of less than 5 cells
  – Usually seen at the leading edge of tumors, but also may be intratumoral
• Significance of tumor budding
  – When present in significant amount (i.e. a “high degree of tumor budding”) is associated with lymph node metastases and poorer prognosis
  • In malignant polyps, tumor budding has similar significance and may affect management of polyps
What is the data for this association?

- Essentially every publication that has evaluated tumor budding, regardless of methodology, has found it to be significant, often more significant than other factors like lymphatic invasion or perineural invasion
  — See Mitrovic et al (including Dr. Riddell) Mod Pathol 2012: 25: 1315-1325 for one of many supportive editorials
- So, why is it not a “required” element
Why is not a required element?

• Not being a CAP/AJCC insider, I don’t know
• However, the usual criticisms revolves around
  – Lack of consensus on how to evaluate tumor budding and
  – Lack of consensus on if it can be evaluated by H and E or needs cytokeratin staining

Methods of evaluation

• Range from the Ueno “hot spot” method to complicated methods involving analysis of multiple fields
• May or may not recommend cytokeratin staining

Ueno method
Histopathology 2002; 40: 127-132

• Identify the area of tumor with the most evident tumor budding
• Count the number of buds per 20X high power field (technically per 0.785 mm²)
• Report the number of buds
  – CAP recommends reporting as low (0 – 4), intermediate (5 – 9) or high (10 or more)
  – CAP recommends reporting for all polyps and for Stage I and II cancers but does not require it
Cytokeratin or H and E alone

- There is no question that use of cytokeratin stain allows easier identification of tumor buds resulting in greater numbers of tumors with a high degree of tumor budding
- Studies using cytokeratin have found results similar to H and E
- However, only one study directly compared H and E and cytokeratin and in multivariate analysis only H and E identified buds had prognostic significance.
- In the end, given the extra expense and time of CK staining and the lack of proof that the results are more meaningful than H and E, I would not recommend using CK as a routine but may be useful if tumor buds are obscured by inflammation and the CAP also does not suggest using CK.

Summary of changes in the 8th edition

- Revision of grading of colon carcinoma
  - 4 grades instead of 2
- Definition of invasion
  - High grade dysplasia is not included in Tis
  - Into but not through muscularis mucosa is included as Tis
- Definition of T4a
  - Tumor with perforation and tumor within inflammatory debris extending to surface is T4a
- Redefinition of non-nodal tumor deposits
  - If vascular or perineural invasion present these are not considered non-nodal tumor deposits and are not included in pN1c
- New category of distant metastasis
  - M1c, peritoneal carcinomatosis

Web site for CAP protocol