Introduction:
On January 1, 2010, the new 7th edition of the AJCC staging system for breast cancer went into effect. The changes reflect advances in both management options and in prognostic information; they also reflect clarifications in definitions used in the 6th edition. Nevertheless, there are still issues in the new system that require careful reading to understand and there are some that remain controversial or vague. This lecture highlights the key AJCC changes and also offers some recommendations for scenarios that remain vague or controversial. The content presented as Recommendations is based on our own practice patterns here at UCSF and is offered only as a guide for your consideration.

Relevance of AJCC Staging Today:
Advances in biomarkers, targeted therapy, and gene expression profiling have offered new ways of understanding the biology of breast cancer, its behavior, and response to specific therapy, compared to what was available when AJCC staging was first developed fifty years ago. The status of estrogen receptor, progesterone receptor and HER2 expression is now vital to management. Gene expression profiling is becoming useful in managing subsets of early stage breast cancer. Despite these advances, anatomic staging (i.e. AJCC staging) remains relevant. Even in tertiary care centers, AJCC staging is essential and is used alongside biomarkers and gene expression profiling for individual patient management, for entry into clinical trials, and for clinical research.

Summary of Changes to 7th Edition AJCC:
The changes can be divided into 4 areas:

- Tumor size definition
- Node classification
- Metastasis classification
- Special issues in patients who received neoadjuvant chemotherapy.

Clinical-radiologic-pathologic correlation is vital to AJCC staging. In particular, it is essential for the pathologist to know the following pre-operative data:

- clinical diagnosis (primary or recurrent tumor)
- anatomic location in breast
- unifocal vs multifocal
- neoadjuvant treatment with chemotherapy, hormone therapy or radiation therapy, and clinical/radiologic response to treatment.

Summary of Tumor Size Definitions:

Method to define pathologic tumor size (pT): AJCC states that invasive tumors should be recorded to the nearest millimeter (i.e. 1.3 cm, 2.2 cm, 4.7 cm). AJCC also states that small invasive tumors should be defined by microscopic measurement and larger tumors by gross measurement; however, AJCC acknowledges that gross measurement may be inaccurate for the following reasons:

1.) the gross appearance of invasive versus non-invasive tumor may not always be distinctive
2.) invasive tumor may extend microscopically further than is grossly visible

Recommendation: We use gross-microscopic correlation to define tumor size. This approach uses the gross findings to guide sampling for microscopic evaluation and correlates the anatomic specimen location of the tissue block with the microscopic findings. We slice (i.e. breadloaf) the specimen into parallel slices of equal thickness, ideally no thicker than 0.5 cm each, and number the slices consecutively. We record
the gross size of the tumor and which slices are involved. We submit representative tissue from the mass as well as tissue from the slices flanking the mass. We then correlate the microscopic findings with the slice numbers and gross findings. This requires detailed recording of the specimen and slice dimensions as well as uniform thickness of slices. It is labor-intensive but it does afford a more accurate measurement than relying on gross size alone. To simplify the process, we use templates for gross descriptions. A typical gross description would look like this (not all details are provided in this example):

SIZE OF SPECIMEN:
Medial to lateral: 7.5 cm
Superior to inferior: 6 cm
Anterior to posterior: 6 cm

Total # of slices: 15
First Slice (slice #1): Medial Margin
Last Slice (slice #15): Lateral Margin

Gross Description: A 2.5 cm firm white stellate mass is present in the upper outer part of the specimen in slices #8 to #12.

Cassettes:
A1: mass, slice 8, closest approach to deep margin
A2 mass, slice 9
A3: mass, slice 10,
A4: mass, slice 11
A5: mass, slice 12, closest approach to lateral margin
A6: normal tissue, slice 7
A7: normal tissue, slice 13
A8: normal tissue, medial margin, slice 1
A9: normal tissue, lateral margin, slice 15

If all the cassettes from slices of the gross mass (slices #8-12) contain invasive cancer AND the flanking slices (slices #7 and #13) are benign, then the tumor size is the gross size of 2.5 cm. If the flanking slices contain invasive cancer, then we submit tissue from the next row of flanking slices (i.e. slices #6 and/or #14) until there is no microscopic invasive cancer. In that case, the tumor size is the gross size (2.5 cm) PLUS the thickness of each additional flanking slice (i.e. if slice #7 is involved, then 0.5 cm is added for a total size of 3 cm).

Controversy: Lymphatic invasion and pT: AJCC does not mention how lymphatic invasion should be handled in terms of tumor size and pT. In fact, AJCC does not define the term “invasive carcinoma” except to distinguish it from what it calls non-invasive carcinoma (DCIS, LCIS and Paget’s disease of the nipple). It is not clear whether “invasive carcinoma” refers only to stromal invasion or to either stromal invasion or lymphatic invasion. This subtle detail becomes important in rare cases in which extensive lymphatic invasion is present to a much larger degree than the size of the stromal invasive component. We have encountered cases in which the stromal invasive component is a pT1 tumor but the lymphatic component size would bump the tumor to pT2 or rarely pT3. AJCC rules do not contain any language that address this uncommon scenario nor does the literature.

Recommendation: Our practice is to provide two AJCC stages, one based on stromal invasive size only, the other incorporating the span of lymphatic invasion, and to explain the issue in a comment. We do not use intralymphatic tumor for the official margin status reporting but we do describe in a comment if margins are close for intralymphatic component even though in our institution, the clinicians are typically less concerned about intralymphatic tumor.

Should the core needle biopsy findings be used to define tumor size? AJCC states that the size of the tumor in the core biopsy should not be added to the size in the excisional specimen. The larger of the two sizes should be used, but not added together.

Definition of microinvasive carcinoma and pT: AJCC defines microinvasive carcinoma as an invasive carcinoma no larger than 0.1 cm. Microinvasive carcinoma typically presents within a background of extensive DCIS and may be a single focus or multiple foci.

Potential Pitfall: Although AJCC states that tumor size should be rounded to the nearest millimeter, in the case of tumors near the threshold of microinvasion, rounding should not occur. In other words, 0.09 cm (0.9 millimeter) should not be rounded up to 0.1 cm nor should 0.12 cm (1.2 mm) be rounded down to 0.1 cm (1 mm).

For multifocal microinvasive cancers, AJCC states that each focus should be measured individually and not added together. As long as none of the foci are larger than 0.1 cm each, the term “microinvasive” is used.
If one of the foci is larger than 0.1 cm, then that size should be used for staging and the term “microinvasive” should not be used. AJCC states that the clinical significance of uni-focal versus multi-focal microinvasive carcinoma remains to be studied.

**Recommendation:** If multiple foci of true microinvasion are present, we report in a comment the approximate number of foci and clarify that the tumor measurement is based on a single focus.

Example:

Multiple foci of microinvasive ductal carcinoma. Three foci of invasive carcinoma (each under 0.1 cm) are present within high grade DCIS that spans 4 cm.

It may be worth considering to prove stromal microinvasion by using myoepithelial immunostains unless the morphology of the stromal invasion is clear beyond a doubt. We tend to have a low threshold for utilizing myoepithelial immunostains when evaluating DCIS with suspicious growth patterns. We also tend to heavily sample specimens in which the DCIS is growing in a large bulky or mass-like pattern as these may harbor small foci of invasion that are not visible grossly.

**Definition of multiple synchronous carcinomas and pT:** Occasionally multiple primary carcinomas may be found in one breast specimen (i.e. multiple simultaneous/synchronous ipsilateral primary carcinomas). AJCC defines multiple cancers as those that are grossly or macroscopically distinct. AJCC defines 0.5 cm as the minimum distance required between two macroscopic cancer foci to call them multiple cancers; anything closer than 0.5 cm likely represents a single cancer with a complex shape that appears multi-focal but is probably contiguous if further sampling is performed; in this case, the entire cancer dimension should be used for pT.

AJCC states that tumor size (pT) should be based only on the single largest tumor; do not add the sizes together from the multiple foci. AJCC does advise reporting in the comment of the report the total number of foci and sizes of each one. The code “m” is used to indicate “multiple” tumors. Example: if the largest of multiple tumors is 3.2 cm, the AJCC stage is pT2(m). Alternatively, AJCC states that the “m” can be replaced by the total number of invasive cancers. Example: if the largest of 3 cancers is 3.2 cm, the AJCC stage can be reported as pT2(3).

AJCC states that simultaneous bilateral primary cancers are staged separately (i.e. one pTNM generated for the right breast and another pTNM generated for the left breast).

Clinical significance of multiple tumors within the same pT category remains to be thoroughly studied. There is controversy as to whether multiple cancers may predict for involvement of axillary nodes; much of the controversy is rooted in methodologic issues in defining multiplicity in these studies (reviewed by Jain S et al. Pathology 2009; 41: 57-67). Survival does not appear to be affected by multiple synchronous breast cancers compared to unifocal breast cancer, though it appears that margin positivity may be an issue if breast conservation surgery is chosen. AJCC states that there is not enough compelling evidence to increase stage based on multiple cancers or to base pT on aggregate tumor measurement.

**Recommendation:** If there is suspicion for multiple ipsilateral primary cancers, additional sampling of tissue in between the two foci should be done to confirm that there is no microscopic tumor connecting the two foci together in dimensions not represented in the initial slides. If there is microscopic invasive cancer connecting the two macroscopic foci, this should be managed as a single, unifocal cancer and measured across the entire span of all foci rather than managed as multiple foci.

Whether ER/PR/HER2 should be done on all foci of multiple cancers in a single breast is not clearly defined. A recent study of 32 patients with multicentric breast cancers found equivalent ER/PR/HER2 profiles in all tumor foci, as well as equivalent morphologic features (Middleton et al. Cancer 2002; 94: 1910-6). In general, if the morphology and grade appears similar in all of them, performing prognostic markers on the largest or two largest is reasonable; however if the morphologies or grades are distinctly different, it may be prudent to test each distinct focus.
Controversy: Terminology of multifocal or multicentric cancer: Some authors refer to the terms multifocal breast cancer and multicentric breast cancer, though the AJCC does not refer to either term and instead uses the term “multiple carcinomas”. These terms have not been used uniformly by various authors and some have even interchanged them. Traditionally, the distinction between multifocal and multicentric breast cancer is based on anatomic distribution of the tumor relative to a breast quadrant. Tumors within a single quadrant are multifocal whereas tumors involving several quadrants are multicentric (Jain S et al. Pathology 2009; 41: 57-67). Multifocal breast cancers are defined as being no more than 5 cm apart from each other in the same quadrant. Multicentric breast cancers are defined as being in different quadrants or as being in the same quadrant but more than 5 cm apart from each other. These definitions rely upon careful dissection of the specimens to exclude microscopic cancer connecting the foci and detailed measurements; this is perhaps why there is variation in the application of this terminology. Whether there is a biological basis for distinguishes multifocal and multicentric breast cancer is suggested by some early studies but remains to be fully elucidated. Various types of clonality studies suggest that multifocal tumors are clonally related in contrast to multicentric tumors, though these studies are small in number (Jain S et al. Pathology 2009; 41: 57-67). As mentioned above, there is controversy regarding the clinical significance of multiple synchronous carcinomas and more studies are needed. In the meantime, we follow suit of AJCC and use the term “multiple cancers” rather than multifocal or multicentric cancer.

Definition of inflammatory carcinoma and pT: AJCC defines inflammatory carcinoma as a clinical entity. Staging as pT4d requires these clinical features to be present: diffuse erythema and edema involving a third or more of the skin of the breast. Microscopically, dermal lymphatic invasion is typically seen in this setting, however dermal lymphatic invasion alone is NOT sufficient (nor necessary) to diagnose inflammatory carcinoma or stage pT4d. The clinical features must be present; if they are present but involve less than a third of the breast, AJCC states this should be staged as pT4b, not pT4d. Carcinoma that ulcerates the skin is staged as pT4b. If the clinical features are present but dermal lymphatic invasion is not, the patient may still be classified as inflammatory carcinoma and asT4d (though obviously this requires detailed information from the clinician). The detailed distinction between the T4 subcategories is based on outcome data justifying strict criteria for defining a patient as T4d.

Recommendation: Detailed clinical information is not always given to pathologists. We never use the term “inflammatory carcinoma” as a diagnostic line. Instead, “invasive ductal carcinoma with extensive dermal lymphatic invasion” is a more precise diagnostic line. If we see dermal lymphatic invasion but are not given any clinical information details, we provide the AJCC pT stage based solely on the pathologic findings (i.e. not pT4d) and then comment that if the appropriate clinical findings are present, stage pT4d should be considered. This transfers the determination of the final stage back to the surgeon, who has the first hand data that is required.

Definition of Paget disease and pT: Paget disease of the nipple is defined as intraepidermal adenocarcinoma and is typically accompanied by the clinical features of exudate or crust involving the nipple/areola. Paget disease may present in three forms:

1.) Pure form, without underlying invasive or non-invasive carcinoma in the breast parenchyma; this is stage pTis.

2.) With parenchymal DCIS; stage pTis.

3.) With parenchymal invasive carcinoma; stage is based on the parenchymal invasive carcinoma.

Summary of Regional Lymph Node Staging:

Grossing axillary non-sentinel lymph nodes: AJCC states that each lymph node should be entirely submitted for microscopic evaluation. If it is too big to fit in a single cassette, slicing into 0.2 cm thick slices is advised. AJCC states that a single H&E section from each block is sufficient for axillary nodes; level sections are not necessary as a routine procedure.

Grossing axillary sentinel lymph nodes: AJCC does not specify a grossing protocol for sentinel nodes. The literature is replete with controversy regarding optimal grossing of sentinel lymph nodes; most
proposals involve some permutation of multi-step level sections and/or keratin immunohistochemical stains. The “right” method is still a matter of debate. There are ongoing prospective clinical trials looking at the role of keratin-positive cells in sentinel lymph nodes however these studies have not yet accumulated sufficient follow up time to report on.

**Recommendation:** In our institution, our breast cancer oncologists, surgeons and radiologists are in consensus with our pathologists to await the results of ongoing prospective clinical trials evaluating the significance of keratin-positive cells in sentinel lymph nodes. Thus, our current approach is to submit all slices of sentinel lymph nodes at 0.2 to 0.3 cm maximum thickness. Three step sections of each block are cut for H&E, with 1 unstained section from the center of the block reserved for immunohistochemistry, if needed later. We do not perform keratin immunostaining unless there is some atypical finding meriting further investigation.

**Definition of a positive node (pN1, pN2 or pN3):** AJCC defines a pathologically positive axillary node as containing a metastasis measuring at least 0.2 millimeter or >200 tumor cells. Positive node status is further subdivided by 4 factors: 1.) the size of metastasis; 2.) the anatomic node involved; 3.) the total number of positive nodes; and 4.) the method of detection (tissue biopsy versus FNA or clinical detection). The latter factor is somewhat confusing because it incorporates clinical findings into the pathologic staging, something that is easily overlooked by pathologists, particularly if the information is not clearly communicated by the clinician. AJCC uses the term “clinical detection” to refer to either positive FNA or positive clinical exam or positive radiologic findings. The sub-classification of positive nodes is summarized as follows:

- **By size of the metastasis**
  - 0.2 mm (or >200 cells) up to 2 mm is a micrometastasis: pN1mic
  - >2 mm is a macrometastasis: pN1, pN2, pN3, depending on total number of positive nodes

- **By specific anatomic node**
  - Positive internal mammary sentinel affects pN depending on status of other nodes.
  - Positive infraclavicular axillary node is pN3a
  - Positive supraclavicular axillary node is pN3c

- **By total number of positive nodes**
  - Total of 1-3 positive nodes is pN1
  - Total of 4-9 positive nodes is pN2
  - Total of >9 positive nodes is pN3

New to the 7th edition AJCC is the separation of pN1mic from pN1 in the overall staging. Because there is only limited survival effect of pN1mic compared to pN0 for pT1 tumors (which are among the most common tumors), pN1mic is Stage IB, whereas pN1a or higher is Stage IIA or higher. AJCC based this on outcome data from a recent SEER national cancer database study showing that 10 year survival among pT1 cancers dropped from 78% for pN0 to only 77% for pN1mic but down to 73% for pN1. In the overall population (not just pT1), micrometastases exhibited a statistically significant behavior that was in between that for pN0 and pN1. (Chen SL et al. Ann Surg Oncol 2007; 14:3378-84).

**Recommendation regarding node anatomy:** In our experience, clinicians rarely provide the anatomic name of a lymph node. We do not dig beyond the information provided on the submitted pathology specimen requisition form for such information. However, from time to time a clinician will notify us after the fact that one of the positive nodes may have been an infraclavicular or supraclavicular node, which upstages the patient. In such cases we will amend the original report to reflect the higher stage.

**Controversy: Definition of micrometastasis:** The size threshold of 2 millimeter or larger was used by AJCC to define positive nodes up until the 6th edition AJCC. With the advent of sentinel lymph node technique and enhanced pathologic examination methods (multitstep level sections and keratin immunohistochemistry), studies suggested that there was clinical significance of metastasis smaller than 2 millimeters. The 6th edition AJCC lowered the size threshold of a positive node to 0.2 millimeter based on one retrospective study (Nasser IA et al Human Pathology 1993; 24:950-7) and created the category of “micrometastasis, pN1mic” for deposits that are 0.2 mm to 2 mm each and “macrometastasis, pN1 or
greater" for deposits 2 mm or larger. AJCC acknowledges that the lower limit of 0.2 mm may need to be revised lower as evidence from future studies evaluating smaller deposits become available.

Controversy: Measurement of multiple small metastases: AJCC does not specifically state what device (handheld ruler, handheld ocular micrometer, in-scope ocular micrometer) should be used to measure small metastatic clusters. At the resolution of fractions of a millimeter, a handheld ruler is not likely accurate and we recommend an ocular micrometer, either hand-held or, preferably, an in-scope micrometer. The definition of a “cluster” of cells is critical to understand and apply. AJCC states that a cluster is a group of cells that are touching each other (confluent or contiguous). Although AJCC does not explicitly state how to deal with multiple clusters that are in proximity to each other, the implication of the rule of confluent/contiguous cells is that clusters that are not touching each other should be considered independent and measured independently. The controversy here is that the anatomic distribution of multiple clusters may be variable. In one scenario, two tiny clusters may be present on opposite ends of the node; these should clearly be measured independently. In another scenario, two tiny clusters may be present within a fraction of a millimeter from each other. AJCC does not explain how to manage the latter scenario and instead leaves it to the judgment of the pathologist:

The pathologist should use judgment, and not an absolute cutoff of 0.2 mm or exactly 200 cells, in determining the likelihood of whether the cluster of cells is an ITC or a true micrometastasis. (7th edition AJCC, page 364).

In practice, it is challenging to deal with these cases and we cannot offer a better solution other than using one’s best judgment, as AJCC recommends, and to explain the interpretation in a comment.

Controversy: Measurement of non-confluent single cell metastases: Another problem with the AJCC definition requiring micrometastases to be confluent clusters >0.2 mm is that some metastases are nonconfluent, such as metastatic lobular carcinoma. By definition, the loss of E-cadherin results in loss of cell to cell cohesion and in a lymph node, the metastases can be present as single cells distributed within the subcapsular sinus or cortex. Large amounts of metastatic tumor may be present without any cell to cell cohesion or confluence. To get around this issue, AJCC states that the lower limit of a true metastatic deposit contains about 200 tumor cells. Using this guide, AJCC states that if at least 200 tumor cells are present, the node can be coded positive even if there is no cell confluence. This addresses the issue of larger deposits of scattered metastatic lobular carcinoma, however according to this rule, lobular carcinoma deposits that are smaller than 200 cells should not be coded as positive. We would advise using judgment here, as permitted by AJCC, and not be bound strictly by the 200 cell count rule.

Controversy: Matted nodes: AJCC does not provide instruction regarding how matted nodes should be counted. We do our best to estimate the number of nodes but in some cases this is not possible; a diagnostic description of "metastatic carcinoma involving matted lymph nodes" is a reasonable resolution, with a staging of “at least pN1 but could be higher due to matted nodes”.

Controversy: Cancerous nodules in axillary fat: AJCC states that cancerous nodules in axillary fat that are not associated with any evidence of residual lymph node tissue should be classified as positive nodes (pN1 or greater). Attention should be paid to the surrounding fatty tissue to ensure that this is not simply axillary breast tissue containing cancer. Some patients have breast tissue that extends superiorly into the axillary region and this may be involved by malignancy but should not be counted as nodal metastasis simply because it is in the axilla. Although AJCC does not mention this level of detail, we would be cautious about classifying axillary cancerous nodules if normal breast parenchyma is seen immediately adjacent to these nodules, particularly if DCIS is also present (which would further suggest the invasive tumor is axillary parenchymal tumor rather than nodal metastasis). At the least, a descriptive comment outlining the two possible interpretations is warranted.

Definition of a negative node (pN0 or pN0i+): AJCC defines a negative node as one without any evidence of metastatic tumor (pN0) or one with isolated tumor cell clusters (ITC) that are smaller than 0.2 millimeter each or fewer than 200 cells each (using either H&E alone or keratin immunostaining alone or both H&E and immunostaining). If multiple tumor groups are present, do not add the sizes together. AJCC states that a 0.2 millimeter solid sphere of tumor cells is about 1000 cells and therefore when looking at a cross-section of such a sphere, there will be about 200 cells present; this is the origin of the 200 cell
maximum threshold for defining ITC. Also of note, the label “i+” in pN0i+ stands for “isolated tumor cells”, not “immunohistochemistry”. This was a source of confusion in the 6th edition AJCC. pN0i+ can be used when only H&E slides were evaluated without any use of immunohistochemistry.

Controversy: Multiple foci of small clusters of tumor cells: Some lymph nodes may contain not one single cluster of ITC, but several small clusters of tumor cells grouped near each other. The distribution of these clusters may be such that it is difficult to tell whether it is 1.) a single but dispersed metastatic deposit that should be measured from one end to the other or 2.) several groups of ITC that should be individually measured. This subtle difference is the difference between a true pN1mic micrometastasis (scenario 1) or several pN0i+ ITC. AJCC attempts to clarify this by stating that a single tumor deposit is a group of cells that are touching one another (“confluent or contiguous tumor cells”). This definition is helpful in some cases, but in other cases the cells may not be confluent and may be scattered in a discohesice pattern along the subcapsular sinus. These scenarios are difficult to resolve and the AJCC simply states that pathologists “should use judgment”. Such judgment will lead to observer variation and inconsistent staging, but it is the best that can be done using the current AJCC system.

See discussion above (Measurement of small metastases) for further details.

Controversy: Stromal reaction around isolated tumor cells and pN status: Some isolated tumor cells may be embedded in a fibrous, stromal (desmoplastic) reaction. AJCC states that the size of the tumor deposit should include this stromal reaction. This may convert what appears to be ITC (pN0i+) to micrometastasis (pN1mic). For example, the largest tumor deposit may measure 0.1 millimeter in span (pN0i+) but if it is embedded in a stromal reaction spanning 0.3 millimeter, the metastasis size is defined as 0.3 millimeter (pN1mic). In our experience, measuring the size of the stromal reaction can be difficult if it is irregularly shaped or involved by hemorrhage or histiocytes. At the least, if this approach upstages from pN0i+ to pN1mic, it is probably a good idea to explain in the comment that the stromal reaction was included in the measurement.

Summary of Distant Metastasis Staging:

The main issue to consider for pM staging is that AJCC now separates out incidentally detected cancer cells (<0.2 millimeter) in distant, non-regional nodal tissue if there is no clinical or radiologic evidence of metastasis. The example raised by AJCC is incidental metastasis <0.2 mm found in a prophylactic oophorectomy; in the absence of any clinical/radiologic evidence of ovarian involvement, this finding should not be staged as pM1 distant metastasis but as pM0i+.

Summary of Staging Patients After Neoadjuvant Therapy:

Neoadjuvant chemotherapy is now a standard option for patients with locally advanced or bulky tumors. The goal of this approach is to shrink the tumor to make surgery easier, and possibly allow for conservation surgery rather than mastectomy. These patients typically are diagnosed by core needle biopsy in the setting of clinical and radiologic findings of locally advanced or bulky disease. They then typically receive 4 cycles of chemotherapy over several months, followed by either lumpectomy and some form of node dissection or mastectomy with node dissection.

Evaluation for residual cancer in the breast and lymph nodes can be difficult because of tumor shrinkage, cytologic changes in the appearance of residual tumor, and stromal alterations due to chemotherapy. The gross appearance of residual tumor may not resemble that of a tumor which has not received neoadjuvant treatment. Some residual tumors are not grossly visible at all. Furthermore, stromal alterations (i.e. fibrosis, hemorrhage) may grossly resemble residual tumor. Similarly in lymph nodes, stromal alterations may cause the gross appearance of the nodes to resemble residual metastatic disease.

Details of these gross and cytologic alterations are presented in a separate lecture syllabus. The remainder of this discussion centers on the AJCC staging of neoadjuvant treated patients.
**Definition of residual tumor size (ypT):** AJCC states that ypT is based on the largest single focus of residual invasive cancer; stromal fibrosis in the residual tumor bed should not be used to increase the size beyond that of actual invasive tumor cells (7th edition AJCC, page 359). If the residual tumor consists of microscopic nests in fibrotic stroma, ypT should be based on the largest contiguous area of invasive carcinoma (7th edition AJCC, page 366). AJCC "suggests" that the cellularity of the residual tumor be included in the report, though formal rules for defining cellularity are not provided.

**Controversy: Measuring scattered residual tumor:** Cancers may shrink in one of two patterns following neoadjuvant chemotherapy: Scenario 1.) concentric shrinkage, resulting in a single residual focus smaller than the pre-treatment tumor size or Scenario 2.) patchy, non-concentric shrinkage, resulting in multifocal residual tumor that may span the same size as the pre-treatment tumor size (but with reduced cellularity) or that may span a smaller size than the pre-treatment tumor size. Application of the AJCC rules for ypT is straightforward in Scenario 1 but less clear in Scenario 2. AJCC does not provide a definition of what constitutes separate multiple foci or of whether the definition applies to macroscopic tumor or microscopic tumor. Some cancers may simply have diffusely scattered microscopic clusters of residual tumor in a low cellularity pattern across several centimeters, sometimes the same span as the pre-treatment tumor size. AJCC does not define how such cases should be managed for ypT.

**Recommendation for measuring residual tumor:** AJCC acknowledges that their ypT definition is “an unresolved problem” in neoadjuvant treated patients and that “no single method of assessing response has been shown to be a superior predictor of outcome”. Therefore, we provide two measurements:

- **Measurement 1.** the total, maximal span of all residual invasive tumor foci seen microscopically.
- **Measurement 2.** if a distinct single tumor mass can be clearly identified within the overall residual tumor, (for example, if a gross mass can be detected within the larger bed of microscopic cancer) then we report the size of that largest single tumor mass

For cases of concentric tumor shrinkage, both measurements are the same. For patchy, non-concentric tumor shrinkage, we often cannot clearly identify a distinct single mass within the overall residual tumor and therefore, both measurements are the same. This is typical in cases in which there are scattered microscopic foci distributed over large territories of fibrosis. However, if a distinct mass can be separated from other foci of residual tumor, then that measurement (Measurement 2) is used for ypT.

We generally provide a descriptive comment explaining the pattern of the residual tumor and explaining how we derived the measurements.

**Controversy: Defining residual tumor cellularity:** Initial studies suggest that cellularity of the residual cancer may have prognostic value. In other words, a residual 4 cm tumor that is highly cellularity (i.e., mostly cancer) may behave differently than the same size tumor composed of a scant, low cellularity (i.e., mostly fibrosis with rare tumor cells). Furthermore, in some tumors the cellularity may be heterogeneous, with some foci of high and other foci of scant cellularity. AJCC does not define how cellularity should be measured or reported (qualitative versus quantitative cellularity).

**Recommendation for reporting cellularity:** Currently, a qualitative estimate seems reasonable (low, moderate, high cellularity), with reference to the relative cellularity compared to the pre-treatment core biopsy, if available for review.

**Controversy: Measuring residual intralymphatic tumor:** A small subset of neoadjuvant treated cancers will harbor extensive residual intralymphatic carcinoma without stromal invasive carcinoma or with limited stromal invasive carcinoma. In some cases, the span of the residual intralymphatic component may be several centimeters (matching the pre-treatment tumor size). AJCC does not comment on whether intralymphatic tumor should be included in ypT. We have demonstrated in a recent study that such intralymphatic tumor does carry adverse prognostic significance, even in the absence of residual stromal invasion (Rabban J et al. Am J Surg Pathol 2009; 33: 56). Therefore, we report the residual tumor size based on stromal invasive cancer (and use this for ypT) and we also report the residual tumor size based on both the stromal and intralymphatic cancer in a comment.
**Definition of residual lymph node status (ypN):** AJCC states that lymph nodes following neoadjuvant treatment should be classified in the same manner as they are in patients without neoadjuvant treatment.

**Controversy: Minimal residual metastatic tumor and ypN:** One of the indications for neoadjuvant treatment is nodal involvement at presentation. The degree of nodal involvement is typically clinically apparent and constitutes macrometastases or micrometastases in most cases; these are not ITC nodes. Nodal metastases may respond to neoadjuvant therapy by completely disappearing (ypN0) or by partially disappearing. Even if the residual metastatic deposit is small, it represents the vestiges of what was originally a true metastasis, not ITC of questionable clinical relevance. Therefore, even the smallest residual deposits are likely biologically different than ITC and probably should be considered as ypN1; however, the AJCC states that residual isolated tumor clusters should be viewed with the same rules governing non-neoadjuvant treated patients. Thus, it is possible to have nodes that are ypN0i+. It is unclear from the AJCC manual whether this decision to allow for ypN0i+ instead of simply coding all residual nodal involvement as ypN1 is based on published evidence.

A subtle point that may be overlooked is that AJCC advises incorporating the background stromal fibrosis that accompanies the residual nodal metastases into the size of the deposit. Thus, a 1.6 millimeter focus of fibrosis containing scant tumor cells measuring less than 0.2 mm should be classified as a 1.6 mm metastasis (ypN1mic), not as ITC. In our experience, most residual nodal metastases are accompanied by enough of a stromal reaction to bump even the smallest tumor foci out of the ITC category and into the ypN1 category.

**Recommendation for minimal residual metastatic tumor and ypN:** If the residual nodal metastasis is coded as ypN1 based on incorporating stromal fibrosis into the measurement of the residual tumor cells which, on their own, would be less than 0.2 mm or <200 cells, this should be explained in the comment so another observer understands how the staging classification was made.