The Eighth Edition of TNM: Anatomical and Molecular Markers
AAPA—San Antonio—September 28, 2017

Pierre Denoix
Cuthbert Dukes

Frederick L. Greene, MD
Professor of Surgery, UNC School of Medicine
Medical Director, Cancer Data Services
Levine Cancer Institute
Charlotte, NC

Manual for Staging of Cancer (1977), American Joint Committee for Cancer Staging & End Result Reporting, 1st Edition

“Philosophy of staging by the TNM system”:

• “It is intended to provide a way by which designation for the state of a cancer at various points in time can be readily communicated to others to assist in decisions regarding treatment and to be a factor in judgment as to prognosis. Ultimately, it provides a mechanism for comparing like or unlike groups of cases, particularly in regard to the results of different therapeutic procedures”
The AJCC Cancer Staging Manual, Eighth Edition is dedicated to all CANCER REGISTRARS in recognition of their:

- education and unique commitment to the recording and maintenance of data that are so vital for the care of the cancer patient;
- professionalism in the collection of factors that are fundamental to sustaining local, state and national cancer registries;
- dedication to the cataloging of information crucial to cancer research;
- leadership, support and promulgation of the principles of cancer staging;
- AND THEIR POSITIVE IMPACT ON CANCER PATIENT OUTCOMES

Staging

- Provides a framework for discussion
- Helps stratify patients into groups that are prognostically and therapeutically similar
- Facilitates comparison across large populations
Biologic Progression of Tumor

- Tumor first grows locally
- Metastasizes to regional lymph nodes
- Finally, metastasizes systemically

Prognostic Factor

Variable that can explain some of the heterogeneity associated with the expected course and outcome of a disease.

from Tannock & Hill. The Basic Science of Oncology, 1998

CANCER PROGNOSIS MARKERS

- Prognostic markers are used to help a physician assess the potential outcome for a patient regardless of treatment. They can help assess the aggressiveness of disease.
- An example of a prognostic marker is CA19-9 in pancreatic cancer which can help assess the resectability of the tumor and provide insight into potential survival.
- The expression of CD44 is often associated with a poor prognosis in bladder cancer, whereas expression of cyclin D1 is associated with a better prognosis with lower odds of recurrence.
Predictive markers are used to determine potential for response to a specific treatment. Targeted therapies often use companion diagnostics to direct treatment decisions. These tests use predictive markers to identify which drugs may provide a favorable response for a patient.

**CANCER PREDICTIVE MARKERS**
- HER2: Predict response to HER2 targeted therapy (breast cancer)
- Estrogen receptor: Predict response to endocrine therapy (breast cancer)
- EGFR mutation: Predict response or resistance to EGFR inhibitor TKI therapy (lung adenocarcinoma)
- ALK or ROS1 gene rearrangement: Predict response to treatment with Crizotinib (lung adenocarcinoma)
- PD-L1: Predict response to treatment with checkpoint inhibitors (multiple cancer types)
- BRAF V600E: Predict response to treatment with vemurafenib (melanoma)
- RAS mutation: Resistance to anti-EGFR treatment (colon cancer)
- KIT activating mutation: Predict response to imatinib/sunitinib (GIST, melanoma)
- Oncotype Dx: Predict response to chemotherapy (ER+ breast cancer), this test is both prognostic and predictive

**EXAMPLES OF PREDICTIVE TESTS**
- HER2: Predict response to HER2 targeted therapy (breast cancer)
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**Criteria for Prognostic Factors**
I. Statistically significant - prognostic value only rarely occurs by chance
II. Independent - retains prognostic value when combined with other factors
III. Clinically relevant - has a major impact on prognostic accuracy
National Cancer Data Base (NCDB)
- A community-based oncology management and outcomes database
- A joint project: ACS/ACoS

NCDB Clinical Surveillance
- Diagnosis / AJCC Stage
- Treatment by AJCC Stage
- Patient Demographics
- Survival by Treatment & Stage

National Cancer Data Base
- 30 million cases
- 30 year follow-up
- Plan for open access
Pathologic Classification

- Timing
  - After neoadjuvant therapy including surgery
  - Multimodality must be primary therapy
- Eligible information
  - All information
  - Clinical info combined with surgical findings
  - Exam of tissue required
- No residual cancer
  - ypT0 ypN0 cM0
  - No stage group

Pathological Complete Response (pCR)
ypT0N0 or ypTisN0

Tumor Related Prognostic Factors
- Pathology
  - morphology, grade, growth pattern,
- Anatomic tumor extent
  - TNM, tumor bulk, number, tumor markers
- Tumor biology
  - proliferation indices, molecular markers, genetic markers
- Symptoms
- Performance status
Traditional Prognostic Parameters for Human Mammary Carcinoma

<table>
<thead>
<tr>
<th>Tumor Factors</th>
<th>Host Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node status</td>
<td>Age</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Menopausal status</td>
</tr>
<tr>
<td>Histologic/nuclear grade</td>
<td>Familial history</td>
</tr>
<tr>
<td>Lymphatic/vascular invasion</td>
<td>Previous neoplastic disease</td>
</tr>
<tr>
<td>Pathologic stage (TNM)</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Steroid receptor status (ER/PR)</td>
<td>Host inflammatory response</td>
</tr>
<tr>
<td>DNA content (ploidy, S-phase)</td>
<td>Nutrition</td>
</tr>
<tr>
<td>EIC (in situ)</td>
<td>Prior chemotherapy</td>
</tr>
<tr>
<td>Prior radiation</td>
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</tbody>
</table>

AJCC Staging System (anatomic)

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>I</td>
</tr>
<tr>
<td>0-2</td>
<td>0-1</td>
<td>0</td>
<td>IIa</td>
</tr>
<tr>
<td>2-3</td>
<td>0-1</td>
<td>0</td>
<td>IIb</td>
</tr>
<tr>
<td>0-3</td>
<td>1-2</td>
<td>0</td>
<td>IIIa</td>
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<tr>
<td>4 or 0-1</td>
<td>1-2</td>
<td>0</td>
<td>IIIb</td>
</tr>
<tr>
<td>Any</td>
<td>3</td>
<td>0</td>
<td>IIIc</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>1</td>
<td>IV</td>
</tr>
</tbody>
</table>

BREAST CANCER

SURVIVAL ACCORDING TO AJCC STAGE
Summary: Breast

Axillary nodes (routine H&E or IHC)
- N1: 1 to 3
- N2: 4 to 9
- N3: 10+
- Infraclavicular nodes are N3
- Supraclavicular nodes reclassified as N3

Breast - Additional Descriptors

“sn” suffix: Based only on sentinel lymph node dissection without an axillary node dissection, eg. pN0(sn) or pN1(sn)

“f” suffix: FNA or core biopsy of node

Challenges for the 8th Edition

Importance of lymph node ratio

Effect of multifocality and multicentricity on staging and survival

Review of sub-classification of T4

Addition of prognostic factors—ER, PR, HER2, and grade

What about LCIS?
Two stage group tables have been developed. These are the Anatomic Stage Group table and the Prognostic Stage Group table. The Anatomic Stage Group table provides a stage that can be applied to all breast cancer patients worldwide, regardless of availability and performance of breast biomarker or multigene assays.

Lobular carcinoma in situ (LCIS) is removed as a pTis category for T-categorization. Lobular carcinoma in situ is a benign entity and is removed from TNM staging.

**Patient Related Prognostic Factors**
- Demographics
  - age, race, gender, level of education, socioeconomic status, religion
- Co-morbidity
  - fixed - inherited conditions
  - changeable - weight, coexistent illness, cardiac and renal function
- Performance status
- Compliance
New H & N Additions to Eighth Edition

- Separate staging for Human papilloma virus (HPV)+ (p16 or FISH) tumors
- H & N specific cutaneous malignancy chapter
- Three components of pharynx staging
- T-category changes
- Extranodal tumor extension in N category

Extranodal Extension (ENE)

- ENE is a profound adverse prognostic factor in H & N cancer except in high risk (HR) HPV+ tumors
- Imaging modalities are limited in ability to identify ENE+
- Pathological ENE defined as tumor within a node that extends beyond the lymph node capsule

Age in Thyroid Cancer

- Age is a recognized prognostic factor
- Older patients have a worse outcome
- Traditionally age 45 years used as cut off
- 45 years is the median age of most major published datasets
AJCC

Is Age 45 Most Appropriate?

- 45 was picked due to convenience rather than due to statistical validity
- Experience suggests that patients >45y may be at low risk also
- This is our fastest growing group of patients, many of who may be being inaccurately upstaged

An International Multi-Institutional Validation of Age 55 Years as a Cut off In the AJCC Staging System for Well Differentiated Thyroid Cancer

Memorial Sloan Kettering Cancer Center, New York
Mount Sinai Hospital, Toronto, Canada
University of California, San Francisco, USA
University of Sydney Endocrine Surgical Unit, Australia
Instituto Nacional do Cancer do Rio de Janeiro, Brasil
Universidade Federal do Rio de Janeiro, Brazil
Conclusion

• A change in age cut off from 45 to 55 years in the AJCC system would migrate many low risk patients from higher to lower stages, thereby improving the prognostic value of TNM staging.

Prognostic Factors - Environment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician focus</td>
<td>• Quality and accuracy of diagnosis,</td>
</tr>
<tr>
<td></td>
<td>• Expertise, timeliness of action</td>
</tr>
<tr>
<td>Health care system focus</td>
<td>• Access to care, diagnostics, screening</td>
</tr>
<tr>
<td>Society focus</td>
<td>• Socioeconomic status, insurance status</td>
</tr>
<tr>
<td></td>
<td>• Distance from treatment center</td>
</tr>
</tbody>
</table>
Residual Tumor Classification

- Strongest predictor of outcome
- Reflects effects of therapy
- Influences further therapeutic procedures
- Importance of identification by surgeon
- Histologic confirmation of gross residual tumor

Category I: Well supported by the literature, generally used in patient management and of sufficient importance to modify TNM stage group

Residual Tumor (R)

- RX: Presence of residual tumor cannot be assessed
- RO: No residual tumor
- R1: Microscopic residual tumor
- R2: Macroscopic residual tumor

Prognostic Factors

TNM + R + Prognostic Factors
Isolated Tumor Cells (ITC) (single tumor cells or small clusters) \( \leq 0.2 \) mm

VS

Micrometastases \( \leq 0.2 \) cm in greatest dimension

Isolated Tumor Cells and Micrometastasis

- **pNO:** No regional lymph node metastasis histologically; no examination for isolated tumor cells (ITC)
- **pNO(i-):** No regional lymph node metastasis histologically; negative morphologic findings for ITC
- **pNO(i+):** No regional lymph node metastasis histologically; positive morphologic findings for ITC

Molecular Staging

- **pNO(mol-):** No regional lymph node metastasis histologically; negative nonmorphologic findings for ITC
- **pNO(mol+):** No regional lymph node metastasis histologically; positive nonmorphologic findings for ITC
Stage Groupings

Stage I  Small and localized
Stage II Large but still localized
Stage III Regional Nodes
Stage IV Distant Metastases

Treatment and Prognosis

Spread to other organs

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Rectal Cancer Staging-Ongoing Issues

- Effect of Neoadjuvant Treatment
- Is response associated with overall survival?
- 7th Edition “Site-Specific Factors”
- Four-point Tumor Regression Grade
  (Ryan et al, Histopathology 2005;47:141-6 and CAP Guidelines)

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Tumor Regression Grade-AJCC 7th Edition

- No viable cancer cells—Grade 0—complete response
- Single cells or small groups of cells—Grade 1—moderate response
- Residual cancer outgrown by fibrosis—Grade 2—minimal response
- Minimal or no tumor kill; extensive residual cancer—grade 3-poor response
Lung Staging (IASLC)

- For NSCLC and small cell
- T1 = T1a (2 cm or less); T1b (2-3 cm)
- T2= T2a (>3-5 cm); T2b (>5-7 cm)
- T3 (>7 cm)
- Multiple nodules same lobe --- T3
- Multiple nodules same lung but different lobe --- T4

Staging and Molecular Diagnostics

- Microarray analyses
- Fluorescent flow cytometry
- Immunohistochemistry
- Chromosomal analysis
- Comparative genomic hybridization

Staging and Tumor-Related Prognostic Factors

- Cancer-related proteins
  - Cell-cycle control
    - p53, cyclins, Ki67
  - Metastasis and angiogenesis
    - CD 44, VEGF, angiogenesis inhibitors

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- Cell-cycle control
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AJCC Vision

...and Where It Fits in the 8th Edition:

Cancer Stage ➔ Comprehensive Cancer Profile

- Definitions of TNM
- Prognostic Factors
- Clinical Trial Stratification
- Prognostic and Risk Assessment Models

AJCC Vision

Adjuvant! for Breast Cancer (Version 7.0)

Patient Information:
- Age:
- Comorbidity:
- ER Status:
- Tumor Grade:
- Tumor Size:
- Positive Nodes:
- Ethnicity:
- 10 Year Risk:

Adjuvant Therapy Effectiveness:
- Hormone Therapy:
- Chemotherapy:
- Radiation Therapy:

No additional therapy:
- 50.2% alive 10 years.
- 62.5% alive of cancer.
- 7.7% alive of other causes.
- With hormonal therapy: Benefit = 10.8 alive.
- With chemotherapy: Benefit = 7.8 alive.
- With endocrine therapy: Benefit = 33.6 alive.

Circulating Tumor DNA


- Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer
- Detection of circulating DNA in peripheral blood
- Clinical implications of circulating DNA

- The use of circulating tumor DNA for monitoring patients with breast cancer
- The potential for early detection and improved management of metastatic breast cancer
- The role of circulating tumor DNA in personalized medicine and precision oncology

- The significance of circulating tumor DNA as a biomarker for breast cancer
- The impact of circulating tumor DNA on clinical decision-making in breast cancer treatment and follow-up
The presence of CTCs in the blood or DTC clusters (≤ 0.2 mm) in the bone marrow or other nonregional nodal tissues does not constitute M1 in the absence of other apparent clinical and/or radiographic findings of metastases that correspond to pathological findings. Designate cM0(i+).
Change

“All organizations need to know that virtually no program or activity will perform effectively for a long time without modification and redesign. Eventually every activity becomes obsolete....”

—Peter Drucker

american joint committee on cancer