



HAPPY HALLOWEEN

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THE FOLLOWING NEWSLETTERS AND REPORTS ARE CURRENTLY AVAILABLE FROM THE FCDS WEBSITE:

EDUCATION AND TRAINING WEB MODULES

(Under Edu and Training)

- Reporting Requirements for Intracranial and CNS Tumors, with Handouts/notes pages
- Interactive Web-Based Edits Tutorial

FCDS REGISTER VOL. 25

2004 FCDS DATA ACQUISITION MANUAL

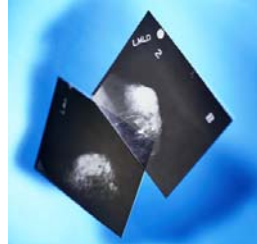
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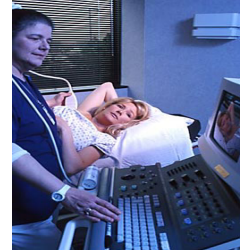
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- **THE SUSAN G. KOMEN BREAST CANCER FOUNDATION**
<http://www.komen.org>
- **NATIONAL ALLIANCE OF BREAST CANCER ORGANIZATIONS (NABCO)**
<http://hci-w1.hci.utah.edu/hope/holdingDetail.stm?holdingId=416>
- **Y-ME NATIONAL BREAST CARE ORGANIZATION (Y-ME)**
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FLORIDA CANCER DATA SYSTEM OCTOBER 2004 MONTHLY MEMO



BREAST CANCER TREATMENT

National Cancer Institute (NCI) Website:
http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/allpages#Section_1



CELLULAR CLASSIFICATION

The following is a list of breast cancer histologic classifications. [1] Infiltrating or invasive ductal cancer is the most common breast cancer histologic type, comprising 70% to 80% of all cases.

- Carcinoma, NOS (not otherwise specified)
- Ductal
 - ◆ Intraductal (in situ)
 - ◆ Invasive with predominant intraductal component
 - ◆ Invasive, NOS

- ◆ Comedo
- ◆ Inflammatory
- ◆ Medullary with lymphocytic infiltrate
- ◆ Mucinous (colloid)
- ◆ Papillary
- ◆ Scirrhous
- ◆ Tubular
- ◆ Other
- Lobular.
 - ◆ In situ
 - ◆ Invasive with predominant in situ component
 - ◆ Invasive [2]

- Nipple
 - ◆ Paget's disease, NOS
 - ◆ Paget's disease with intraductal carcinoma
 - ◆ Paget's disease with invasive ductal carcinoma
- Other
 - ◆ Undifferentiated carcinoma

The following are tumor subtypes that occur in the breast

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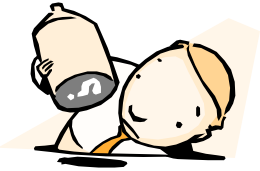
OCTOBER IS NATIONAL BREAST CANCER AWARENESS MONTH

**NATIONAL MAMMOGRAPHY DAY
WILL BE CELEBRATED ON OCTOBER 15.**



To learn which facilities in your area are taking part in the event, call:

- | | |
|---|----------------|
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| Y-ME NATIONAL BREAST CANCER ORGANIZATION | (800) 221-2141 |



FCDS Q & A

BREAST



SEER Inquiry System: <http://seer.cancer.gov/seer inquiry/>

REFERENCES

CS Manual, Part II ;pgs 465 (Vers 1.0, Jan. 1, 2004)

QUESTION

CS Site Specific Factor--Breast: Pathology report states "1.1 cm infiltrating duct carcinoma. No extensive intraductal component." Can we interpret this as "minimal"?

ANSWER

Yes. Based on the information provided above, the in situ component is "minimal" for the purpose of coding Breast CS Site Specific Factor 6. The phrase "no extensive intraductal component" suggests that there is some intraductal carcinoma present.

REFERENCES

Coding Complex Morph Dx's ;pgs 3 (Rule 3 & 4 (Revised Aug. 2002)

QUESTION

Histology--Breast: Are diagnoses of "infiltrating duct and mucinous carcinoma" and "duct carcinoma, mucinous type" both coded to the histology code of 8523/3?

ANSWER

No. Code the Histology field for a "ductal carcinoma, mucinous type" to 8480/3 [Mucinous carcinoma].

Rule 4 on page 3 of Coding Complex Morphologic Diagnoses, states you are to code the specific type if the diagnosis is

"Duct carcinoma, _____ type."

"Infiltrating duct and mucinous carcinoma" is coded to 8523/3 per rule 3 on page 3 of Coding Complex Morphologic Diagnoses. Code 8523/3 is used if the diagnosis is duct carcinoma mixed with another type of carcinoma. Look for "and" or "mixed" in the diagnosis.

CLARIFICATION OF COLLABORATIVE STAGING QUESTIONS



Several questions arose during the **Data Reporting, Casefinding and Collaborative Staging** presentation, at this year's annual meeting, regarding interpretation of some of the CS data definitions. We requested and received clarification from the CS Task Force.

The first question involved a case of a patient with colon cancer, negative liver involvement based upon observation at surgery and negative CT scans of the chest, abdomen and pelvis. The CS Mets Eval code as presented by our staff is 0 because the CT scans document information about metastatic involvement farthest from the primary site. The CS Task Force agreed that this is the correct answer because the CT scans show that potential metastatic sites outside of the surgical field are negative.

The second question involved a case of a patient with breast cancer, negative regional lymph nodes (RLN's), and less than .2mm ITC's detected by immunohistochemistry. The CS Lymph Nodes code provided by the CS Task Force and presented by our staff was 05, "RLN's with ITC's detected on routine H&E stains". The correct answer is 00, "ITC's detected by immunohistochemistry or molecular methods only". The CS Task Force has updated their training materials to reflect this change. In addition, they agreed that the definitions for codes 00 and 05 in the CS Lymph Nodes table for breast are unclear and therefore will be rewritten.

(Continued from page 1)

but are not considered to be typical breast cancers:

- Cystosarcoma phyllodes.[3]
- Angiosarcoma.
- Primary lymphoma.

References:

Breast. In: American Joint Committee on Cancer.: AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 171-180.

Yeatman TJ, Cantor AB, Smith TJ, et al.: Tumor biology of infiltrating lobular carcinoma. Implications for management. *Ann Surg* 222 (4): 549-59; discussion 559-61, 1995.

Chaney AW, Pollack A, McNeese MD, et al.: Primary treatment of cystosarcoma phyllodes of the breast. *Cancer* 89 (7): 1502-11, 2000.

STAGE INFORMATION

The American Joint Committee on Cancer (AJCC) staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions are formulated in part according to staging categories but primarily according to tumor size, lymph node status, estrogen-receptor and progesterone-receptor levels in the tumor tissue, menopausal status, and the general health of the patient.

The AJCC has designated staging by TNM classification.[1] This system was modified in 2002 and classifies some nodal categories as stage III that were previously considered stage II.[2] It has been pointed out that, as a result of the "stage migration" phenomenon, this means that survival by stage for case series classified by the new system will appear superior to those using the old system.[3]

TNM DEFINITIONS

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic

measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated invasion of normal breast tissue
 - Tis (DCIS): Ductal carcinoma in situ
 - Tis (LCIS): Lobular carcinoma in situ
 - Tis (Paget's): Paget's disease of the nipple with no tumor. [Note: Paget's disease associated with a tumor is classified according to the size of the tumor.]
- T1: Tumor ≤ 2.0 cm in greatest dimension
 - T1mic: Microinvasion ≤ 0.1 cm in greatest dimension
 - T1a: Tumor >0.1 cm but ≤ 0.5 cm in greatest dimension
 - T1b: Tumor >0.5 cm but ≤ 1.0 cm in greatest dimension
 - T1c: Tumor >1.0 cm but ≤ 2.0 cm in greatest dimension
- T2: Tumor >2.0 cm but ≤ 5.0 cm in greatest dimension
- T3: Tumor >5.0 cm in greatest dimension
- T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
 - T4a: Extension to chest wall, not including pectoralis muscle
 - T4b: Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
 - T4c: Both T4a and T4b

- T4d: Inflammatory carcinoma

REGIONAL LYMPH NODES (N)

- NX: Regional lymph nodes cannot be assessed (e.g., previously removed)
- N0: No regional lymph node metastasis
- N1: Metastasis to movable ipsilateral axillary lymph node(s)
- N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis
 - N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
 - N2b: Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
- N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
 - N3a: Metastasis in ipsilateral infraclavicular lymph node(s)
 - N3b: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
 - N3c: Metastasis in ipsilateral supraclavicular lymph node(s)

*[Note: Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.]

PATHOLOGIC CLASSIFICATION (PN)*

- pNX: Regional lymph nodes cannot

(Continued on page 4)

(Continued from page 3)

be assessed (e.g., not removed for pathologic study or previously removed)

- pN0: No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

[Note: Isolated tumor cells (ITCs) are defined as single tumor cells or small cell clusters ≤ 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but that may be verified on H&E stains. ITCs do not usually show evidence of malignant activity, e.g., proliferation or stromal reaction.]

- pN0(I-): No regional lymph node metastasis histologically, negative IHC
- pN0(I+): No regional lymph node metastasis histologically, positive IHC, no IHC cluster >0.2 mm
- pN0(mol-): No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)**
- pN0(mol+): No regionally lymph node metastasis histologically, positive molecular findings (RT-PCR)**

* [Note: Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(I+) (sn).]

** [Note: RT-PCR: reverse transcriptase/polymerase chain reaction.]

- pN1: Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
 - pN1mi: Micrometastasis (>0.2 mm but ≤ 2.0 mm)
 - pN1a: Metastasis in 1 to 3 axillary lymph nodes
 - pN1b: Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
 - pN1c: Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with >3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
- pN2: Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent ** internal mammary lymph nodes in the absence of axillary lymph node metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures
 - pN2a: Metastasis in 4 to 9 axillary lymph nodes (at least 1 tumor deposit >2.0 mm)

- pN2b: Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
- pN3: Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph node(s) in the presence of 1 or more positive axillary lymph node(s); or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
 - pN3a: Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit >2.0 mm), or metastasis to the infraclavicular lymph nodes
 - pN3b: Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph node(s); or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
 - pN3c: Metastasis in ipsilateral supraclavicular lymph nodes

* [Note: Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.]

** [Note: Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.]

Distant metastasis (M)

- MX: Presence of distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC STAGE GROUPINGS

Stage 0

- Tis, N0, M0

Stage I

- T1*, N0, M0

Stage IIA

- T0, N1, M0
- T1*, N1, M0
- T2, N0, M0

Stage IIB

- T2, N1, M0
- T3, N0, M0

(Continued on page 5)

(Continued from page 4)

Stage IIIA

- T0, N2, M0
- T1*, N2, M0
- T2, N2, M0
- T3, N1, M0
- T3, N2, M0

Stage IIIB

- T4, N0, M0
- T4, N1, M0
- T4, N2, M0

Stage IIIC**

- Any T, N3, M0

Stage IV

- Any T, Any N, M1
- * [Note: T1 includes T1 mic]

** [Note: Stage IIIC breast cancer includes patients with any T stage who have pN3 disease. Patients with pN3a and pN3b disease are considered operable and are managed as described in the section on Stage I, II, IIIA, and operable IIIC breast cancer. Patients with pN3c disease are considered inoperable and are managed as described in the section on Inoperable stage IIIB or IIIC or inflammatory breast cancer.]

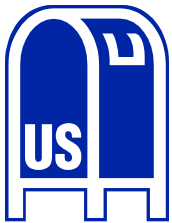
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1. Breast. In: American Joint Committee on Cancer.: AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 171-180.
2. Singletary SE, Allred C, Ashley P, et al.: Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 20 (17): 3628-36, 2002
3. Woodward WA, Strom EA, Tucker SL, et al.: Changes in the 2003 American Joint Committee on Cancer staging for breast cancer dramatically affect stage-specific survival. J Clin Oncol 21 (17): 3244-8, 2003.

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NEW BREAST CANCER VACCINE PASSES FIRST HURDLE

*Experimental Breast
Cancer Vaccine Halts
Tumors in Mice*



alternative for breast cancer treatment and prevention.

The results appear in the Sept. 15 issue of the *Journal of the National Cancer Institute*.

WebMD Health, <http://my.webmd.com/content/article/94/102645.htm>

Sept. 14, 2004 -- An experimental breast cancer vaccine may eventually help treat or prevent up to 80% of breast cancers, according to preliminary tests.

Researchers say the vaccine is based on the protein mammaglobin-A, which has been found in 80% of breast cancer tumors but is largely absent in normal, healthy breast cells.

In a new study, researchers found that vaccination against the protein reversed tumor growth in mice bred to have breast cancer. The vaccine is thought to work by stimulating the immune system to launch an attack against breast cancer tumor cells.

Researchers say the results show for the first time that vaccination with the mammaglobin-A protein may provide a new

Researchers say that given the high frequency of mammaglobin-A in breast cancer tumors, and its total lack or low levels of the protein in normal breast tissue, this protein seems to be an important breast cancer-specific protein that could be used to induce a protective immune response in people at risk for breast cancer.

But this is only the first successful test of the breast cancer vaccine in laboratory mice, and researchers say much more study is needed before the treatment can be tested in humans.

For example, they say the mammaglobin-A protein is also found in low levels in some healthy breast tissue, and further research is needed avoid potentially dangerous side effects.

SOURCE: Nareyanan, K. *Journal of the National Cancer Institute*, Sept. 15, 2004; vol 96: pp 1388-1396.

EDUCATION AND TRAINING

FLORIDA CANCER DATA SYSTEM'S WEB TRAINING MODULES NOW AVAILABLE ONLINE!

REPORTING REQUIREMENTS FOR INTRACRANIAL AND CNS TUMORS

Presented by Stuart Herna

DATA ACCESS FOR DEPT. OF HEALTH PERSONNEL AND APPROVED RESEARCHERS

Presented by Jill MacKinnon

INTERACTIVE WEB-BASED EDITS*

Presented by Jill MacKinnon and Mark Rudolph

The Florida Cancer Data System (FCDS) is pleased to announce the FCDS Web Training Modules, now available on the FCDS website under Education and Training. The modules are designed to assist registrars and their staff with the clarification of rules, reporting requirements, data definitions, policies, and procedures.

***Web-Based Edits will be implemented in mid-November. Please review the tutorial for the new upload and editing instructions.**

Coming Soon...

COLLABORATIVE STAGING MODULES



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In response to industry demands for HIPAA Privacy Training, AHIMA has developed an online Specialty Advancement Program in Privacy. Specialty Advancement Training will prepare participants to assume roles of greater responsibility or enhance current job skills by exploring professional practice issues above and beyond the basic HIPAA curriculum or available job experience.

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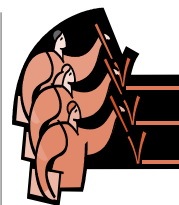
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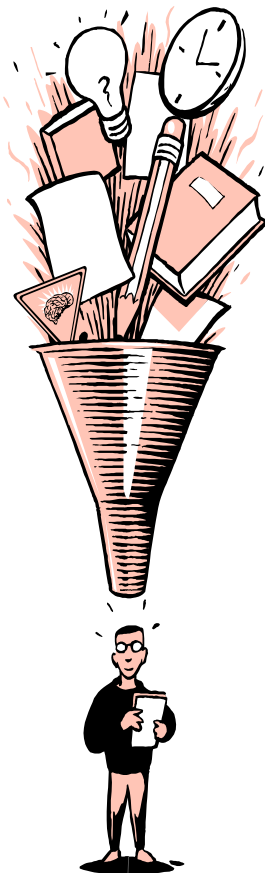
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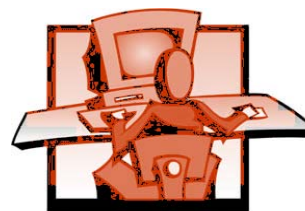
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NCRA Members = \$200 US
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For more information on the CTR Exam , go to www.ctrexam.org.



GI STROMAL TUMORS 'A MODEL FOR WHAT'S COMING'

College of American Pathologists Website:
http://www.cap.org/apps/docs/cap_today/covers_stories/0904GIST.html

CAP Today, September 2004
William Check, PhD

In the beginning, there were smooth muscle tumors of the gastrointestinal tract. And darkness reigned over the face of these tumors. "Among the small number of pathologists who cared what they were," says Christopher Corless, MD, PhD, of Oregon Health and Science University, "no one had any idea how to classify them." During the 1970s and 1980s, these tumors were variously called leiomyomas (benign), leiomyosarcomas (malignant), or Schwannomas.

Then, in 1998, light shined forth over this "mass of confusion," when Japanese and Swedish investigators independently identified expression of the cell surface receptor KIT (also known as CD117) in up to 95 percent of a subset of GI tumors. "This was a real breakthrough," says Dr. Corless, who is professor of pathology and director, OHSU Cancer Pathology Shared Resource. "It was the first marker indicating that some of these tumors were distinct." The darkness was rolled back and a new category of GI tumors appeared, called gastrointestinal stromal tumors, or GISTs. "Detection of KIT became the new gold standard in making a diagnosis [among abdominal tumors]," Dr. Corless says.

Not only was KIT expression recognized in GISTs, but mutations in the *kit* gene were established as the initiating neoplastic events, says Christopher Fletcher, MD, FRCPath, professor and director of surgical pathology at Brigham and Women's Hospital. Dr. Fletcher calls these findings "revolutionary."

"Prior to this discovery, the term GIST was used," he says, "but purely descriptively. It was a diagnostic wastebasket for many spindle cell tumors in the GI tract." Now the term GIST is specifically used for a subset of GI lesions that are almost always KIT-positive. "KIT provides us with an immunohistochemical marker that we can use to identify most of these tumors, which was a big coup for pathologists," Dr. Fletcher says.

Markku Miettinen, MD, chairman of the Department of the Soft Tissue Division and distinguished scientist at the Armed Forces Institute of Pathology, says, "We now know that almost all tumors previously considered gastric or intestinal smooth muscle tumors are actually GISTs."

Recognition of KIT expression in GISTs provided a huge benefit beyond classification. "Obviously what is most newsworthy is that KIT is a tyrosine kinase receptor," Dr. Fletcher says. "All of a sudden there was a way to treat [GISTs]." Imatinib (Gleevec, Novartis) had just been proved to be effective therapy for chronic myelogenous leukemia, or CML, which is also initiated by a runaway tyrosine kinase, in that case produced by a chromosome translocation. A researcher at Dana Farber Cancer Institute, David Tuveson, hypothesized that the KIT receptor was structurally and functionally similar to BCR/ABL in CML and would also be inhibited by imatinib, Dr. Fletcher says. Tuveson produced *in vitro* evidence for this idea, which was followed by successful clinical trials in patients with GISTs. "So we rapidly went from having a nice classification, which was good because we pathologists could diagnose GISTs more reproducibly and define them in a meaningful way, to the marvelous discovery that there was a way to inhibit this new mechanism in patients," Dr. Fletcher says.

"This is one of the fastest examples I know of a bench-to-bedside story," he adds. "It sets the paradigm for developing targeted therapeutics by specifically switching off the mechanism that drives tumor cells. Most cancer treatments smash up DNA. You hope you kill more tumor cells than normal cells. Now we are beginning to see targeted therapies."

Dr. Corless agrees that GISTs are "basically a model for what is coming." For example, the kinase inhibitor gefitinib (Iressa, AstraZeneca) is being developed

for lung and colon cancer. "We have a lot better handle on the biology of those tumors than for many other cancers," he says. "The correlation between mutation testing and treatment is pointing to where a lot of other cancer therapies will be going in the future."

At the root of all this is immunohistochemistry, or IHC. Dr. Fletcher wrote in an editorial: "As other new pharmacologic agents are discovered by screening for small molecule inhibitors of oncoproteins, it is likely that there will be a rapid increase in the immunohistochemical stains that pathologists will be asked to perform to detect potential therapeutic targets" (*Am J Clin Pathol.* 2003; 119: 325-327).

Says Dr. Miettinen: "Pathologists have become very aware of GISTs because they represent a new type of diagnosis that has a special clinical correlation. There is a receptor tyrosine kinase activation that can be countered with a specific inhibitor drug." He sees KIT IHC as the key to GIST diagnosis: "GIST is one of not so many tumors that are almost always KIT-positive."

Elizabeth Montgomery, MD, associate professor of pathology and director of clinical GI pathology at the Johns Hopkins Medical Institutions, says, "When confronted with a spindle cell tumor in the GI tract, the two main points are that stromal tumors should always be in the differential diagnosis and that CD117 IHC should virtually always be performed." Anatomic pathologists are now so aware of GISTs that they sometimes overdiagnose them, though, for the most part, she says, "they do an excellent job with GISTs."

Beyond the simple fact of doing IHC for KIT in suspected GISTs lie a number of complex and challenging issues:

- How do mutant KIT oncoproteins induce tumors?
- How does imatinib kill KIT-positive tumors?
- What histological features tip off the pathologist that a tumor is a possible GIST?
- Is there anything to help choose among antibodies or assays for KIT?
- What should be done when the KIT

(Continued on page 9)

DEADLINES AND REMINDERS

COMPLETENESS REPORT

The number of new cases added to the FCDS Masterfile in September 2004 is **17,070**.

As of October 1, **100%** of the 2003 Cancer Admissions has been reported to FCDS.

ALL VENDOR SOFTWARE USERS:

Once your software has been upgraded to the NAACCR V10.1 format, you must upload 10 cases to FCDS and must also submit hard copies of these same cases, either via fax or mail. You will not be able to submit any new cases to FCDS until these 10 cases have been received and approved by your Field Coordinator.

PATH LABS

Every anatomic pathology laboratory that reads biopsy and surgical resection specimens collected from patient encounters within the state of Florida **MUST** electronically submit the specified data for every malignant cancer case. **Specimens read between January 1, 2004 and June 30, 2004 must be submitted to FCDS on or before December 31, 2004.**

(July 1, 2004 through December 31, 2004 data are due June 30, 2005.)

GI STROMAL TUMORS (CONT'D)

(Continued from page 8)

- IHC turns up negative?
- What non-GIST tumors can give positive KIT results?
- Are all KIT-positive tumors candidates for imatinib therapy?
- Is it possible to determine the likelihood of an individual GIST responding to imatinib?
- How does the pathologist predict malignant potential in a GIST?

Clear answers are available to some of these questions, while answers to others are evolving.

In its wild-type state, kit is a cell surface receptor whose natural ligand is stem cell growth factor. At the same time that the Japanese scientists recognized KIT on the surface of GISTs, they found that mutations in the gene coding for this receptor activate the kinase constitutively. Mutant isoforms of KIT become autonomous—they phosphorylate tyrosine residues on all types of signaling proteins that bind to or interact with them in the absence of the growth factor. Mutant KIT receptors also phosphorylate each other, called autophosphorylation. "Assessing KIT autophosphorylation is a commonly used approach in assessing the effectiveness of inhibitors like imatinib," Dr. Corless says.

"Mutant KIT escapes normal regulation," Dr. Miettinen adds. It sends signals into the interior of the cell along the signal transduction pathway that ultimately leads to

the nucleus to promote cell proliferation and inhibition of apoptosis.

Imatinib inhibits autophosphorylation of KIT. Dr. Corless says that several groups, including his, proposed to Novartis to treat GIST with imatinib. "Their response," he recalls, "was 'What the hell is a GIST?' Outside pathology, few people had heard of GISTs." Eventually, a patient in Finland was given imatinib for metastatic GIST to the liver in a compassionate-use protocol. "The patient responded beautifully," Dr. Corless says. "Clinical trials with imatinib subsequently showed that about 80 percent of patients have a response or significant stabilization of their disease" (Demetri GD, et al. *N Engl J Med.* 2002;347: 472-480). Imatinib is now approved for treating advanced GISTs, which make up about one-third of the approximately 5,000 new cases of GIST diagnosed each year in the United States.

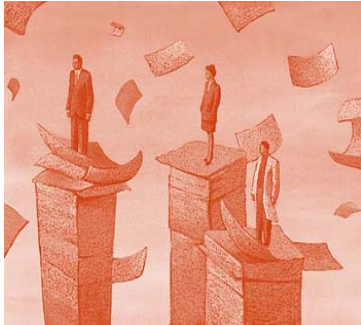
"Inhibitor treatment is now given to patients who have metastatic or unresectable GISTs," Dr. Miettinen says. "Neoadjuvant imatinib has also been used as a precautionary measure immediately following surgery even without evidence of metastasis, mostly in clinical trials."

Already a second kinase inhibitor, SU-11248 (Pfizer), is in phase three trials for GIST patients who show imatinib resistance. About 65 percent of such patients have had either partial response or stabilization on this new agent, Dr. Corless says. "Based on mutation analysis, we suspect it might do even better as a first-line drug for some patients," he proposes.

What we now know as GISTs were initially considered smooth muscle tumors simply because they occur in the gastric or intestinal wall amidst smooth muscle, Dr. Miettinen explains. "However, it has turned out that these tumors are closely related to interstitial cells of Cajal [ICC], which are cellular intermediates between nerves and smooth muscle cells," he says. GISTs either arise from ICC or share a common stem cell with them. What is key to the GIST story is that ICC express kit.

Even before staining for KIT, a pathologist will typically suspect a GIST based on histology. "You always know," Dr. Montgomery says. GISTs have a characteristic morphological pattern and histologic features somewhat akin to—but not identical to—smooth muscle tumors. "When one is confronted with a tumor that looks almost, but not quite, like a classic muscle tumor," she says, "one says, 'Aha! This is a GI stromal tumor.'"

Dr. Miettinen says Cajal cells are normally dispersed around the myenteric plexus and in the muscle layer of the GI tract. "Whenever you see these cells in masses," he says, "it is either Cajal cell hyperplasia or a GIST." Another clue is that, in the stomach, GIST is by far the most common mesenchymal tumor. In the intestine the proportion of GISTs to other tumors is less striking, but still the majority of mesenchymal tumors in the intestine are GISTs as well.



FLORIDA CANCER DATA SYSTEM
**Path Reporting
 and
 Radiation Therapy
 Reporting**

FCDS Florida Cancer Data System
A Joint Project of the Sylvester Comprehensive Cancer Center and the Florida Department of Health

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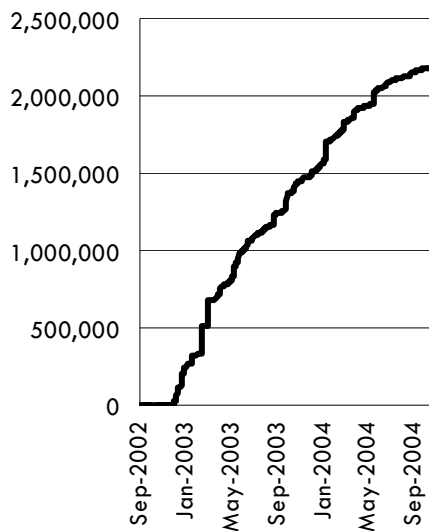
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