The N of TNM and isolated tumor cells

A GIPS forum discussion,
Galen Cortina 2016

The **Second Amendment** of the United States Constitution reads: "A well regulated Militia, being necessary to the security of a free State, the right of the people to keep and bear Arms, shall not be infringed."

N, ITCs & Staging (extent of disease)

- "…staging provides those with cancer and their physicians with the critical benchmark for defining prognosis and the likelihood of over coming their cancer…"*
- 'T, N, and M remain purely anatomic' – [paraphrased]
- Grouping is based on prognosis (stage I, II, III, and IV)

*AJCC Cancer Staging Manual, 7th ed, S B Edge editor , preface; Roman numerals for stage grouping.

Isolated tumor cells

- Cluster of cells less not more than 0.2mm in a lymph node
- "The appropriate N classification for cases with nodes only involved by ITCs is defined in the disease site chapters for those cancers where this commonly occurs"*
  - ?room for interpretation?
- Today, we are talking about H&E only, not IHC or molecular analysis of occult cells
- We are not talking about sentinel nodes

*AJCC Cancer Staging Handbook, 7th ed, S B Edge editor, p18

ITCs, easy background

- Breast- ITCs are N0 with very good supporting information
- Melanoma- ITCs are N1 with very good supporting information
- What about colon?
- What about the rest of GI carcinoma?
- CAP protocols are not always = to AJCC (but we know that, so no anxiety needed)

Framing the debate

- Overview of AJCC/CAP
- General rules AJCC
- Breast example
- Colon
- The rest of GI
- Other cancers in AJCC
- Survey results and audience participation

assign pN. However, if N is based on microscopic confirmation of the highest N category, it is pN regardless of whether T is pT or cT. For example, in the case of breast cancer with pT defined by resection, pN may be assigned solely on the basis of resected level I or II nodes, or a level I sentinel node without biopsy of level III or supraclavicular nodes. However, if there is microscopic confirmation of supraclavicular node involvement, the case may also be classified as pN3.

Specialized pathologic techniques such as immunohistochemistry or molecular techniques may identify limited metastases in lymph nodes that may not have been identified without the use of the special diagnostic techniques. Single tumor cells or small clusters of cells are classified as *isolated tumor cells* (ITC). The standard definition for ITC is a cluster of cells not more than 0.2 mm in greatest diameter. The appropriate N classification for cases with nodes only involved by ITC's is defined in the disease site chapters for those cancers where this commonly occurs. In most of such chapters, these cases with ITC only in lymph nodes or distant sites are classified as pN0 or cM0. This rule also generally applies to cases with findings of tumor cells or their components by nonmorphologic techniques such as flow cytometry or DNA analysis. There are specific designators to identify such cases by disease site [e.g., N0 (i+) in breast cancer to denote nodes with ITC only].

Pathologic M. The pathologic assignment of the presence of *metastases* (*pM1*) requires a biopsy positive for cancer at the metastatic site (Table 1.7). Pathologic M0 is an undefined concept and the category pM0 may not be used. Pathologic classification of the absence of distant metastases can only be made at autopsy. However, the assessment of metastases to group a patient by pathologic TNM groupings may be either clinical (cM0 or cM1) or pathologic (pM1) (e.g., pTNM = pT; pN; cM or pM). Cases with a biopsy of a possible metastatic site that shows ITC such as circulating tumor cells (CTCs) or disseminated tumor cells (DTCs), or bone marrow

TABLE 1.7. M classification rules

Clinical M classification only requires history and examination
Imaging of distant organ sites not required to assign cM0
Infer status as clinical M0 status unless known clinical M1
"MX" is not a valid category and may not be assigned
Elimination of "MX" is new with AJCC/UICC, 7th edition
Pathologic M classification requires a positive biopsy of the metastatic site (pM1)
Pathologic M0 ("pM0") is not a valid category and may not be assigned
Stage a case with a negative biopsy of suspected metastatic site as cM0
Case with pathologic T and N may be grouped as pathologic TNM using clinical M designator (cM0 or cM1) (e.g., pT1 pN0 cM0 = pathologic stage I)
Case with pathologic M1 (pM1) may be grouped as clinical and pathologic Stage IV regardless of "c' or "p" status of T and N (e.g., cT1 cN1 pM1 = clinical or pathologic stage IV)
ITC in metastatic sites (e.g., bone marrow)
Or circulating or DTCs classified as cM0(i+)
Disease-specific rules may apply

micrometastases detecte
cM0(i+) to denote the
and to classify the stage

Pathologic staging
whether or not the prin
mary tumor cannot be
remove it, and if the hig
tumor can be confirmed
cation and staging have
tumor. Note that micros
necessarily require remo

Posttherapy or Postneo
where systemic and/or r
juvant) or where no sur
assessed at the conclusio
resection performed). Th
extent of response to the
tion to patients and help
and/or radiation therapy
as for clinical or patholo
are recorded using the p
yc prefix is used for the c
for the pathologic stage
neoadjuvant therapy. Bo
the medical record, thou
ypTNM in cases where s
be classified by the M st
therapy. If a biopsy of a
clinical and pathologic S
is recorded using the clin
stage used for case comp
should be the clinical (cT

Retreatment Classificati
assigned when further tre
disease-free interval. The
nosis and treatment does
The use of this staging for
prefix (rTNM). All inform
be used in determining th
cancer is important if clin
priate for each componen
nent by clinical, endoscop

Autopsy Classification. T
by postmortem examinati
prior to death. This autop
prefix (aTNM) and shoulc
obtained at the time of dea

GENERAL…"The appropriate N designation for cases with nodes only involved by ITCs is defined in disease specific chapters for those cancers where this commonly occurs. In most such chapters these cases with ITC only in lymph nodes…are classified as pN0"

reported as 1.2 mm in size should be recorded for staging as a 1-mm tumor, and a 1.7-mm tumor should be recorded as a 2-mm tumor. If the tumor is not resected, but a biopsy of the primary tumor is performed that is adequate to evaluate the highest pT category, the pT classification is assigned. Some disease sites have specific rules to guide assignment of pT category in such cases.

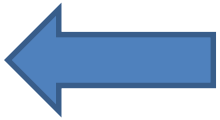
Pathologic N. The pathologic assessment of *regional lymph nodes* (*pN*) ideally requires resection of a minimum number of lymph nodes to assure that there is sufficient sampling to identify positive nodes if present (Table 1.6). This number varies among diseases sites, and the expected number of lymph nodes is defined in each chapter. The recommended number generally does not apply in cases where sentinel node has been accepted as accurate for defining regional node involvement and a sentinel node procedure has been performed. However, in cases where lymph node surgery results in examination of fewer than the ideal minimum number, the N category is still generally classified as pathologic N according to the number of positive nodes and/or location of the most advanced pathologic node resected. At least one node with presence or absence of cancer documented by pathologic examination is required for pathologic staging N. The impact of use of pathologic N classification with fewer than the minimum resected nodes may be subsequently defined by review of the number of resected nodes as recorded in a cancer registry.

Pathologic assessment of T (pT) is generally necessary to assign pathologic assessment of lymph nodes. In conjunction with pT, it is not necessary to have pathologic confirmation of the status of the highest N category to

TABLE 1.6. N classification rules

Categorize N by disease-specific rules based on number and location of positive regional nodes
Minimum expected number and location of nodes to examine for staging defined by disease type
If lymph node surgery is performed, classify N category as pathologic even if minimum number is not examined
Pathologic assessment of the primary tumor (pT) is necessary to assign pathologic assessment of nodes (pN) except with unknown primary (T0). If pathologic T (pT) is available, then any microscopic evaluation of nodes is pN
In cases with only clinical T in the absence of pT excision of a single node or sentinel node(s) is classified as clinical nodal status (cN)
Microscopic examination of a single node or nodes in the highest N category is classified as pN even in the absence of pathologic information on other nodes
Sentinel lymph node biopsy is denoted with (sn), e.g., pN0(sn); pN1(sn)
Lymph nodes with ITC only generally staged as pN0; disease-specific rules may apply (e.g., melanoma)
Direct extension of primary tumor into regional node classified as node positive
Tumor nodule with smooth contour in regional node area classified as positive node
When size is the criterion for N category, stage by size of metastasis, not size of node when reported (unless specified in disease-specific rules)

GENERAL. “Lymph nodes with ITC only generally staged as pN0…”



*Pathologic (pN)**

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i–)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes

BREAST; clearly designated ITC data element in paragraph and tabular formats in 11 lines of text.

ITCs and Breast cancer prognosis

- "Isolated tumor cells or micrometastases in regional lymph nodes were associated with a reduced 5-year *disease-free* survival among women with favorable early stage breast cancer who did not receive adjuvant therapy"
- "….in patients with isolated tumor cells or micrometastases who received adjuvant therapy, disease-free survival was improved."
- "In view of our results, a reevaluation of the current AJCC classification is warranted."
- Data for ITCs was independent of micrometastases and held true (this was NOT a hybrid category)
- N0(i+) is worse than N0
- N Engl J Med 2009;361:653-63
- The effect on overall survival is not known.

ITC data element in GI
[Site specific ITC classified as N0 for staging]

Organ	AJCC 7th edition	CAP protocol (Sep 2015)
Esophagus	Not mentioned	Not mentioned
Stomach	Not mentioned	Yes
Small bowel	Not mentioned	Not mentioned [no special technique*]
Appendix	Not mentioned	Not mentioned
Colon and rectum	Yes (p.153) [Not in 6th ed.]	Yes [also N(mic) and M(mic)]
Anus	Not mentioned	Not mentioned
Gallbladder	Not mentioned	Not mentioned [no special technique*]
Bile ducts, extra-hepatic	Not mentioned	No [no special technique]
Ampulla	Not mentioned	Not mentioned [no special technique*]
Pancreas	Not mentioned	Not mentioned

**Note: Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

***Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 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

Note: A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

ANATOMIC STA

Stage	T
0	Tis
I	T1 T2
IIA	T3
IIB	T4a
IIC	T4b
IIIA	T1– T1
IIIB	T3– T2– T1–
IIIC	T4a T3– T4b
IVA	Any
IVB	Any

Note: cTNM is the
y prefix is used fo
(e.g., ypTNM). Pa
that may be simila
that have recurred

*Dukes B is a con
groups, as is Duke
Coller classificatio

PROGNOSTIC
(Recommend

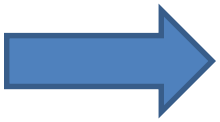
Required for sta

Clinically signifi

COLON

This is typical for all GI cancers-No tabular detailed ITC N-data elements like that in breast

COLON; there is a paragraph indication that ITCs are N0(i+); but appears after a conditional statement about future technology



of tu[r] all regional nodes, are removed intact. Thus, the circumferential surface (CRM) of TME resection specimens is the mesorectal or Waldeyer's fascia. Rectal resection performed by less precise techniques may be associated with incomplete excision of the mesorectum. It is critical that the analysis of the surgical specimen follows the CAP guidelines that refer to examination of the TME specimen. In addition, it is essential that the distance between the closest leading edge of the tumor and the CRM (known as the surgical clearance) be measured pathologically and recorded in mm in the CRM field on the staging form. A margin of greater than 1 mm is required with TME to be considered a negative margin because surgical clearance of 1 mm or less is associated with a significantly increased risk of local recurrence and should be classified as positive (Figure 14.3).

Residual Tumor (R). The completeness of resection is largely dependent on the status of the CRM, although the designation is global and would include the transverse margins and other disease observed but not removed at surgery. The resection (R) codes should be given for each procedure:

- R0—Complete tumor resection with all margins histologically negative
- R1—Incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved)
- R2—Incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, macroscopic margin involvement)

Isolated Tumor Cells and Molecular Node Involvement. As technology progresses and sentinel node biopsy or other procedures may become feasible in colon and rectal surgery, the issue of interpretation of very small amounts of detected tumor in regional lymph nodes will continue to be classified as pN0, and the universal terminology for these isolated tumor cells (ITC) will follow the terminology referenced in Chap. 1. The prognostic significance of ITCs, defined as single malignant cells or a few tumor cells in microclusters, identified in regional lymph nodes that otherwise would be considered to be negative is still unclear. Therefore, ITC identified the collection of data on ITC that may be generated by pathologists who use special immunohistochemical stains or molecular analysis procedures to identify ITC in nodes that might otherwise be considered negative for metastasis by standard hematoxylin and eosin (H&E). It should be noted that isolated tumor cells identified on H&E stains alone are also classified as ITC and are annotated in the same fashion as ITC seen on immunohistochemical stains (i.e., pN0(i+); "i" = "isolated tumor cells").

KRAS. Analysis of multiple recent clinical trials has shown that the presence of a mutation in either codon 12 or 13 of KRAS (abnormal or "mutated" KRAS) is strongly associated with a lack of response to treatment with anti-EGFR antibodies in patients with metastatic colorectal carcinoma. It is recommended that patients with advanced colorectal carcinoma be tested for the presence of mutations in KRAS if treatment will include an anti-EGFR antibody. Where the status of KRAS is known, it should be recorded as a site-specific factor as either Normal ("Wild Type") or Abnormal ("Mutated").

Anatomic Boundary. The most often has been equa pathologically. However, w defining the boundary bet ring, which corresponds to palpable on digital rectal e

TNM Stage of Disease. Sin data with regard to surviva of both Stages II and III (T prognosis has been shown f disease in SEER analyses for cancer (Tables 14.6 and 14.7 lesions have been subdivide visceral peritoneum) and T organs or structures). In adc has been shown to influen separate analyses of SEER (cancer, Tables 14.4–14.7; Fi and observed survival are l is survival corrected by age mation). Also the total nun on survival in colon and re increased nodes examined i better outcome in colon car whereas the association hol be less important in T4a anc preoperative radiation or c of patients in the rectal carc

Stage Group II has t (T4aN0), and IIC (T4bN These differences are shov (Tables 14.4 and 14.5) and

Within Stage III, a nu ferential prognosis found i 14.3), the SEER rectal anc the NCDB colon cancer ar prognosis more akin to III to IIIC. In addition, severa akin to IIIA (the T1N2a g groups) and have been shi

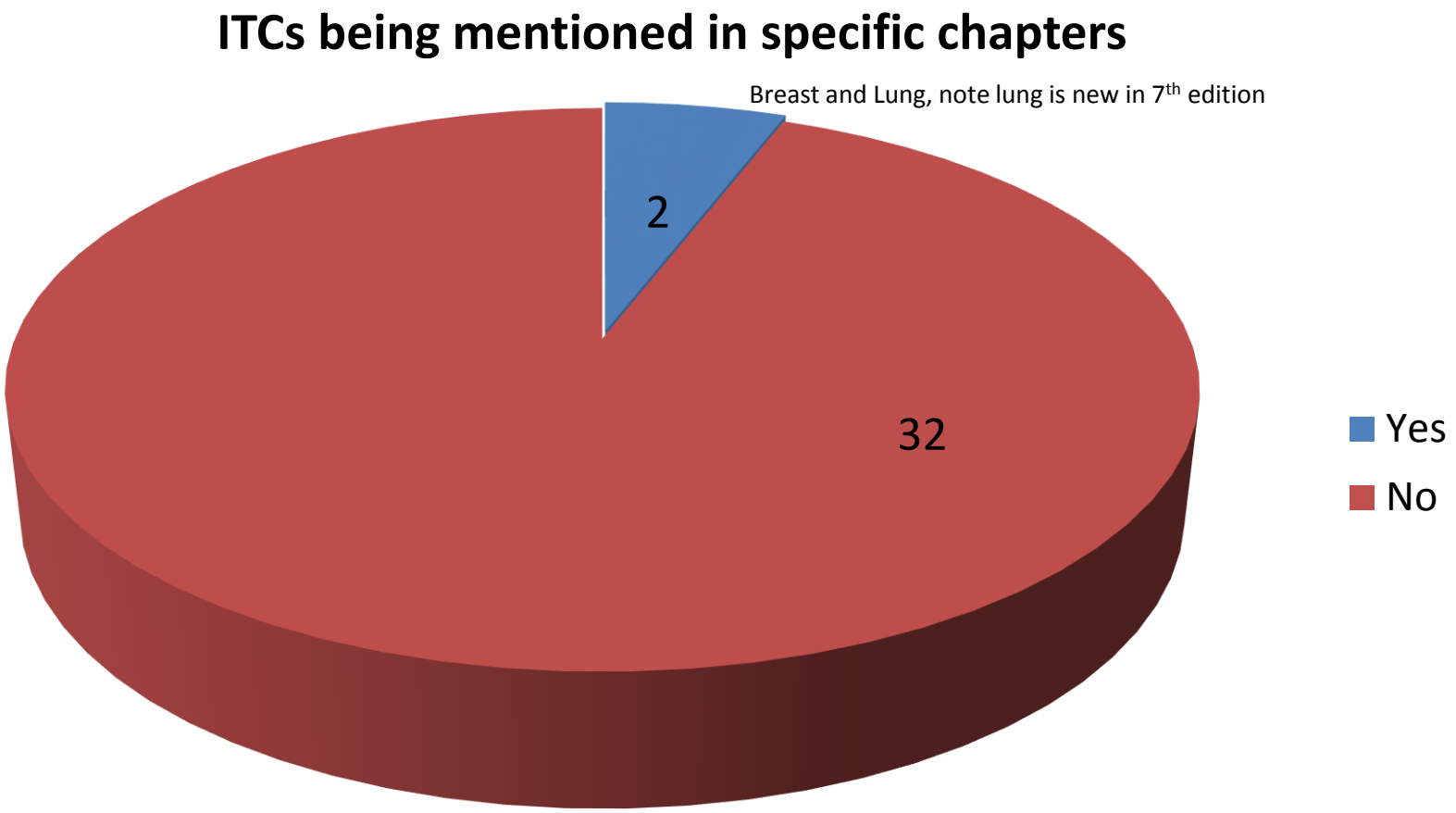
Figures 14.4 and 14.5 with adenocarcinoma of th rates for 9,860 cases with a

Independent Prognostic the TNM, independent pr management and are well ease, histologic type, hist and cytokine levels, extra

"It should be noted that isolated tumor cells identified on H&E stains alone are classified as ITC …pN0(i+); 'i'= 'isolated…"

This paragraph does not appear in other GI cancer chapters

AJCC 7th edition Non-GI site specific chapters (excluding neuro, sarcoma and lymphoma) and ITCs

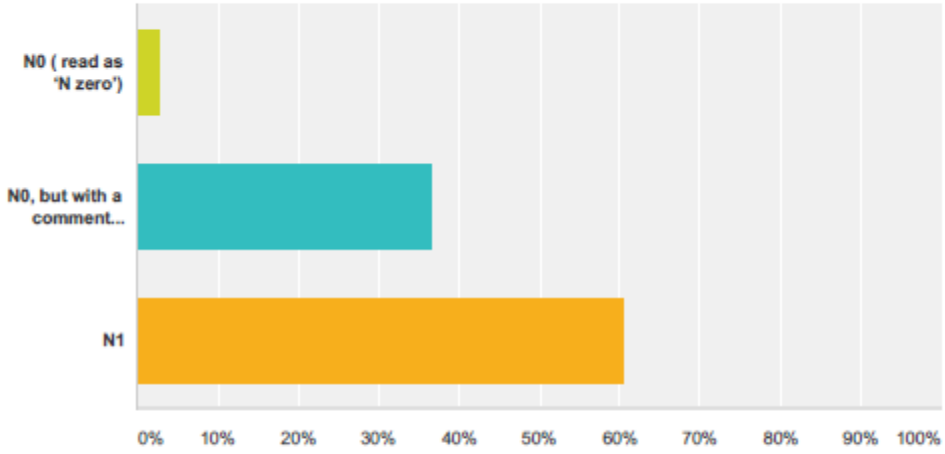


Moving forward

- Grateful to AJCC (and CAP)
- Data from GIPS survey
- Discussion

Q1 How do you report ITCs in esophageal carcinoma?

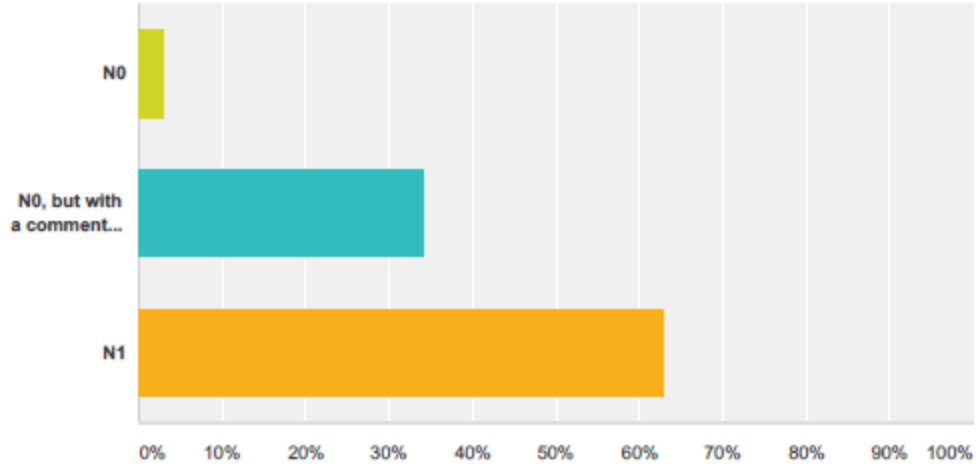
Answered: 71 Skipped: 0



Answer Choices	Responses	
N0 (read as 'N zero')	2.82%	2
N0, but with a comment indicating ITCs are present [or some other similar notation, eg. N0(i+)]	36.62%	26
N1	60.56%	43
Total		71

Q2 How do you report ITCs in gastric carcinoma?

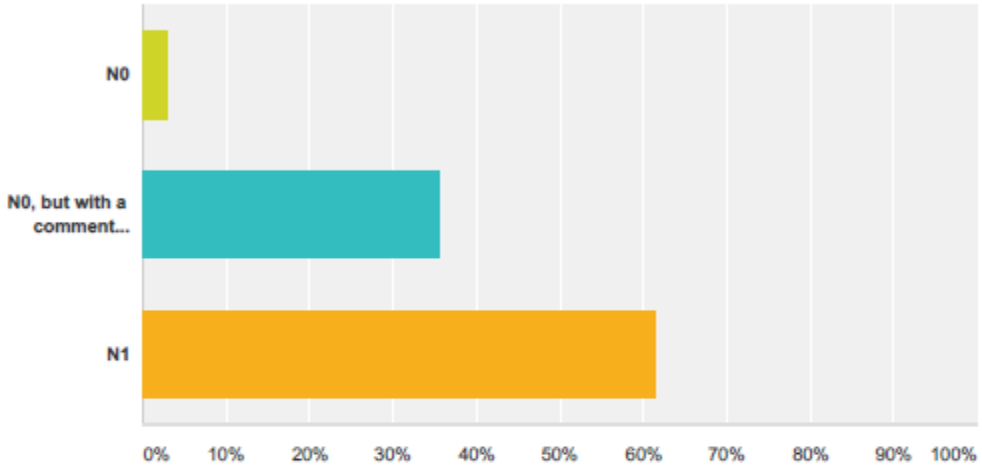
Answered: 70 Skipped: 1



Answer Choices	Responses	
N0	2.86%	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	34.29%	24
N1	62.86%	44
Total		70

Q3 How do you report ITCs in small bowel carcinoma?

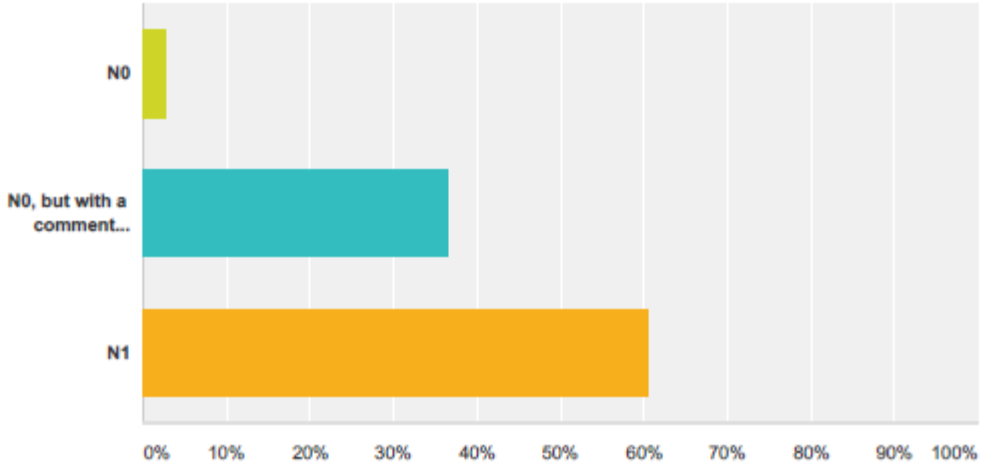
Answered: 70 Skipped: 1



Answer Choices	Responses	
N0	2.86%	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	35.71%	25
N1	61.43%	43
Total		70

Q4 How do you report ITCs in appendiceal carcinoma?

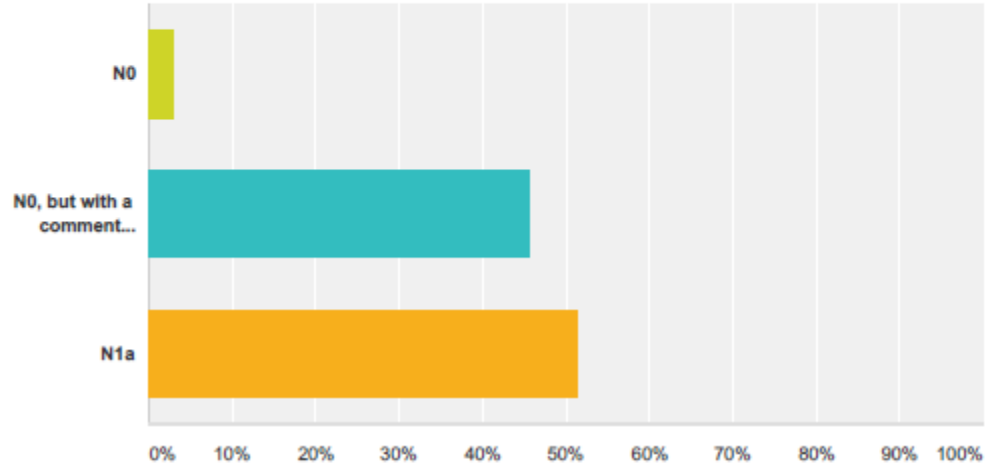
Answered: 71 Skipped: 0



Answer Choices	Responses	
N0	2.82%	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	36.62%	26
N1	60.56%	43
Total		71

Q5 How do you report ITCs in colorectal carcinoma?

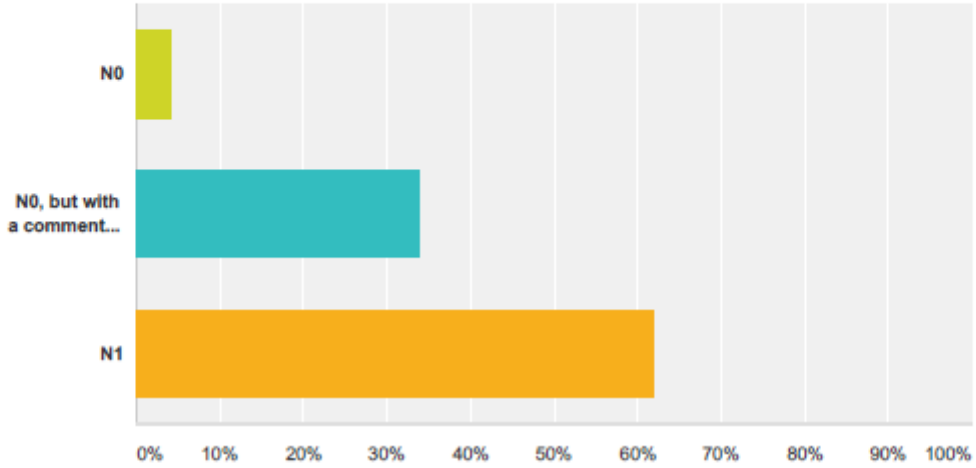
Answered: 70 Skipped: 1



Answer Choices	Responses	
N0	**2.86%**	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	**45.71%**	32
N1a	**51.43%**	36
Total		**70**

Q6 How do you report ITCs in anal carcinoma?

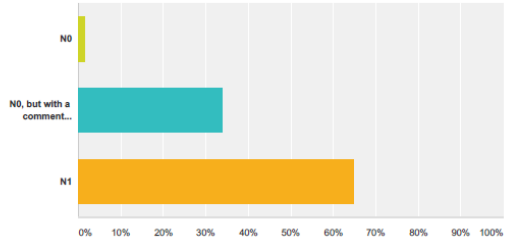
Answered: 71 Skipped: 0



Answer Choices	Responses	
N0	4.23%	3
N0, but with a comment indicating ITCs are present (or some other similar notation)	33.80%	24
N1	61.97%	44
Total		71

Q8 How do you report ITCs in extra-hepatic bile duct carcinoma?

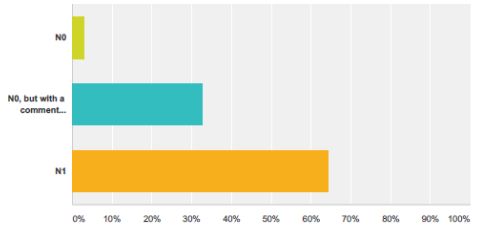
Answered: 68 Skipped: 3



Answer Choices	Responses	
N0	1.47%	1
N0, but with a comment indicating ITCs are present (or some other similar notation)	33.82%	23
N1	64.71%	44
Total		68

Q9 How do you report ITCs in ampullary carcinoma?

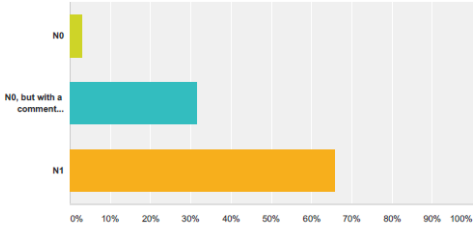
Answered: 70 Skipped: 1



Answer Choices	Responses	
N0	2.86%	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	32.86%	23
N1	64.29%	45
Total		70

Q10 How do you report ITCs in pancreatic carcinoma?

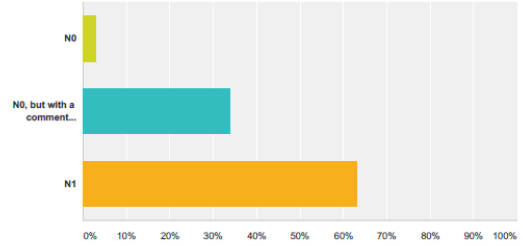
Answered: 70 Skipped: 1



Answer Choices	Responses	
N0	2.86%	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	31.43%	22
N1	65.71%	46
Total		70

Q7 How do you report ITCs in gallbladder carcinoma?

Answered: 68 Skipped: 3

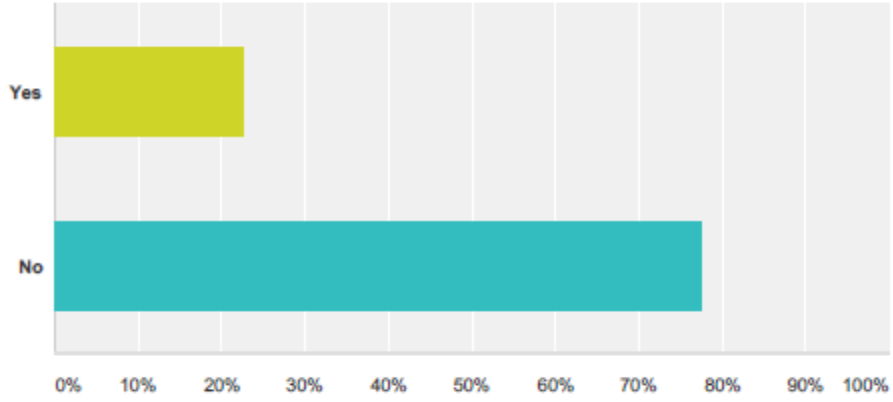


Answer Choices	Responses	
N0	2.94%	2
N0, but with a comment indicating ITCs are present (or some other similar notation)	33.82%	23
N1	63.24%	43
Total		68

Discussion

Q11 This question refers to micrometastases in any GI/biliary/pancreas resection. Do you specifically comment on the presence of nodal micrometastases in a way that distinguishes them from routine nodal metastases? For example N1mi?

Answered: 71 Skipped: 0



Answer Choices	Responses	
Yes	22.54%	16
No	77.46%	55
Total		71