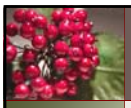

AJCC 2010 (7th edition) Staging Changes

Stomach, colon, lung, liver, others

Dean W. Joelson, M.D.

AJCC 2010 Staging Changes

- Handbook version has gone from 469 pages to 718 pages

!!!!

A Tale of Two Cities (Dickens): 496 pages
The Grapes of Wrath (Steinbeck): 464 pages
The Republic (Plato): 480 pages

The Chronicles of Narnia (the entire thing!) (Lewis): 768 pages
The History of the Decline and Fall of the Roman Empire (Gibbons): 848 pages

Guinness Book of World Records 2011: 288 pages
(last year the GBWR was 287 pages; the 288th page was added to document a new world record for longest "handbook" ever.)

Some General Notes

- A key feature of the 7th edition of TNM is coordination with the UICC
  - Establishes a consistent worldwide standard for cancer staging
  - International collaboration for data collection
    - Especially lung, esophagus, stomach, melanoma, and gynecologic malignancies
- The MX category is no more
  - The use of MX may result in exclusion from staging
  - cMX is inappropriate as the clinical assessment of metastasis can be based on physical examination alone
  - If the pathologist does not have knowledge of the clinical M, MX should NOT be recorded
  - pMX: does not exist; pM0: does not exist (except at autopsy)
  - cM0 Clinically no distant metastasis
  - cM1 Distant metastasis clinically (i.e. colon cancer with liver metastasis based on CT)
  - pM1 Distant metastasis proven microscopically (i.e. needle biopsy)
- If a cM1 (e.g., liver met) is biopsied and is negative, it becomes cM0, not pM0

AJCC 2010 Staging Changes

- New Chapters:*
  - Mucosal Melanoma of the Head and Neck
  - Appendix (previously used the same system as colon)
  - Gastrointestinal Stromal Tumor (GIST)
  - Neuroendocrine Tumors (of digestive system)
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*AJCC Cancer Staging Manual, 7th edition. 2009

AJCC 2010 Staging Changes

- Most Changed Systems:*
  - Stomach
  - Colon and Rectum
  - Liver
  - Lung
  - Cutaneous Squamous Cell Carcinoma
  - Melanoma of the Skin
  - Breast
  - ~~Urinary Bladder~~ Prostate
  - Malignant Melanoma of the Uvea

*Per AJCC pamphlet "Understanding the Changes from the Sixth to the Seventh Edition of the *AJCC Cancer Staging Manual.*" 2009

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Breast 2010 AJCC Changes

Tumor (T)

- • Identified specific imaging modalities that can be used to estimate clinical tumor size, including mammography, ultrasound, and magnetic resonance imaging (MRI).
- • Made specific recommendations that (1) the microscopic measurement is the most accurate and preferred method to determine pT with a small invasive cancer that can be entirely submitted in one paraffin block, and (2) the gross measurement is the most accurate and preferred method to determine pT with larger invasive cancers that must be submitted in multiple paraffin blocks.
- • Made the specific recommendation to use the clinical measurement thought to be most accurate to determine the clinical T of breast cancers treated with neoadjuvant therapy. Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings.
- • Made the specific recommendation to estimate the size of invasive cancers that are unapparent to any clinical modalities or gross pathologic examination by carefully measuring and recording the relative positions of tissue samples submitted for microscopic evaluation and determining which contain tumor.
- • Acknowledged "ductal intraepithelial neoplasia" (DIN) as uncommon, and still not widely accepted, terminology encompassing both DCIS and ADH, and clarification that only cases referred to as DIN containing DCIS (±ADH) are classified as Tis (DCIS).
- • Acknowledged "lobular intraepithelial neoplasia" (LIN) as uncommon, and still not widely accepted, terminology encompassing both LCIS and ALH, and clarification that only cases referred to as LIN containing LCIS (±ALH) are classified as Tis (LCIS).
- • Clarified that only Paget's disease NOT associated with an underlying noninvasive (that is, DCIS and/or LCIS) or invasive breast cancer should be classified as Tis (Paget's) and that Paget's disease associated with an underlying cancer be classified according to the underlying cancer (Tis, T1, and so on).
- • Made the recommendation to estimate the size of noninvasive carcinomas (DCIS and LCIS), even though it does not currently change their T classification, because noninvasive cancer size may influence therapeutic decisions, acknowledging that providing a precise size for LCIS may be difficult.
- • Acknowledged that the prognosis of microinvasive carcinoma is generally thought to be quite favorable, although the clinical impact of multifocal microinvasive disease is not well understood at this time.
- • Acknowledged that it is not necessary for tumors to be in separate quadrants to be classified as multiple simultaneous ipsilateral carcinomas, providing that they can be unambiguously demonstrated to be macroscopically distinct and measurable using available clinical and pathologic techniques.
- • Maintained that the term "inflammatory carcinoma" be restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.
- • Recommend that all invasive cancer should be graded using the Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom Richardson grading system).

Breast 2010 AJCC Changes

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Breast 2010 AJCC Changes

Nodes (N)

- • Classification of isolated tumor cell clusters and single cells is more stringent. Small clusters of cells not greater than 0.2 millimeters, or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section are classified as isolated tumor cells.
- • Use of the (sn) modifier has been clarified and restricted. When six or more sentinel nodes are identified on gross examination of pathology specimens the (sn) modifier should be omitted.
- • Stage I breast tumors have been subdivided into Stage IA and Stage IB; Stage IB includes small tumors (T1) with exclusively micrometastases in lymph nodes (N1mi).

Metastases (M)

- • Created new M0(i+) category, defined by presence of either disseminated tumor cells detectable in bone marrow or circulating tumor cells or found incidentally in other tissues (such as ovaries removed prophylactically) if not exceeding 0.2 millimeters. However, this category does not change the stage grouping. Assuming that they do not have clinically and/or radiographically detectable metastases, patients with M0(i+) are staged according to T and N.

Postneoadjuvant Therapy (yc or ypTNM)

- • In the setting of patients who received neoadjuvant therapy, pretreatment clinical T (cT) should be based on clinical or imaging findings.
- • Postneoadjuvant therapy T should be based on clinical or imaging (ycT) or pathologic findings (ypT).
- • A subscript will be added to the clinical N for both node negative and node positive patients to indicate whether the N was derived from clinical examination, fine needle aspiration, core needle biopsy, or sentinel lymph node biopsy.
- • The posttreatment ypT will be defined as the largest contiguous focus of invasive cancer as defined histopathologically with a subscript to indicate the presence of multiple tumor foci. Note: Definition of posttreatment ypT remains controversial and an area in transition.
- • Posttreatment nodal metastases no greater than 0.2 millimeters are classified as ypN0(i+) as in patients who have not received neoadjuvant systemic therapy. However, patients with this finding are not considered to have achieved a pathologic complete response (pCR).
- • A description of the degree of response to neoadjuvant therapy (complete, partial, no response) will be collected by the registrar with the posttreatment ypTNM. The registrars are requested to describe how they defined response (by physical examination, imaging techniques [mammogram, ultrasound, magnetic resonance imaging (MRI)] or pathologically).
- • Patients will be considered to have M1 (and therefore Stage IV) breast cancer if they have had clinically or radiographically detectable metastases, with or without biopsy, prior to neoadjuvant systemic therapy, regardless of their status after neoadjuvant systemic therapy.

Stomach
Prior AJCC TNM Staging

Primary Tumor (T)

- pTX: Cannot be assessed
- pT0: No evidence of primary tumor
- pTis: Carcinoma in situ
- pT1: Tumor invades lamina propria or submucosa
  - pT1a: Tumor invades lamina propria
  - pT1b: Tumor invades submucosa
- pT2: Tumor invades muscularis propria or subserosa
  - pT2a: Tumor invades muscularis propria
  - pT2b: Tumor invades subserosa
- pT3: Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures
- pT4: Tumor directly invades adjacent structures

Stomach
New 2010 AJCC TNM Staging

- Primary Tumor (T)
- pTX Cannot be assessed
- pT0 No evidence of primary tumor
- pTis Carcinoma in situ
- pT1 Tumor invades lamina propria, muscularis mucosae, or submucosa
  - pT1a: Tumor invades lamina propria or muscularis mucosae
  - pT1b: Tumor invades submucosa
- pT2 Tumor invades muscularis propria (used to be pT2a)
- pT3 Tumor invades subserosal connective tissue, without involvement of visceral peritoneum or adjacent structures (used to be pT2b)
- pT4 Tumor involves serosa (visceral peritoneum) or adjacent structures
  - pT4a: Tumor invades serosa (visceral peritoneum) (used to be pT3)
  - pT4b: Tumor invades adjacent structures (used to be T4 by itself)

The very definition of gastric cancer has changed.

In fact, sometimes gastric cancer isn't even gastric cancer!

Stomach
New 2010 AJCC TNM Staging

- Previously, a pathologist[1] could stage a GE junction tumor as either esophageal or gastric based on from where he/she thought it was arising
  - As intelligent as it was to place this critical staging power in the hands of a pathologist[2], some claimed this system was arbitrary and confusing
- According to the new stomach staging criteria:
  - *Tumors arising at the esophagogastric junction, or arising in the stomach 5 cm or less from the esophagogastric junction and crossing the esophagogastric junction, are staged using the TNM system for esophageal carcinoma. The revised gastric cancer staging system applies to tumors arising in the more distal stomach and to tumors arising in the proximal 5 cm but not crossing the esophagogastric junction.*

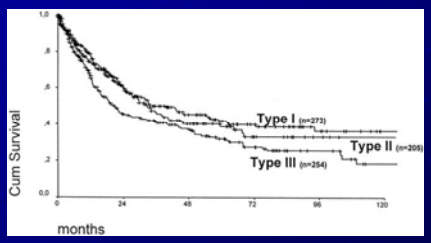
[1] or other physician
[2] or other physician

Classification of GE Junction Adenocarcinoma

- Siewert *et al* (2000) came up with three different categories:
  - **Type I:** adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett esophagus) and infiltrate the esophagogastric junction from above;
  - **Type II:** true carcinoma of the cardia arising immediately at the esophagogastric junction;
  - **Type III:** subcardial gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below.

Siewert JR *et al.* "Adenocarcinoma of the Esophagogastric Junction: Results of Surgical Therapy Based on Anatomical/Topographic Classification in 1,002 Consecutive Patients." *Ann Surg.* 2000 September; 232(3): 353–361.

Survival with GE Junction Adenocarcinomas

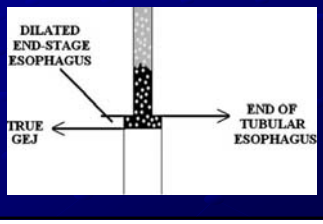


This implies that true adenocarcinoma of the cardia behaves more like esophageal adenocarcinoma than gastric adenocarcinoma.

Siewert JR *et al.* "Adenocarcinoma of the Esophagogastric Junction: Results of Surgical Therapy Based on Anatomical/Topographic Classification in 1,002 Consecutive Patients." *Ann Surg.* 2000 September; 232(3): 353–361.

Furthermore…

- Chandrasoma P *et al*. "Adenocarcinomas of the distal esophagus and 'gastric cardia' are predominantly esophageal carcinomas. *Am J Surg Pathol.* 2007;31(4):569-575.



Best Staging System for GE Junction Tumors

- Both esophageal and gastric systems work, but…
- Gaur P *et al* (2010) showed that among all patients with GE junction tumors:
  - 6th edition gastric staging system best 2.4% of the time
  - 6th edition esophageal staging system was best 2.93% of the time
  - ***7th edition esophageal staging system was best 94.67% of the time***

Gaur P *et al*. "Comparison Between Established and the Worldwide Esophageal Cancer Collaboration Staging Systems." *Ann Thorac Surg* 2010;89:1797– 804)

Just in case you thought everyone agreed on everything...

- Huang Q et al. "Gastric cardiac carcinomas involving the esophagus are more adequately staged as gastric cancers by the 7th edition of the American Joint Commission on Cancer Staging System." *Modern Pathology*. 2010 Sep 17.
- Gertler R et al. "How to Classify Adenocarcinomas of the Esophagogastric Junction: As Esophageal or Gastric Cancer?" American Journal of Surgical Pathology. Oct 2011.
  - *Conclusions: Neither the esophageal nor the gastric scheme proves to be clearly superior over the other*

Where were we?

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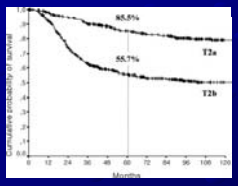
- pT4: Tumor involves serosa (visceral peritoneum) or adjacent structures
  - pT4a: Tumor invades serosa (visceral peritoneum) - used to be T3
  - pT4b: Tumor invades adjacent structures – used to be T4 (by itself)

The T Dilemma

- Abundant evidence shows that there are significant differences between T2 lesions in the old 6th edition staging system



Old T2a = invasion of muscularis propria
Old T2b = invasion of subserosa

Gastric tumor staging now more closely resembles that of the rest of tubular GI tract (i.e. T2-T4 stages based on invasion into muscularis propria, subserosa, and serosa/adjacent structures, respectively).

Park DJ *et al.* "Subclassification of pT2 gastric adenocarcinoma according to depth of invasion (pT2a vs pT2b) and lymph node status (pN)." *Surgery* 2007;Volume 141(6):757-763.

Stomach
Prior AJCC TNM Staging

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1 to 6 perigastric lymph nodes
- N2 Metastasis in 7 to 15 perigastric lymph nodes
- N3 Metastasis in greater than 15 perigastric lymph nodes

Distant Metastasis (M)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stomach
New 2010 AJCC TNM Staging

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1 to 2 perigastric lymph nodes
- N2 Metastasis in 3 to 6 perigastric lymph nodes
- N3 Metastasis in 7 or more perigastric lymph nodes
  - N3a Metastasis in 7 to 15 perigastric lymph nodes
  - N3b Metastasis in 16 or more perigastric lymph nodes

Distant Metastasis (M)

- pM1 Distant metastasis
- Not applicable

Stomach
New 2010 AJCC TNM Staging

Regional Lymph Nodes (N)

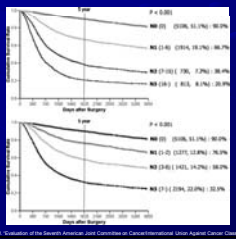
- NX — Regional lymph nodes cannot be assessed
- N0 — No regional lymph node metastasis
- N1 — Metastasis in 1 to 2 perigastric lymph nodes
- N2 — Metastasis in 3 to 6 perigastric lymph nodes **(used to be part of N1)**
- N3 — Metastasis in 7 or more perigastric lymph nodes
  - N3a — Metastasis in 7 to 15 perigastric lymph nodes **(used to be N2)**
  - N3b — Metastasis in 16 or more perigastric lymph nodes **(used to be N3 by itself)**

Stomach
The N Dilemma

- Overall analysis of the data did not demonstrate a statistically significant cutoff value for any number of positive LNs >6
- *But!... (not surprisingly)*
- Studies have shown survival is worse the more positive lymph nodes a patient has
  - Therefore, N3 is broken into N3a (7-15 positive nodes) and N3b (greater than 16 positive nodes)

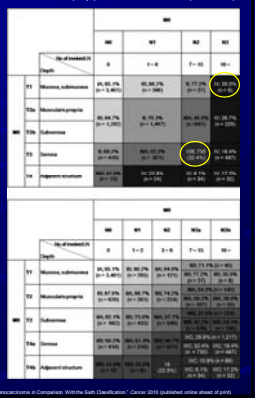
6th ed.

7th ed.



Stage Groupings

6th edition (top) and 7th edition (bottom)



Ahn HS et al. "Evaluation of the Seventh American Joint Committee on Cancer/International Union Against Cancer Classification of Gastric Adenocarcinoma in Comparison With the Sixth Classification." *Cancer* 2010 (published online ahead of print)

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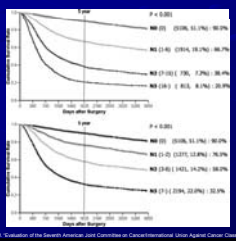
Ahn HS et al. "Evaluation of the Seventh American Joint Committee on Cancer/International Union Against Cancer Classification of Gastric Adenocarcinoma in Comparison With the Sixth Classification." *Cancer* 2010 (published online ahead of print)

Stomach
The N Dilemma

- Overall analysis of the data did not demonstrate a statistically significant cutoff value for any number of positive LNs >6
- *But!... (not surprisingly)*
- Studies have shown survival is worse the more positive lymph nodes a patient has
  - Therefore, N3 is broken into N3a (7-15 positive nodes) and N3b (greater than 16 positive nodes)

6th ed.

7th ed.



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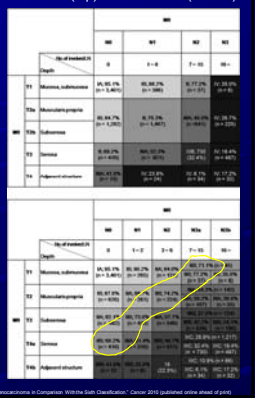

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Stomach

I'm not done, yet

- M1 category now encompasses positive peritoneal fluid cytology

Non-staging related note:

- In October 2011, CAP proposed adding additional elements to their protocol, including detailed information of Her-2/neu status

Colon

Colon
Prior AJCC TNM Staging

Primary Tumor (T)

- TX — Primary tumor cannot be assessed
- T0 — No evidence of primary tumor
- Tis — Carcinoma in situ: intraepithelial or invasion of lamina propria
- T1 — Tumor invades submucosa
- T2 — Tumor invades muscularis propria
- T3 — Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
- T4 — Tumor directly invades other organs or structures, and/or perforates visceral peritoneum

Colon
New 2010 AJCC TNM Staging

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- TX — Primary tumor cannot be assessed
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- Tis — Carcinoma in situ: intraepithelial or invasion of lamina propria
- T1 — Tumor invades submucosa
- T2 — Tumor invades muscularis propria
- T3 — Tumor invades through the muscularis propria into pericolic tissues
- T4a — Tumor penetrates to the surface of the visceral peritoneum
- T4b — Tumor directly invades or is adherent to other organs or structures

Colon
Prior AJCC TNM Staging

Regional Lymph Nodes (N)

- NX — Regional lymph nodes cannot be assessed
- N0 — No regional lymph node metastasis
- N1 — Metastasis in 1 to 3 regional lymph nodes
- N2 — Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

- MX — Distant metastasis cannot be assessed
- M0 — No distant metastasis
- M1 — Distant metastasis

Colon
New 2010 AJCC TNM Staging

Regional Lymph Nodes (N)

- NX — Regional lymph nodes cannot be assessed
- N0 — No regional lymph node metastasis
- N1 — Metastasis in 1 to 3 regional lymph nodes
  - N1a — Metastasis in one regional lymph node
  - N1b — Metastasis in 2-3 regional lymph nodes
  - N1c — Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 — Metastasis in four or more regional lymph nodes
  - N2a — Metastasis in 4-6 regional lymph nodes
  - N2b — Metastasis in seven or more regional lymph nodes

Colon
New 2010 AJCC TNM Staging

Distant Metastasis

- Not applicable
- M1 Distant metastasis
  - M1a Metastasis confined to one organ or site (e.g. liver, lung, ovary, nonregional lymph node)
  - M1b Metastasis in more than one organ/site or the peritoneum

Colon
New 2010 AJCC Stage Grouping

Stage	T	N	M	Dukes	Mod. Astler-Coller	5-Year Survival
0	Tis	N0	M0	-	-	
I	T1	N0	M0	A	A	74.3%-78.7%
	T2	N0	M0	A	B1	
IIA	T3	N0	M0	B	B2	66.7%
IIB	T4a	N0	M0	B	B2	60.6%
IIC	T4b	N0	M0	B	B3	45.7%
IIIA	T1-T2	N1/N1c	M0	C	C1	64.7%-73.7%
	T1	N2a	M0	C	C1	
IIIB	T3-T4a	N1/N1c	M0	C	C2	42.8%-58.2%
	T2-T3	N2a	M0	C	C1/C2	
	T1-T2	N2b	M0	C	C1	
IIIC	T4a	N2a	M0	C	C2	12.9%-32.5%
	T3-T4a	N2b	M0	C	C2	
	T4b	N1-N2	M0	C	C3	
IVA	Any T	Any N	M1a	-	-	Dismal
IVB	Any T	Any N	M1b	-	-	More dismal

Colon
New 2010 AJCC Changes

- What inspired stage grouping changes:
  - Essentially, data* showed relative increased importance of T category in survival compared with N category
    - i.e. T1-T2/N2 patients showed better survival (62%) compared to T3-4/N2 patients (16%-43%)
      - Thus the shift of T1-T2/N2 patients from stage IIIC to stage IIIA/B
    - i.e. T4/N1 patients showed worse survival (47%) than T3/N1 patients (55%)
      - Thus the shift of T4/N1 patients from IIIB to IIIC

*"Revised TN Categorization for Colon Cancer Based on National Survival Outcomes Data." *Journal of Clinical Oncology* 2010;28(2):264-271.

Colon
New 2010 AJCC Stage Grouping

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	T2	N0	M0	A	B1	
IIA	T3	N0	M0	B	B2	66.7%
IIB	T4a	N0	M0	B	B2	60.6%
IIC	T4b	N0	M0	B	B3	**45.7%**
IIIA	T1-T2	N1/N1c	M0	C	C1	64.7%-73.7%
	T1	N2a	M0	C	C1	
IIIB	T3-T4a	N1/N1c	M0	C	C2	42.8%-58.2%
	T2-T3	N2a	M0	C	C1/C2	
	T1-T2	N2b	M0	C	C1	
IIIC	T4a	N2a	M0	C	C2	12.9%-32.5%
	T3-T4a	N2b	M0	C	C2	
	T4b	N1-N2	M0	C	C3	
IVA	Any T	Any N	M1a	-	-	Dismal
IVB	Any T	Any N	M1b	-	-	More dismal

Colon
New 2010 AJCC Changes

- What inspired N changes:
  - The presence of N2 disease does not, by itself, confer poor prognosis
  - Patients with one involved lymph node (N1a) have 5% to 13% better 5-year survival than those with two to three positive nodes (N1b)
    - EXCEPT for T1/N1a versus T1/N1b (these have similar survivals)
  - Those with four to six involved nodes (N2a) have a 5% to 19% better survival than those with seven or more positive nodes (N2b)

**"Revised TN Categorization for Colon Cancer Based on National Survival Outcomes Data." *Journal of Clinical Oncology* 2010;28(2):264-271.

Colon
New 2010 AJCC TNM Staging

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  - N1c — Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 — Metastasis in four or more regional lymph nodes
  - N2a — Metastasis in 4-6 regional lymph nodes
  - N2b — Metastasis in seven or more regional lymph nodes

But then there is N1c…

Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis

Which begs the question, "What, exactly, is a tumor deposit?"

Tumor Deposits

- Prior colonic AJCC staging:
  - Stage IIA and IIB: Locally advanced cancer with spread completely through or beyond colon wall (pT3 and pT4)
  - Stage III: Lymph node metastases (pN1-N2)
  - Stage IV: Distant metastases (pM1)
- Tumor deposits: foci of tumor in pericolonic adipose tissue without definitive lymph node
  - Such tumor deposits may represent discontinuous spread, lymph-vascular spread with extravascular extension, or totally replaced lymph nodes.
  - (Stage III) behaved as if they had distant metastases (Stage IV)

Tumor Deposits

- So the staging folk knew they needed to do something
- But where do they go? In the N category? Or in the M category?
  - Wasn't easy to tell which patients with tumor deposits would behave like they had distant metastases
- Not enough evidence, so they got placed into the N category, but *only if there were no other positive nodes*.
- If there were positive nodes, the tumors got classified according to the appropriate N category into which they fell.
  - In this case, the tumor deposits are relegated to an item worthy of being diagnosed, but not worthy of influencing stage.

This seems very silly, and, in reality, is.

This seems very silly, and, in reality, is.

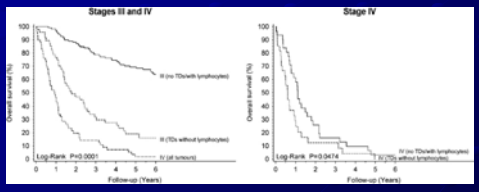
But! It does ensure that patients who might not have been treated with chemotherapy before (i.e. as N0 patients) might now get that therapy (as N1 patients)

That still doesn't help us determine which N1c patients are going to act like Stage IV patients

So people are very diligently trying to better define tumor deposits and what they mean

Tumor Deposits

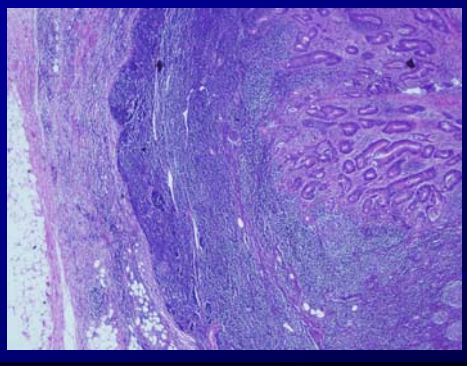
- Two kinds of tumor deposits (ignoring shape):
  - Tumor deposits with lymphocytes
  - Tumor deposits without lymphocytes



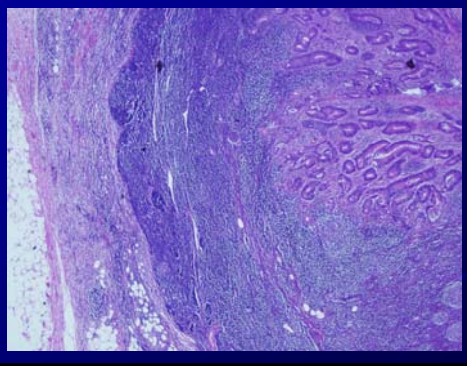
Puppa G *et al.* "Tumor deposits are encountered in advanced colorectal cancer and other adenocarcinomas: an expanded classification with implications for colorectal cancer staging system including a unifying concept of in-transit metastases." *Modern Pathology* (2009) 22, 410–415.

QUIZ!!!

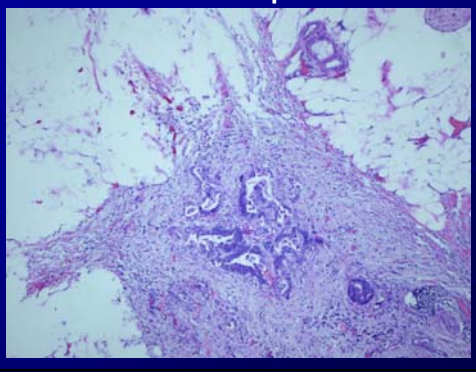
Tumor Deposit?



Lymph node metastasis



Tumor Deposit?



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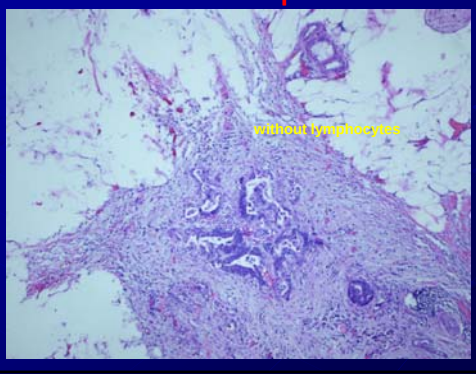

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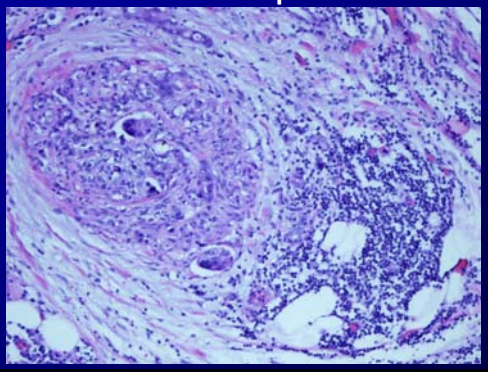

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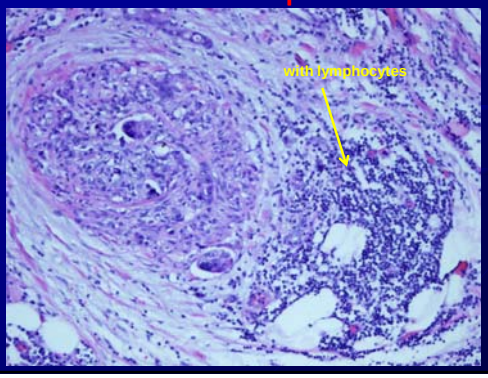

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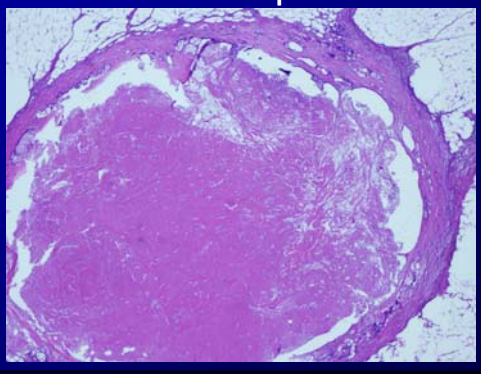
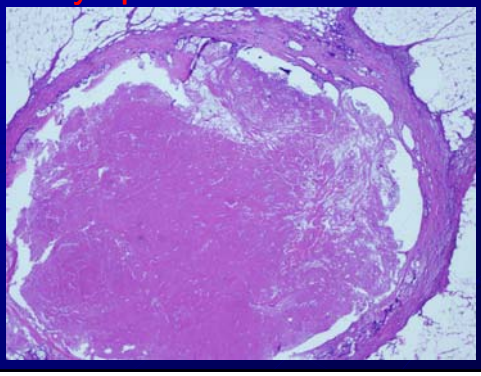


Lymph node metastasis



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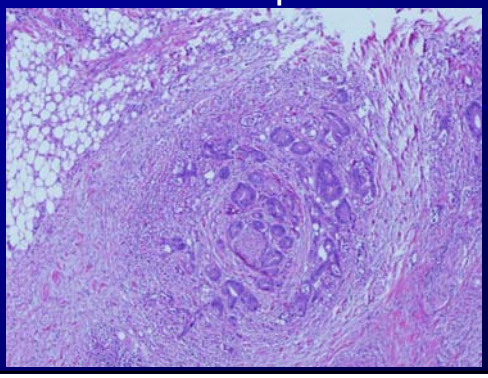

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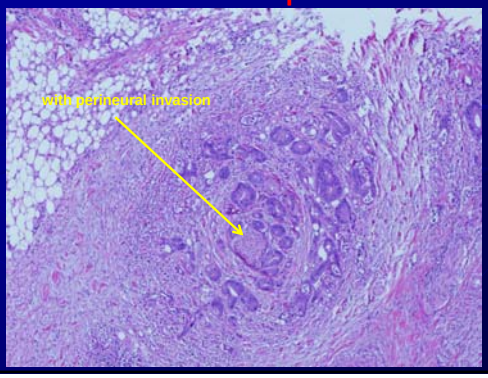

A few notes…

- Rectal cancer and colon cancer showed strikingly similar SEER outcomes
- Future staging manuals will incorporate data with regard to:
  - Tumor deposits (!)
  - Radial margin status
  - Molecular markers
- In February 2011, CAP amended their protocol to include "lymph node ratio" (LNR) information
  - *Number of positive nodes*
  - *Number of nodes examined*
  - Hong KD et al. "Lymph node ratio as determined by the 7th edition of the American Joint Committee on Cancer staging system predicts survival in stage III colon cancer." *Journal of Surgical Oncology.* Apr 2011.

Lung Cancer

- AJCC 6th edition was based on:
  - 4,351 lung cancer patients treated at MD Anderson Cancer Center from 1975 to 1988
  - 968 lung cancer patients treated by the National Cancer Institute Cooperative Lung Cancer Study Group from 1977 to 1982.

  That's only 5,319 patients 20-30 years ago!
- AJCC 7th edition is based on:
  - An international collection of more than 81,000 patients treated from 1990-2000.

Lung
Prior AJCC TNM Staging

Primary Tumor (T)

- TX — Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- T0 — No evidence of primary tumor
- Tis — Carcinoma in situ
- T1 — Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
- T2 — Tumor with any of the following features of size or extent:
  - More than 3 cm in greatest dimension
  - Involves main bronchus, 2 cm or more distal to the carina
  - Invades the visceral pleura
  - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- T3 — Tumor of any size which meets one of the following criteria:
  - Directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium
  - Or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina
  - Or associated atelectasis or obstructive pneumonitis of the entire lung
- T4 — Tumor of any size which meets one of the following criteria:
  - Invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina
  - Or separate tumor nodules in the same lobe
  - Or tumor with malignant pleural effusion

Lung
New 2010 AJCC TNM Staging

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  - T1a — Tumor 2 cm or less in greatest dimension
  - T1b — Tumor more than 2 cm but 3 cm or less in greatest dimension
- T2 — Tumor more than 3 cm but 7 cm or less *OR* tumor with any of the following features:
  - Involves main bronchus, 2 cm or more distal to the carina
  - Invades the visceral pleura
  - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
  - T2a — Tumor more than 3 cm but 5 cm or less in greatest dimension
  - T2b — Tumor more than 5 cm but 7 cm or less in greatest dimension
- T3 — Tumor which meets one of the following criteria:
  - More than 7 cm
  - Directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium
  - Or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina
  - Or associated atelectasis or obstructive pneumonitis of the entire lung
- T4 — Tumor of any size which meets one of the following criteria:
  - Invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina
  - Or separate tumor nodules in a different ipsilateral lobe

Lung
Prior AJCC TNM Staging

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  - Invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina
  - Or separate tumor nodules in a different ipsilateral lobe

Lung
Prior AJCC TNM Staging

Regional Lymph Nodes (N)

- NX — Regional lymph nodes cannot be assessed
- N0 — No regional lymph node metastasis
- N1 — Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
- N2 — Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3 — Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis

- MX — Distant metastasis cannot be assessed
- M0 — No distant metastasis
- M1 — Distant metastasis [includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)]

Lung
New 2010 AJCC TNM Staging

Regional Lymph Nodes (N) — No changes!

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- N2 — Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3 — Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

- Not applicable
- M1a — Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules, or malignant pleural (or pericardial) effusion
- M1b — Distant metastasis

Lung
New 2010 AJCC TNM Staging

No changes!

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Distant Metastasis (M)

- Not applicable
- M1a — Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules, or malignant pleural (or pericardial) effusion
- M1b — Distant [in an organ far, far away…] metastasis

Lung
New 2010 AJCC Stage Grouping

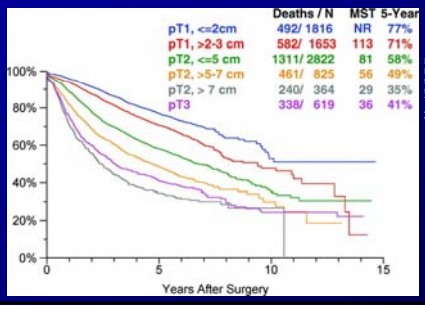
Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0

Stage	T	N	M
IIIB*	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
IV	Any T	Any N	M1a
	Any T	Any N	M1b

*All T4, M0 lesions used to be IIIB; now T4 lesions with N0 or N1 are classified as IIIA

Lung
New 2010 AJCC Changes

- What inspired T1-T3 changes:



Rami-Porta R, *et al.* "The IASLC Lung Cancer Staging Project: Proposals for the Revision of the T Descriptors in the Forthcoming (Seventh) Edition of the TNM Classification for Lung Cancer." *Journal of Thoracic Oncology* 2007 Volume 2(7): 593-602.

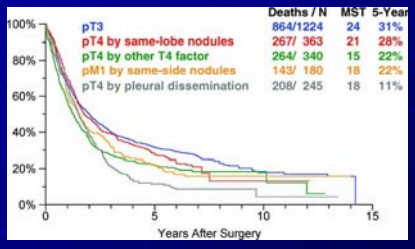
Lung
New 2010 AJCC TNM Staging

Primary Tumor (T)

- TX — Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- T0 — No evidence of primary tumor
- Tis — Carcinoma in situ
- T1 — Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
  - T1a — Tumor 2 cm or less in greatest dimension
  - T1b — Tumor more than 2 cm but 3 cm or less in greatest dimension
- T2 — Tumor more than 3 cm but 7 cm or less *OR* tumor with any of the following features:
  - Involves main bronchus, 2 cm or more distal to the carina
  - Invades the visceral pleura
  - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
  - T2a — Tumor more than 3 cm but 5 cm or less in greatest dimension
  - T2b — Tumor more than 5 cm but 7 cm or less in greatest dimension
- T3 — Tumor which meets one of the following criteria:
  - More than 7 cm
  - Directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium
  - Or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina
  - Or associated atelectasis or obstructive pneumonitis of the entire lung
- T4 — Tumor of any size which meets one of the following criteria:
  - Invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina
  - Or separate tumor nodules in a different ipsilateral lobe

Lung
New 2010 AJCC Changes

- What inspired T4 and M changes:



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Lung
New 2010 AJCC TNM Staging

Primary Tumor (T)

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- T1 — Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
  - T1a — Tumor 2 cm or less in greatest dimension
  - T1b — Tumor more than 2 cm but 3 cm or less in greatest dimension
- T2 — Tumor more than 3 cm but 7 cm or less *OR* tumor with any of the following features:
  - …
  - T2a — Tumor more than 3 cm but 5 cm or less in greatest dimension
  - T2b — Tumor more than 5 cm but 7 cm or less in greatest dimension
- T3 — Tumor which meets one of the following criteria:
  - More than 7 cm
  - …
- T4 — Tumor of any size which meets one of the following criteria:
  - …
  - Or separate tumor nodules in a different ipsilateral lobe

Distant Metastasis (M)

- Not applicable
- M1a — Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules, or malignant pleural (or pericardial) effusion
- M1b — Distant metastasis

Liver (intrahepatic bile ducts) Prior AJCC TNM Staging

(actually combined with HCC System)

Primary Tumor

- TX — Primary tumor cannot be assessed
- T0 — No evidence of primary tumor
- T1 — Solitary tumor without vascular invasion
- T2 — Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- T3 — Multiple tumors more than 5 cm or tumor involving major branch of the portal or hepatic vein(s)
- T4 — Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

The 6th edition AJCC staging system for liver tumors was based on data ***exclusively*** from patients with HCC

Intrahepatic bile ducts New 2010 AJCC TNM Staging

Primary Tumor

- TX — Primary tumor cannot be assessed
- T0 — No evidence of primary tumor
- Tis — Carcinoma in situ (intraductal tumor)
- T1 — Solitary tumor without vascular invasion
- T2a — Solitary tumor with vascular invasion
- T2b — Multiple tumors with or without vascular invasion
- T3 — Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
- T4 — Tumor with periductal invasion

Nathan H, *et al.* "A proposed staging system for intrahepatic cholangiocarcinoma." *Ann Surg Oncol.* 2009 Jan;16(1):14-22.

What happened to tumor size!?

Intrahepatic bile ducts
New 2010 AJCC TNM Staging

Primary Tumor

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- T2b Multiple tumors with or without vascular invasion
- T3 Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
- T4 Tumor with periductal invasion

What happened to tumor size!?

It doesn't matter for cholangiocarcinoma.[1]

1. Nathan H, *et al*. "A proposed staging system for intrahepatic cholangiocarcinoma." *Ann Surg Oncol*. 2009 Jan;16(1):14-22.

Also…

Multiple tumors and vascular invasion had similar effects on prognosis, but the presence of both of these factors did not confer additional risk beyond either one alone[1]

1. Nathan H, *et al*. "A proposed staging system for intrahepatic cholangiocarcinoma." *Ann Surg Oncol*. 2009 Jan;16(1):14-22.

Intrahepatic bile ducts New 2010 AJCC TNM Staging

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- T4 Tumor with periductal invasion

Intrahepatic bile ducts New 2010 AJCC TNM Staging

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M)

- Not applicable
- M1 Distant metastasis

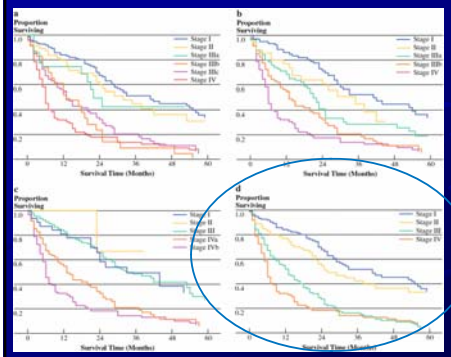
Intrahepatic bile ducts
New 2010 AJCC Stage Grouping

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IVA	T4	N0	M0
	Any T	N1	M0
IVB	Any T	Any N	M1

Intrahepatic bile ducts
New 2010 AJCC Stage Grouping

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IVA	T4	N0	M0
	Any T	N1	M0
IVB	Any T	Any N	M1

And the best system is…



Kaplan–Meier survival curves for all patients. **a** Current AJCC/UICC liver cancer staging system, **b** Okabayashi ICC staging system, **c** Liver Cancer Study Group of Japan (LCSGJ) ICC staging system, **d** Proposed ICC staging system

Nathan H, *et al*. "A proposed staging system for intrahepatic cholangiocarcinoma." *Ann Surg Oncol*. 2009 Jan;16(1):14-22.

Or is it?

- Farges O. "AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: by the AFC-IHCC-2009 study group." *Cancer*. May 15, 2011.
  - **CONCLUSIONS:** The 7th edition is clinically relevant and may be applicable worldwide, provided routine lymphadenectomy at the time of surgery for IHCC becomes the standard of care.
- Ribero D et al. "Comparison of the prognostic accuracy of the sixth and seventh editions of the TNM classification for intrahepatic cholangiocarcinoma." *HPB Oxford*. 2011 Mar.
  - **CONCLUSIONS:** The new seventh edition of the AJCC/UICC Staging System proved to be adequate although further studies are need to confirm its superiority compared with the previous edition.

Liver (hepatocellular carcinoma) Prior AJCC TNM Staging

- Primary Tumor
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Solitary tumor without vascular invasion
- T2 Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- T3 Multiple tumors more than 5 cm or tumor involving major branch of the portal or hepatic vein(s)
- T4 Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Hepatocellular carcinoma New 2010 AJCC TNM Staging

Primary Tumor (T)

- pTX — Cannot be assessed
- pT0 — No evidence of primary tumor
- pT1 — Solitary tumor without vascular invasion
- pT2 — Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- pT3a — Multiple tumors more than 5 cm
- pT3b — Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic veins
- pT4 — Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

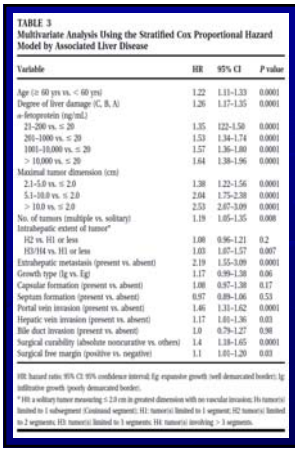


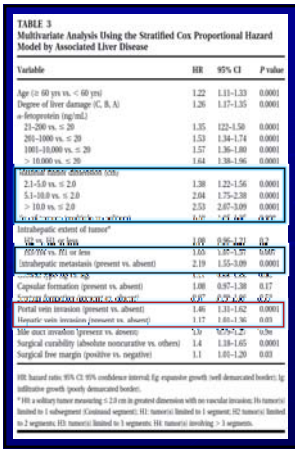
TABLE 3
Multivariate Analysis Using the Stratified Cox Proportional Hazard Model by Associated Liver Disease

Variable	HR	95% CI	*P* value
Age (≥ 60 yrs vs. < 60 yrs)	1.22	1.11–1.33	0.0001
Degree of liver damage (C, B, A)	1.26	1.17–1.35	0.0001
α-fetoprotein (ng/mL)			
21–200 vs. ≤ 20	1.35	122–1.50	0.0001
201–1000 vs. ≤ 20	1.53	1.34–1.74	0.0001
1001–10,000 vs. ≤ 20	1.57	1.36–1.80	0.0001
> 10,000 vs. ≤ 20	1.64	1.38–1.96	0.0001
Maximal tumor dimension (cm)			
2.1–5.0 vs. ≤ 2.0	1.38	1.22–1.56	0.0001
5.1–10.0 vs. ≤ 2.0	2.04	1.75–2.38	0.0001
> 10.0 vs. ≤ 2.0	2.53	2.07–3.09	0.0001
No. of tumors (multiple vs. solitary)	1.19	1.05–1.35	0.008
Intrahepatic extent of tumor*			
H2 vs. H1 or less	1.08	0.96–1.21	0.2
H3/H4 vs. H1 or less	1.03	1.07–1.57	0.007
Extrahepatic metastasis (present vs. absent)	2.19	1.55–3.09	0.0001
Growth type (Ig vs. Eg)	1.17	0.99–1.38	0.06
Capsular formation (present vs. absent)	1.08	0.97–1.38	0.17
Septum formation (present vs. absent)	0.97	0.89–1.06	0.53
Portal vein invasion (present vs. absent)	1.46	1.31–1.62	0.0001
Hepatic vein invasion (present vs. absent)	1.17	1.01–1.36	0.03
Bile duct invasion (present vs. absent)	1.0	0.79–1.27	0.98
Surgical curability (absolute noncurative vs. others)	1.4	1.18–1.65	0.0001
Surgical free margin (positive vs. negative)	1.1	1.01–1.20	0.03

HR: hazard ratio; 95% CI: 95% confidence interval; Eg: expansive growth (well demarcated border); Ig: infiltrative growth (poorly demarcated border).
* H0: a solitary tumor measuring ≤ 2.0 cm in greatest dimension with no vascular invasion; H1: tumor(s) limited to 1 subsegment (Couinaud segment); H2: tumor(s) limited to 1 segment; H3: tumor(s) limited to 2 segments; H4: tumor(s) involving > 3 segments.

HCC
The Importance of Vascular Invasion

Ikai I *et al*. "Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey." *Cancer* 2004;101(4):796-802.



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[illegible]			
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[illegible]			
Intrahepatic extent of tumor*			
[illegible]			
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Hepatocellular carcinoma
New 2010 AJCC TNM Staging

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HCC
New 2010 AJCC Stage Grouping

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

HCC
New 2010 AJCC Stage Grouping

The Verdict

- Cheng CH et al. "Evaluation of the new AJCC staging system for resectable hepatocellular carcinoma." *World Journal of Surgical Oncology*. Sept 2011.
  - **CONCLUSIONS:** In terms of 5-year survival rates, the TNM-7 system is capable of stratifying post-hepatectomy HCC patients into stages I, II, and III but is unable to stratify stage III patients into stages IIIA, IIIB and IIIC. Lack of tumor encapsulation, AST values >68 U/L, blood loss >500 mL, and AFP values >200 ng/mL are independent prognostic factors affecting long-term survival.

Prostate

Prostate
Prior AJCC TNM Staging

Primary Tumor (T)

- Not identified
- pT2: Organ confined
  - *pT2a: Unilateral, involving one-half of 1 side or less
  - *pT2b: Unilateral, involving more than one-half of 1 side but not both sides
  - *pT2c: Bilateral disease
- pT3: Extraprostatic extension
  - pT3a: Extraprostatic extension
  - pT3b: Seminal vesicle invasion
- pT4: Invasion of bladder and/or rectum

**Note: There is no pathologic T1 classification. Subdivision of pT2 disease is problematic and has not proven to be of prognostic significance.*

Prostate
New 2010 AJCC TNM Staging

Primary Tumor (T)

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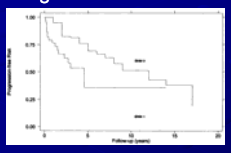
- pT2 Organ confined
  - *pT2a: Unilateral, involving one-half of 1 side or less
  - *pT2b: Unilateral, involving more than one-half of 1 side but not both sides
  - *pT2c: Bilateral disease
- pT3 Extraprostatic extension
  - pT3a: Extraprostatic extension or microscopic invasion of bladder neck
  - pT3b: Seminal vesicle invasion
- pT4 Invasion of rectum, levator muscles and/or pelvic wall

Note: There is no pathologic T1 classification.* ***Subdivision of pT2 disease is problematic and has not proven to be of prognostic significance.*

Prostate
Bladder Neck Involvement

- In 6th edition, *any* bladder involvement = T4
- Aydin *et al* (2004) found that positive bladder neck margins were worse than positive margins elsewhere*



*but, the risk of progression was less than other T4 lesions

Aydin *et al*. "Positive proximal (bladder neck) margin at radical prostatectomy confers greater risk of biochemical progression." Urology 2004;Volume 64(3):551-555.

- Yossepowitch O *et al* (2000) and Dash A *et al* (2002) found that bladder neck involvement (T4) wasn't as bad as seminal vesicle involvement (T3b)

Yossepowitch O *et al*. "Bladder neck involvement at radical prostatectomy: positive margins or advanced T4 disease?" Urology 56: 448–452, 2000.
Dash A *et al*. "Prostate cancer involving the bladder neck: recurrence-free survival and implications for AJCC staging modification." Urology 60: 276–280, 2002.

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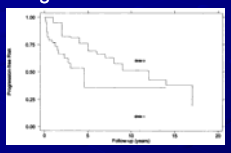

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Note: There is no pathologic T1 classification. Subdivision of pT2 disease is problematic and has not proven to be of prognostic significance.

Prostate
New 2010 Anatomic Stage / Prognostic Groups

Stage	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA < 10	Gleason ≤ 6
	T2a	N0	M0	PSA < 10	Gleason ≤ 6
	T1-T2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA < 20	Gleason 7
	T1a-c	N0	M0	PSA ≥ 10, < 20	Gleason ≤ 6
	T2a	N0	M0	PSA ≥ 10, < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–T2	N0	M0	PSA ≥ 20	Any Gleason
	T1–T2	N0	M0	Any PSA	Gleason ≥ 8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Prostate stage grouping

- Incidence of lymph node metastasis <4%
- PSA - most important predictor of biochemical recurrance after radiotherapy
- Gleason score - most important predictor of death
- Prior AJCC system had essentially been abandoned
  - Replaced by risk stratification schemes using PSA and Gleason score
- So new AJCC system includes PSA and Gleason score in its staging groupings

Roach M *et al*. Staging for prostate cancer: time to incorporate pretreatment prostate-specific antigen and Gleason score?" *Cancer* 2007;109(2):213-220).

A Joke

Three buddies were talking about death and dying. One asked, "When you're in your casket and friends and family are mourning you, what would you like to hear them say about you?"

The first guy says, "I would like to hear them say that I was a great pathologist of my time and a great family man."

The second man says, "I would like to hear that I was the best oncologist in history and a wonderful husband."

The last guy says, "I would like to hear them say LOOK, HE'S MOVING!!!"


The End