TNM Staging System: General Principles

Jae Y. Ro, M.D., Ph.D.

March 16, 2018

Cornell University
Do your BeST!

Category 1 prognostic factors

March 16, 2018
Excel my Diagnostic Skills

1) Normal histology
2) Stage
3) Knowing my limitation with Enjoy

March 16, 2018
1. Basic

- Tumor characters and diagnosis
- Incidence
- Prognostic factors
  - Stage (TNM, UICC) and Grade
  - I CARE (integrity, compassion, accountability, respect, excellence) value
  - 3C (consultation, communication, and collaboration) practice
Diagnostic Approach

Lesions

Neoplastic
- Epithelial
  - Benign
  - Malignant (carcinoma)
- Mesenchymal
  - Benign
  - Malignant (sarcoma)

Non-neoplastic
- Infectious
- Non-Infectious
Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths By Sex, United States, 2018.

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>164,690</td>
<td>Breast</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>121,680</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>75,610</td>
<td>Colon &amp; rectum</td>
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<tr>
<td>Urinary bladder</td>
<td>62,380</td>
<td>Uterine corpus</td>
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<tr>
<td>Melanoma of the skin</td>
<td>55,150</td>
<td>Thyroid</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>42,680</td>
<td>Melanoma of the skin</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,730</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>37,160</td>
<td>Pancreas</td>
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<tr>
<td>Leukemia</td>
<td>35,030</td>
<td>Leukemia</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>30,610</td>
<td>Kidney &amp; renal pelvis</td>
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<tr>
<td><strong>All Sites</strong></td>
<td><strong>856,370</strong></td>
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### Estimated Deaths

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<tr>
<td>Lung &amp; bronchus</td>
<td>83,550</td>
<td>Lung &amp; bronchus</td>
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<tr>
<td>Prostate</td>
<td>29,430</td>
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<tr>
<td>Colon &amp; rectum</td>
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<tr>
<td>Pancreas</td>
<td>23,020</td>
<td>Pancreas</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,540</td>
<td>Ovary</td>
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<tr>
<td>Leukemia</td>
<td>14,270</td>
<td>Uterine corpus</td>
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<td>Esophagus</td>
<td>12,850</td>
<td>Leukemia</td>
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<td>Urinary bladder</td>
<td>12,520</td>
<td>Liver &amp; intrahepatic bile duct</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>10,010</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>323,630</strong></td>
<td><strong>All Sites</strong></td>
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</tbody>
</table>

CA Cancer J Clin 2018; 67(1):7-30
2. Study

- Speed, accuracy and decision
- Prognostic factors
  - Category 1 prognostic factors
    - Stage and grade
  - Non-anatomic prognostic factors (e.g., age, PSA, grade, serum tumor markers, etc)
Prognostic Factors

- **Category I (well supported):** stage, grade (non-anatomical factors; PSA, age, serum markers)

- **Category II (extensively studied but not well established):** DNA ploidy, nuclear proliferation, angiogenesis, apoptosis, tumor suppressor gene

- **Category III (currently studying):** other oncogenes, cytogenetic analysis, growth factors, detection of circulating tumor cells in blood
Tumor Grade

- malignant tumors (Arabic no. 1,2,-- )
  - Histologic grade (overall proportional)
    ▶ original Broders’ grading (4 tier)
    ▶ modified Broders' grading (3 tier)
    ▶ high and low grade (2 tier)
  - Nuclear grade (worst areas)
    ▶ Black NG for breast ca.
    ▶ Fuhrman’s NG for renal cell ca.
  - Combined: FIGO grade
Histologic grade

Original Broders’ grade, 4 tier

• Grade 1: > 75%
• Grade 2: > 50%, ≤ 75%
• Grade 3: > 25%, ≤ 50%
• Grade 4: ≤ 25%

Modified Broders’ grade, 3 tier

• Well, moderate and poorly
Tumor Grade

- High and low grade (2 tier)
  - Urothelial carcinoma
  - Colon Cancer (AJCC, 7th edition): return to 4 tier system in AJCC, 8th edition
Tumor Grade

• Colon cancer (2010 7th ed, 2 tier: 2017 8th AJCC, back to 4-tier)

• Low grade (G1, G2)/high grade (G3, G4)

• 4 tier grading system:
  ✓ G1: Well differentiated
  ✓ G2: Mod differentiated
  ✓ G3: Poorly differentiated
  ✓ G4: Undifferentiated carcinoma

GX: Grade cannot be assessed
Nuclear Grade
WHO/ISUP (Fuhrman’s) Nuclear Grade

Nucleolus visible with 10x objective

- **Yes**
  - G3 or G4
    - Pleo, sarcoma, rhabdoid
      - **Yes**
      - G4
        - (Nuclear size 20µm)
      - **No**
      - G3
        - (Nucleus 15µm)
  - **No**
    - G2
      - (Nucleus 10µm)

- **No**
  - G1 or G2
    - Nucleolus visible with 40x objective or visible chromatin
      - **Yes**
      - G4
        - (Nuclear size 20µm)
      - **No**
      - G3
        - (Nucleus 15µm)
  - **Yes**
    - G1
      - (Nucleus 10µm)
Black Nuclear grade:
nuclear size, chromatin, nucleolus, pleomorphism, mitoses
Combined grade
Combined grade

- FIGO endometrioidal carcinoma
  - $\leq 5\%$ nonsquamous or nonmorular solid growth
  - $6\text{--}50\%$ nonsquamous or nonmorular solid growth
  - $>50\%$ nonsquamous or nonmorular solid growth
  - One up grade based on nuclear features
- No grading for non-endometrioid carcinoma (type 2 cancers)
AJCC Cancer Staging Manual
Eightth Edition
<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Tumor size &lt; 2 cm</th>
<th>Tumor size 2-5 cm</th>
<th>Tumor size &gt; 5 cm</th>
<th>Tumor extends to skin or chest wall</th>
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<tbody>
<tr>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T4</td>
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<table>
<thead>
<tr>
<th>Lymph Nodes</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>No lymph node metastasis</td>
<td>Metastasis to ipsilateral, movable, axillary LNs</td>
<td>Metastasis to ipsilateral fixed axillary, or IM LNs</td>
<td>Metastasis to infraclavicular/supraclavicular LN, or to axillary and IM LNs</td>
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</table>

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis</td>
<td>Distant metastasis</td>
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</table>

© The Best Oncologist™

LNs = Lymph Nodes; IM = Internal Mammary

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Staging System

- AJCC (American Joint Committee on Cancer)
- UICC (International Union Against cancer)
- Dukes, Jewett/Whitmore, Ann Arbor systems, FIGO staging
AJCC Cancer Staging

• AJCC has become the standard for TNM information and the way cancer is communicated worldwide
  ✓ Validating
  ✓ Revising
  ✓ Restructuring
  ✓ Publishing

• Widely used by Clinicians
  ✓ Surveillance community & tumor registrars
  ✓ Researchers
  ✓ Patient advocates
  ✓ Patients
AJCC Cancer Staging (Roles)

• Communication
  *Standardized nomenclature of cancer*

• Clinical practice
  *Staging & prognosis*
  *Treatment recommendations*

• Clinical trials
  *Eligibility and Stratification*

• Research at all levels

• Reporting – population science
  *Longitudinal cancer instance*
  *Changing spectrum of disease*
  *Efficacy of treatment*
  *Quality of care*
TNM Stages

- AJCC first organized in 1959 (c UICC)
- Non-anatomical factors integrated (7th, 2010)
  - Histologic grade (prostate, soft tissue, etc)
  - Serum tumor markers (testis)
  - Age (thyroid cancer)
  - Biologic markers, genetic mutations
- WHO blue book, AFIP fascicles
- ICD10, ICD-O3 and SNOMED
- No acceptable TNM staging for CNS, lymphoma, and pediatric tumors
TNM Stages, 8th edition

- No acceptable TNM staging for CNS, lymphoma/leukemia, and pediatric tumors (included in staging book, except for pediatric tumors)
- GU split (Male genital, part XIII; Urinary system, part XIV)
- Digestive system split (upper, part III, lower, part IV and hepatobiliary and exocrine pancreas, part V)
- Neuroendocrine tumor, added as new part (part VI)
- Endocrine added (part XVII)
- Bone and soft tissue sarcoma split (part VIII and IX)
- Lymphoid neoplasms, renamed as hematologic malignancies, leukemia included (part XVIII)
Changes for 8th Edition

• New features
  – Levels of Evidence
  – Imaging section
  – Risk Assessment Models for select cancer sites
  – Recommendations for Clinical Trial Stratification
  – Prognostic factors
    • Required for prognostic stage grouping
    • Recommended for clinical care
    • Emerging factors
Examples of AJCC level of evidence

- Prostate Cancer
  - Level I: PSA, Grade group/Gleason score (Integrated in AJCC Prognostic stage groups)
  - Level II: Surgical margin status
  - Level III: Histologic types

- Testis Tumor
  - Level I: Serum tumor markers, LVI, International germ cell classification grouping (serum tumor markers, visceral met, mediastinal location)
<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>PSA</th>
<th>Grade Group</th>
<th>Stage group</th>
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<tbody>
<tr>
<td>cT1a-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>cT2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>cT1-c</td>
<td>N0</td>
<td>M0</td>
<td>≥ 10 &lt; 20</td>
<td>1</td>
<td>IIA</td>
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<tr>
<td>cT2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>cT2b-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>1</td>
<td>IIA</td>
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<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>2</td>
<td>IIB</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>3</td>
<td>IIC</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>4</td>
<td>IIC</td>
</tr>
<tr>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>≥ 20</td>
<td>1-4</td>
<td>IIIA</td>
</tr>
<tr>
<td>T3-4</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>1-4</td>
<td>IIIB</td>
</tr>
<tr>
<td>Any T</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>5</td>
<td>IIIIC</td>
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<td>N0</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
<td>IVB</td>
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## AJCC prognostic stage groups

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>S (Serum Tumor Markers)</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>pTis</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage I</td>
<td>pT1-4</td>
<td>N0</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IA</td>
<td>pT1</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>pT3</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>pT4</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IS</td>
<td>Any pT/Tx</td>
<td>N0</td>
<td>M0</td>
<td>S1-3 (measured post orchiectomy)</td>
</tr>
<tr>
<td>Stage</td>
<td>Any pT/Tx</td>
<td>N1-3</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Stage II</td>
<td>Any pT/Tx</td>
<td>N1</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Any pT/Tx</td>
<td>N1</td>
<td>M0</td>
<td>S1</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Any pT/Tx</td>
<td>N2</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any pT/Tx</td>
<td>N3</td>
<td>M0</td>
<td>S0</td>
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<tr>
<td>Stage IIB</td>
<td>Any pT/Tx</td>
<td>N2</td>
<td>M0</td>
<td>S1</td>
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<tr>
<td>Stage IIC</td>
<td>Any pT/Tx</td>
<td>N3</td>
<td>M0</td>
<td>S1</td>
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</table>
AJCC Prognostic Stage Groups

Stage III  Any pT/Tx  Any N  M1  SX
Stage IIIB  Any pT/Tx  N1-3  M0  S2
Stage IIIB  Any pT/Tx  N1-3  M0  S2
Stage IIIC  Any pT/Tx  N1-3  M0  S3
Stage IIIC  Any pT/Tx  N1-3  M0  S3
Stage IIIC  Any pT/Tx  Any N  M1a  S3
Stage IIIC  Any pT/Tx  Any N  M1a  S3
Stage IIIC  Any pT/Tx  Any N  M1b  Any S

***Non-anatomic factors incorporated***
Examples of AJCC level of evidence

- **Kidney Cancer**
  - Level I: beyond T, N, M, no additional factors
  - Level II: NG, sarcomatoid/rhabdoid histology, tumor necrosis, LVI

- **Bladder Tumor**
  - Level I: beyond T, N, M, no additional factors
  - Level II: Concurrent CIS, pT1 substages, total # of LNs, histologic types, margin status
  - Level III: Extranodal extension, LVI

- **Penile cancer**
  - Level I: beyond T, N, M, additional factors (Level I: tumor grade, LVI)
  - Level II: Total # of LN removed
  - Level III: PNI, size of largest LN metastasis
AJCC Prognostic Stage Groups

 AJCC Anatomic (Prognostic) Stage Groups
• Only T, N, M with no other level I integrated

 AJCC Prognostic Stage Groups
• Penile cancer (level I prognostic factors)
  ✓ Differentiation
  ✓ LVI
• But only T, N, M
• Why?
• T1a vs T1b (based on diff, and LVI, PNI, level of evidence III)
Breast Stage Grouping

➢ AJCC Anatomic Stage Groups
  • Only T, N, M with no other level I integrated

➢ AJCC Prognostic Stage Groups
  • T, N, M and
  • ER and PR status
  • Her2/neu
  • Histologic grade (Scarff-Bloom-Richardson System- Nottingham Modification)
  • Oncotype Dx
Changes for 8th Edition

- New paradigms
  - HPV (oropharyngeal ca staging systems based on HPV status)
  - Separate staging system for patients with neoadjuvant therapy (yc or yp systems)
    - Esophagus and Stomach
  - Bone and Soft Tissue Sarcoma (part VIII and IX)
    - Separate staging systems based on anatomic sites (in bone and soft tissue sarcomas)
Changes for 8th Edition

- New chapters/staging systems
  - Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (Part II, Ch 6)
  - Pharynx - HPV-Mediated Oropharynx Cancer (p16+)
  - Cutaneous Squamous Cell Carcinoma of the Head and Neck (Part VII, under thorax, chapter 35)
  - Thymus (Part VIII, under thorax, chapter 35)
  - Bone: Appendicular Skeleton/Trunk/Skull/face, Pelvis, and Spine
  - Soft Tissue Sarcoma of the Head and Neck
  - Soft Tissue Sarcoma of the Trunk and Extremities
  - Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs
  - Soft Tissue Sarcoma of the Retroperitoneum
  - Soft Tissue Sarcoma – Unusual Histologies and Sites
  - Parathyroid
  - Leukemia
  - Part XVII, under Endocrine, Ch 75
  - Part XVIII, Hematologic malignancy, Ch 83
  - **GIST**, Ch 43
Changes for 8th Edition

- Split chapters
  - p16 negative oropharynx and hypopharynx (previously pharynx)
  - Nasopharynx (previously pharynx) Ch 9
  - Pancreas – exocrine (previously endocrine/exocrine pancreas) Pa V, Ch 28
  - Pancreas – endocrine (previously endocrine/exocrine pancreas)
  - Neuroendocrine Tumors of the Stomach Ch 29
  - Neuroendocrine Tumors of the Duodenum and Ampulla of Vater Ch 30
  - Neuroendocrine Tumors of the Jejunum and Ileum Ch 31
  - Neuroendocrine Tumors of the Appendix Ch 32
  - Neuroendocrine Tumors of the Colon and Rectum Ch 33
  - Neuroendocrine Tumors of the Pancreas Ch 34
  - Thyroid – Differentiated and Anaplastic Ch 73
  - Thyroid – Medullary Ch 74
  - Adrenal Cortical Carcinoma Ch 76
  - Adrenal – Neuroendocrine Ch 77
Changes for 8th Edition

• Merged chapters
  – Ovary, Fallopian Tube, and Primary Peritoneal Carcinoma  Pa XII, Ch 55
  In 7th ed: Ovary and primary peritoneal Fallopian tube separately Pa VIII, Ch 37
  Pa VIII, Ch 38

• Deleted chapters
  – Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas
    • See cutaneous carcinoma of the head and neck
Summary

• 8th edition is a significant step forward

• Education planned for physicians and registrars

• Significant disease site changes will be communicated

• AJCC Web site will provide a roadmap for information on 8th edition

• Congratulations to Cancer Registrars on 8th edition dedication
AJCC Vision

The Transition from Population Based to a more “Personalized” Approach

AJCC/UICC TNM Stage (Basic Classification)  
AJCC Stage (Advanced Clinical Relevance)  
AJCC “Personalized” (Advanced Clinical + Personalized Relevance)

Population Survival Outcomes  
Personalized Survival Outcomes
AJCC Vision

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

Cancer Stage ➔ Comprehensive Cancer Profile

8th Edition Chapter Headings

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

Personalized
AJCC Cancer Staging Manual Editions: revision cycle 6-8 years

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<th>Edition</th>
<th>Publication</th>
<th>dates effective for Dx</th>
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<td>2010- 2017</td>
</tr>
<tr>
<td>8</td>
<td>2016</td>
<td>2017, postponed to 2018</td>
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# AJCC Cancer Staging Manual editions

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</tr>
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<td>8&lt;sup&gt;th&lt;/sup&gt;</td>
<td>2016</td>
<td>2017 -</td>
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TNM revision

• Periodically modified in response to newly acquired clinical/pathological data and improved understanding of cancer biology and factors affecting prognosis

• Makes TNM system most clinically useful staging system and accounts for use worldwide

➢ To avoid difficulty to compare outcome of current and past, makes revision carefully and only based on best possible evidence
TNM Stages

• Define prognosis
• Determining appropriate treatment
• Evaluate the results of treatment and clinical trials
• Serve as a basis for clinical and translational cancer research
• Facilitate exchange and comparison of information among treatment centers

✓ cTNM, pTNM, yTNM (rTNM, aTNM)
<table>
<thead>
<tr>
<th>Classification</th>
<th>Data source</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTNM</td>
<td>symptoms, PE, image, endoscopy, bx 1st site, single/sentinel LN</td>
<td>Define prog</td>
</tr>
<tr>
<td></td>
<td>Surg explo s resection</td>
<td>Initial Rx</td>
</tr>
<tr>
<td>pTNM</td>
<td>Surgical resection &amp; pathology</td>
<td>Precise prog</td>
</tr>
<tr>
<td>yc/ypTNM</td>
<td>systemic chemo/XRT before surg or other Rx</td>
<td>Resp to RX</td>
</tr>
<tr>
<td>rTNM</td>
<td>Retreatment for recur</td>
<td>Define Rx</td>
</tr>
<tr>
<td>aTNM</td>
<td>Determine at autopsy</td>
<td>Identify at A</td>
</tr>
</tbody>
</table>
TNM staging

• Clinical staging: extent of cancer before initiation of definitive treatment or within 4 months after the date of diagnosis
  ✓ Essential to select therapy
  ✓ Critical for comparison of different groups of cases (surgery, neoadjuvant chemo, no Rx)

• Pathologic staging: after completion of definitive surgery as part of first course of treatment or within 4 months after diagnosis

• Post treatment (y): tumor regression grade
  ✓ Recurrent/retreatment (r) and autopsy (a)
TNM Classification

T (tumor), N (node) & M (metastasis)

Primary tumor (T)

TX  Primary tumor cannot be assessed

T0  No evidence of primary tumor

Tis  Carcinoma in situ

T1-T4  Increasing size and/or local extent (depth of invasion) of tumor

T4a  (resectable/moderately advanced) and T4b  (unresectable/very advanced)
T4: tumor invades prostate, uterus, and vagina

Subepithelial invasion of prostatic urethra is not pT4 disease

Adjacent organ

Tumor in stomach wall
**T2**

Tumor more than 2 cm but not more than 5 cm in greatest dimension.
T Classification Rules

• Site specific rule based on size/local extension (solid vs. hollow viscus)
• Clinical assessment (cT) based on physical exam, image, endoscopy, biopsy, surgical exploration with no resection
• Pathologic assessment (pT), resection or biopsy if it assigns the highest T category
• > 1 specimens, estimate size/local extension
• Tumor size as whole mm round up (e.g., 1.2mm - 1mm; 1.7mm - 2mm)
• LVI in T system in 3 organs (liver, testis, penis)
TNM Classification

Regional lymph nodes (N)
- NX: Regional LNs cannot be assessed
- N0: No regional LN metastasis
- N1-N3: Number, size, location of regional LNs involvement
  * Direct extension of tumor into a LN classified as a LN metastasis
  ** Met in other than regional LNs classified as “Met (M1)”
  *** Satellites/ in-transit metastases (Melanoma/Merkel)
  **** TD in subserosa, mesentery, nonperitonealized pericolic/perirectal tissue without LN met (N1c) (discontinuous spread, VI_c extravascular, or replaced LN)

Distant metastasis (M)
- MX: no MX in 7th and 8th editions:
- M0: No distant metastasis (no pM0)
- M1: Distant metastasis (M1a, M1b, M1c)
N Classification rule

- Disease specific rule based on number and location, size of tumor met (not size of LN), and ENE
- Minimum expected # of LNs ($\geq 12$); LN surgery performed, classify as pN even minimum # not examined
- Sentinel LN, pN0 (sn), pN1 (sn): up to 5 LN
- ITC only, pN0 (i+, or mol+); $\leq 0.2$mm, $\leq 200$ cells

✓ Melanoma sentinel node exception
M Classification Rules

• Clinical M (cM), only history and exam, not require imaging of distant organs
• MX not valid category
• pM1 requires positive biopsy: biopsy negative on suspected met, cM0, not pM0
• pM1 regardless clinical or pathologic status, stage IV
• ITC (CTCs, DTCs) in bone marrow, cM0(i+)
General Rules for TNM Stages

• Tumor size: 1.2mm - 1mm; 1.7mm - 2mm
e.g.: 1.47 cm--1.5 cm; 2.43 cm—2.4 cm

• No met in LNs, even number of examined LNs less than suggested—classify pN0

• Isolated tumor cells (ITC): single tumor cells or clusters ≤ 0.2 mm in LN or distant sites—classify N0, M0 (also for flow or DNA detected cells) (e.g., ≤ 200 cells): pN0 (i+, or mol+)

• MX category eliminated (dropped M component from pathology template): no pM0
General Rules of TNM Stages

• All cases should be confirmed microscopically: in rare cases with no pathologic diagnosis—analyzed separately, not included in overall disease survival analysis

• Five classification:
  - Clinical: cTNM, TNM (for primary Rx)
  - Pathological: pTNM (for adjuvant Rx, estimation of prognosis, end result)
  - Restage after treatment: yTNM (ycTNM or ypTNM)
  - Recurrent (retreatment) tumor: rTNM (recur after disease free)
  - Autopsy: aTNM (found at autopsy)
General Rules for TNM Stages

- Multiple synchronous tumors (met excluded): tumor with highest T category – T (m) or T (5)
- Metachronous tumor: new TNM (not y or r)
- Bilateral or multiple organs tumor: separate as independent tumors
- Unknown 1st: e.g., +axillary LN (T0N1M0)*, consider as breast cancer
- If uncertainty present (N1 vs. N2), non-anatomic factor (Gleason), use lower value
- Pure unknown primary: TXN1M0 or TXN0M1
General Rules for TNM Stages

• Specified type of grading, 2 tier, 3 or 4 tier
• Histologic grade
  – GX grade cannot be assessed
  – G1 well diff; G2 mod diff
  – G3 poorly diff: G4 undifferentiated
• 3 tier: G1, G2 and G3-G4 (grade together)
• 2 tier: high and low grade (in 7th ed, colon ca)
• Urothelial ca, prostate, breast (own grading sys)
• No grading: thyroid, eyelids, testis, melanoma
• By definition grade 4: small cell ca, LCC of lung, Ewing sarcoma, rhabdomyosarcoma
General Rules for TNM Stages

- Lymph-vascular invasion (LVI)
  - Lymphatic invasion
  - Vascular invasion
  - Lymph-vascular invasion
- Residual tumor (R): RX, R0, R1 (micro), R2 (macro)
- Margins: negative, micro, macro, not assessed
Perineural invasion

<table>
<thead>
<tr>
<th>Pn</th>
<th>Perineural invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PnX</td>
<td>Perineural invasion cannot be assessed</td>
</tr>
<tr>
<td>Pn0</td>
<td>No perineural invasion</td>
</tr>
<tr>
<td>Pn1</td>
<td>Perineural invasion present</td>
</tr>
</tbody>
</table>
Stage grouping

• Separate clinical, pathologic group (c, pT NM)
  ✓ may combine as “working” stage
• Avoid and minimize TX, NX (unstageable), except for TX or NX with M1 (stage IV)
• Non-anatomic factors missing --- use lowest category (e.g., markers, Gleason grading)
• pT, pN, cM0 or cM1 (pathologic stage group)
• cT, cN, pM1 (clinical & pathologic group)
• pTis, cN0, cM0 (stage 0 for both group)
  ✓ ypT0, ypN0, cM0, do not use as Stage 0 (need pretreatment clinical stage)
## AJCC Prognostic Stage Groups

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>PSA</th>
<th>Grade Group</th>
<th>Stage group</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1a-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>cT2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>cT1-c</td>
<td>N0</td>
<td>M0</td>
<td>&gt; 10 &lt; 20</td>
<td>1</td>
<td>IIA</td>
</tr>
<tr>
<td>cT2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT2b-c</td>
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<td>M0</td>
<td>&lt; 20</td>
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<tr>
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<td>M0</td>
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<tr>
<td>T1-2</td>
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<td>M0</td>
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<tr>
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<td>M0</td>
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<td>&gt; 20</td>
<td>1-4</td>
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<tr>
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<td>1-4</td>
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<td>IVA</td>
</tr>
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<td>M1</td>
<td>Any</td>
<td>Any</td>
<td>IVB</td>
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<tr>
<td>Group</td>
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<td>N</td>
<td>M</td>
<td>S (Serum Tumor Markers)</td>
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<td>-------</td>
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<td>M0</td>
<td>S0</td>
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<td>S0</td>
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<td>Stage IB</td>
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<td>M0</td>
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<td>S0</td>
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<td>pT4</td>
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<td>M0</td>
<td>S0</td>
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<tr>
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<td>N0</td>
<td>M0</td>
<td>S1-3 (measured post orchiectomy)</td>
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</tr>
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<td>Stage</td>
<td>pT/Tx</td>
<td>N</td>
<td>M</td>
<td>S</td>
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</tr>
<tr>
<td>II</td>
<td>Any</td>
<td>N1-3</td>
<td>M0</td>
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<td>M0</td>
<td>S0</td>
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</tr>
<tr>
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<td>Any</td>
<td>N1</td>
<td>M0</td>
<td>S1</td>
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</tr>
<tr>
<td>IIB</td>
<td>Any</td>
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<td>M0</td>
<td>S0</td>
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</tr>
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<td>Any</td>
<td>N2</td>
<td>M0</td>
<td>S1</td>
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<tr>
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<td>N3</td>
<td>M0</td>
<td>S0</td>
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<td>N3</td>
<td>M0</td>
<td>S1</td>
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<td>N</td>
<td>M</td>
<td>S</td>
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<td>III</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
<td>SX</td>
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<td>Any</td>
<td>M1a</td>
<td>S0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Any</td>
<td>M1a</td>
<td>S1</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
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<td>N1-3</td>
<td>M0</td>
<td>S2</td>
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</tr>
<tr>
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<td>Any</td>
<td>Any</td>
<td>M1a</td>
<td>S2</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>Any</td>
<td>N1-3</td>
<td>M0</td>
<td>S3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Any</td>
<td>M1a</td>
<td>S3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Any</td>
<td>M1b</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>

***Non-anatomic factors incorporated***
## AJCC Prognostic Stage Groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Stage</th>
<th>N Stage</th>
<th>M Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2 (T3)</td>
<td>N1 (N0)</td>
<td>M0</td>
</tr>
<tr>
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<td>T1-T3</td>
<td>N1, N2</td>
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</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

***Non-anatomic factors not incorporated***
Collaborative Stage (CS) Data (AJCC)

- **Tumor**
  - CS tumor size (in mm)
  - CS extension
  - CS tumor size/extension eval.

- **Nodes**
  - CS LNs
  - CS LN eval (method of eval)
  - LN +, # LN examined

- **Metastases**
  - CS mets at Dx
  - CS mets eval

- **Site specific factors (non-anatomic factors)**
CAP Electronic Cancer Checklists (CAP eCC) Overview

An International Implementation of SNOMED CT®
### Soft Tissue Sarcoma Staging Form

#### Clinical

**Extent of disease before any treatment**
- [ ] TX: Tumor cannot be assessed
- [ ] T0: No evidence of primary tumor
- [ ] T1: Tumor of any size in greatest dimension, superficial to the fascia
- [ ] T1a: Tumor of any size in greatest dimension, superficial to the fascia
- [ ] T1b: Tumor of any size in greatest dimension, deep to the fascia
- [ ] T2: Tumor of any size in greatest dimension, deep to the fascia
- [ ] T2a: Tumor of any size in greatest dimension, superficial to the fascia
- [ ] T2b: Tumor of any size in greatest dimension, deep to the fascia

**Note:** Tumors of any size in greatest dimension, deep to the fascia are considered Stage II.

#### Stage Category Definitions

**Primary Tumor (T)**
- [ ] Primary tumor cannot be assessed
- [ ] No evidence of primary tumor
- [ ] Tumor 5 cm or less in greatest dimension
- [ ] Superficial tumor
- [ ] Deep tumor
- [ ] Tumor more than 5 cm in greatest dimension
- [ ] Superficial tumor
- [ ] Deep tumor

**Regional Lymph Nodes (N)**
- [ ] N0: No regional lymph node metastasis
- [ ] N1: Regional lymph node metastasis

**Distant Metastasis (M)**
- [ ] M0: No distant metastasis (no pathologic M0; use clinical M to complete stage group)
- [ ] M1: Distant metastasis

#### Anatomic Stage - Prognostic Groups

<table>
<thead>
<tr>
<th>GROUP</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1a</td>
<td>N0</td>
<td>M0</td>
<td>G1, G2</td>
</tr>
<tr>
<td>IIA</td>
<td>1a</td>
<td>N0</td>
<td>M0</td>
<td>G2, G3</td>
</tr>
<tr>
<td>III</td>
<td>2a, T2b</td>
<td>N0</td>
<td>M0</td>
<td>G3</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>Any M</td>
<td>Any G</td>
</tr>
</tbody>
</table>

**Stage unknown**

#### Pathologic

**Extent of disease during and from surgery**
- [ ] TX: Tumor cannot be assessed
- [ ] T0: No evidence of primary tumor
- [ ] T1: Tumor of any size in greatest dimension, superficial to the fascia
- [ ] T1a: Tumor of any size in greatest dimension, superficial to the fascia
- [ ] T1b: Tumor of any size in greatest dimension, deep to the fascia
- [ ] T2: Tumor of any size in greatest dimension, deep to the fascia
- [ ] T2a: Tumor of any size in greatest dimension, superficial to the fascia
- [ ] T2b: Tumor of any size in greatest dimension, deep to the fascia

**Regional Lymph Nodes (N)**
- [ ] N0: No regional lymph node metastasis
- [ ] N1: Regional lymph node metastasis

**Distant Metastasis (M)**
- [ ] M0: No distant metastasis (no pathologic M0; use clinical M to complete stage group)
- [ ] M1: Distant metastasis

**Stage unknown**

#### Hospital Name/Address

#### Patient Name/Information

(continued on next page)
# Soft Tissue Sarcoma Staging Form

## Prognostic Factors (Site-Specific Factors)

**Required for Staging:** Grade ____________

**Clinically Significant:**

- Neovascular invasion as determined by pathology: ____________
- Some invasion as determined by imaging: ____________
- If pT0, source of pathologic metastatic specimen: ____________

### Histologic Grade (G) (also known as overall grade)

<table>
<thead>
<tr>
<th>Grading System</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 grade system</td>
<td>Grade I or 1</td>
</tr>
<tr>
<td>3 grade system</td>
<td>Grade II or 2</td>
</tr>
<tr>
<td>4 grade system</td>
<td>Grade III or 3</td>
</tr>
<tr>
<td>No 2, 3, or 4 grade system is available</td>
<td>Grade IV or 4</td>
</tr>
</tbody>
</table>

### Additional Descriptors

- **Lymphatic Vessel Invasion (L) and Venous Invasion (V)** have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists’ (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist.

- **Post-treatment:**
  - Lymph-Vascular Invasion Not Present (absent)/Not Identified
  - Lymph-Vascular Invasion Present/Identified
  - Not Applicable
  - Unknown/Indeterminate

### Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

<table>
<thead>
<tr>
<th>R</th>
<th>R0</th>
<th>Presence of residual tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>No residual tumor</td>
<td>R1</td>
</tr>
<tr>
<td>R2</td>
<td>Macrophagic residual tumor</td>
<td></td>
</tr>
</tbody>
</table>

- **Clinical stage was used in treatment planning (describe):**

- **National guidelines were used in treatment planning:**
  - NCCN
  - Other (describe):

---

**General Notes:**

- For identification of special cases of 'T'NM or 'p'TNM classifications, the '1m' suffix and 'y', 'p', 'q' prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.
- In suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses:
- pT0(p0)

- **y** prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a 'y' prefix. The yT1NM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The 'y' categorization is not an estimate of tumor prior to multimodality therapy.
- r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the 'r' prefix: rT1NM

- **s** prefix designates the stage determined at autopsy. aHN.

- **surgical margins** is data field recorded by registrars describing the surgical margins if the resected primary site specimen as determined only by the pathology report.

- **necadjuvant treatment** is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to definitive surgical procedure. If the surgical procedure is not performed, the administered therapy to longer meets the definition of neoadjuvant therapy.
3. Think

- Determine prognosis
- Determining treatment
- Results of treatment and clinical trials
- Clinical and translational cancer research
- Exchange and comparison of information among treatment centers
Nomenclatures of morphology of cancer

- WHO blue books
- ICD-O 3rd edition
- SNOMED (CAP)
- Collaborative Stage Data Collection (AJCC)
- CAP cancer protocol
- caBIG (cancer bioinformatics grid; NCI)
- Atlas of tumor pathology (AFIP)
- American College of Radiology Appropriateness Criteria
- Practice Guideline of National Comprehensive Cancer Network (NCCN)
Coding of Tumors

- ICD-O 3rd edition
- ICD-10
- SNOMED
- SNOP
- IARC
- ICD-O: Topographic codes C00.0-C80.9
  Morphologic code M8000/0-9989/3
- Grade/Immunophenotypes
  e.g., C34.1 M8070/33
Example

- Poorly differentiated squamous carcinoma. Upper lobe of lung
- C34.1 M8070/33
- Behavior code
  - /0 benign
  - /1 uncertain/unknown malignancy
  - /2 in situ (non-invasive) carcinoma
  - /3 malignant tumor, primary
  - /6 malignant tumor, metastasis
  - /9 malignant tumor, primary vs. metastasis uncertain
Essential to perform multidisciplinary team approach

- Recognition of patients' needs
- Clarifying responsibility
- Respect each other
- Keeping “good Team Work”

✓ I CARE (integrity, compassion, accountability, respect and excellence)
✓ 3Cs (communication, collaboration, consultation)
Future Medicine (4Ps): Try to make 5Ps

- Prevention
- Prediction and Prognosis
- Personalized Medicine (tailored)
- Participatory Medicine
- 5P (?) Pathology
Main Themes of 21\textsuperscript{c} Cancer Research

- **M**olecular dissection

- **M**olecular diagnosis
  - Biomarker
  - Molecular imaging

- **M**olecular therapy
  - Molecular target
  - Gene therapy
4. Enjoy

- BeST
- I CARE value
- 3 C practice
  - Correct diagnosis and prognosis
    - Right patient, drug, time
    - Right doctor and pathologist
Do your BeST!
Tumor stage and grade
March 16, 2018
Outstanding Faculty Award
To
Jae Ro, M.D., Ph.D.

In recognition and appreciation of your dedication to pathology teaching through 11 years of Microscope Conference.

Thank you for giving your BEST to all.

Houston Methodist Residents, Fellows and Faculty
2015-16
BeST

"You must always do your BeST to be a good pathologist."
—Dr. Ro

Besides the literal meaning of best, we have our own "BeST." The "BeST" stands for "B" representing "Basics", "e" for "enjoyment", "S" for "Study" and "T" for "Think".

Basics:

The art of pathology is observing and diagnosing tissue or cells that are abnormal or diseased. Obviously, it is impossible to do this without knowing what "normal" looks like in the first place. Dr. Ro often repeats his favorite mantra: "You must study basic histology!" This is usually said after one of his residents confuses breast tissue with prostate, or skin with mucosa. It is an obvious truth that a solid foundational knowledge of basic normal histology is one of the keys to becoming an excellent pathologist. A diagnosis of "no pathologic alteration" (i.e., normal) is often harder to make than a diagnosis of carcinoma. A pathologist who is well acquainted with histology and all of the unusual variations of morphology that may be seen in "normal" tissues will more easily be able to discern normal from diseased tissue.

enjoyment/enthusiasm:

Although it is not strictly necessary to enjoy pathology, it is the defining feature that separates good pathologists from outstanding pathologists. The difference is obvious in the academic setting, where those who are enthusiastic about their work are effective teachers and admired mentors. These pathologists inspire their pupils to learn more, to work harder, and to enjoy the study and practice of pathology. As with any vocation, those who enjoy their work will perform better and have increased job satisfaction. Enjoyment and enthusiasm help to make the sacrifices worth it, make it easier to stay late when necessary, and keep one from exhaustion and burnout. If pathology is not enjoyable, then why do we do it?
Thank for your attention!