TNM Classification of Malignant Tumours
8th edition
Changes between the 7th and 8th editions
With focus on Pancreas and Biliary Tracy Carcinomas
Dr. James Brierley, MB, FRCR, FRCP, FRCPC

CPAC Stage Lead
AJCC Chair Education and Promotions Committee
UICC Co-Chair TNM Prognostic Factors Committee

No Financial Disclosures

Princess Margaret Cancer Centre
610 University Avenue
Toronto, ON M5G 2M9
james.brierley@rmp.uhn.on.ca
OBJECTIVES

• Understand the reason to update TNM
• Understand the process
• Understand the changes in Pancreatic and Biliary Tract
• Appreciate the future of TNM
Agenda

• Changes between 7th and 8th edition
• Changes in TNM Stage of:
  – Pancreatic Adenocarcinomas
  – Pancreatic Neuroendocrine Carcinomas
• Changes in TNM Stage of Biliary Tract Carcinomas
3 essential factors in the effective management of cancer:

1. **Site**
   - Site of origin of the cancer
   - e.g. breast, prostate – ICD-O-3

2. **Characteristics**
   - Histologic/biologic characteristics
   - E.g. Gleason 8 adenocarcinoma, HER2/neu positive adenocarcinoma – Blue Book

3. **Extent**
   - Anatomical extent of the cancer or its stage
   - E.g. Stage groupings (I, II, III, IV). TNM
Prognostic Factors

- Tumour-related
  - Anatomic disease extent
  - Tumor pathology
  - Tumor profile/biomarkers

- Host-related
  - Age, gender, ethnicity
  - Comorbidities, compliance

- Environmental-related
  - Access to care
  - Quality of care
  - Quality of imaging
  - SES
• Evidence-based anatomic staging continues to be the critical factor to understanding cancer and treating patients.

• New breakthroughs in oncology are opening up ever-more promising possibilities for precisely defining a prognosis and recommending a treatment based on a patient’s individual data

**BUT**

*The clinician/individual patient needs and surveillance community needs are different. Update v Stability*
8th Edition AJCC

- 18 Task Forces
- Worked started
- Some Canadian representation
- AJCC plan for international consultation was variable
  - Strong in Lung, Head and Neck, Esophagus, Melanoma
8th Edition UI CC

- Representation on each AJCC Task Force
- Annual Literature Watch
- Expert Panels
- Shared with AJCC Task Force
Time line 8th Edition

UICC
- Publish Dec 2016
- 1 Jan 2017 Start Using

• AJCC
- Oct 31 Publish 2016
- 1 Jan 2017 Start Using
- But issue with histology codes
Time line 8th Edition

- In order to ensure that the cancer care community has the necessary infrastructure in place for documenting 8th Edition stage, the AJCC Executive Committee, in dialogue with NCI-SEER, CDC, CAP, NCCN, NCDB, and the Commission on Cancer (made the decision to delay the implementation of the 8th Edition Cancer Staging System to January 1, 2018.)
Time line 8th Edition

• Clinicians will continue to use the latest information for patient care, including scientific content of the 8th Edition Manual.

• The time extension will allow all partners (CAP) to develop and update protocols and guidelines and for software vendors to develop, test, and deploy in time for the implementation of the 8th edition in 2018.
Time line 8th Edition

- The UICC TNM Project has published the 8\textsuperscript{th} Edition of the TNM Classification of Malignant Tumours that comes into effect on January 1, 2017.
- Since some organizations may not be ready to adopt the new classification, we recommend that the edition of the TNM classification be always included in data reporting.
TNM-8
New classifications:

- Oropharynx p16+ve
- Unknown primary cervical neck lymph nodes
- Skin head and neck cancers
- Thymus
- **Neuroendocrine tumors: pancreas**
- Osteosarcoma: Pelvic, Spine
- Soft tissue Sarcoma: Head and neck, Retroperitoneal, Thoracic and Abdominal Viscera
Major modifications

- Head and Neck Nodes
- Nasopharynx
- Thyroid
- Esophagus
- Stomach
- Anal Cancer
- Liver
- Lung
- Prostate
- Ovary
Minor or no modifications

- Introduction
- Other Head and Neck carcinomas
- Hepatobiliary
- Small intestine, Colon and rectum
- Neuroendocrine
- Pleura
- Penis, Kidney, Ureter, Bladder, Urethra,
- Eye
- Malignant Lymphoma
Head and Neck Changes

• For all sites there are separate classifications for clinical and pathological neck nodes
• There is a new classification for p16 positive oropharyngeal cancers, that have p16 immunohistochemistry overexpression.
• The classification for nasopharyngeal cancers and thyroid cancers has been modified
• The there is a new classification for squamous cell carcinoma of the skin in the head and neck region
• There is a new classification for cervical nodal involvement with unknown primary
Inseparable OS between stage I-IV ($P=0.56$) and acceptable OS performance ($P=0.004$) in HPV+ OPC (n=573) compared to HPV– OPC (n=237). HPV(+) Stage IV disease does not have the ominous outcome of smoking-related OPC.
• Traditional Local Control at 10 years was 61% due to inability to image disease, safely deliver RT dose, or enhance intensity
  ▪ Hong Kong, (Lee et al IJROBP 1992)

• Today: LC of > 90%, and Shift in Stage with some T4’s to T2 (8th edition TNM) due to better treatment and assessment

Redefining infra-temporal fossa / masticator

Understanding risk of Medial and Lateral Pterygoid muscle invasion with IMRT

Abbreviations: LP = lateral pterygoid, M = masseter
MP = medial pterygoid, T = temporalis.

Pan, Lee, O’Sullivan et al Cancer Nov 2015
Age

Recurrence, Distant Recurrence, & Death in 1528 patients from time of Initial Treatment

Minimal ETE

- As the thyroid capsule is incomplete and it and the gland contains varying proportion of muscle, fibrous and adipose tissue, the criteria for defining minimal (pT3) ETE are subjective and problematic.


Recurrence

- 5% minimal ETE v 30% for gross ETE
Definition of tumour deposit clarified

Tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue’s lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures.

If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumour deposits does not change the primary tumour T category, but changes the node status (N) to N1c if all regional lymph nodes are negative on pathological examination.
### Pancreas Adenocarcinoma

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumour 2 cm or less</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumour 0.5 cm or less</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour greater than 0.5 cm and less than 1 cm</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour greater than 1 cm but no more than 2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but no more than 4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N1</th>
<th>Metastases in 1 to 3 nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>Metastases in 4 or more nodes</td>
</tr>
</tbody>
</table>

| M category unchanged |

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
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<tr>
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<td>Stage IIA</td>
<td>T3</td>
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<td>M0</td>
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<td>Stage IIB</td>
<td>T1, T2, T3</td>
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<td>M0</td>
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<tr>
<td>Stage III</td>
<td>T1, T2, T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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T1 Subdivisions. ? Evidence

T3 >4cm.
Invasion of peripancreatic soft tissue no longer a criteria for T3
PST poorly defined, and often involved. Not discriminatory

N 1 and 2 based on survival

Based on multi-institutional analysis of 2400 post op patients, MSK, MDA, Mass General and John Hopkins
FIGURE 1. Overall survival by T-stage of 767 patients who underwent resection for node-negative pancreatic cancer. T-stage defined by AJCC 7th edition criteria.


Allen, Peter; Kuk, Deborah; Castillo, Carlos; Basturk, Olca; Wolfgang, Christopher; MD, PhD; Cameron, John; Lillemoe, Keith; Ferrone, Cristina; Morales-Oyarvide, Vicente; MD, MPH; He, Jin; MD, PhD; Weiss, Matthew; Hruban, Ralph; Gonen, Mithat; Klimstra, David; Minn-Kudson, Mari

DOI: 10.1097/SLA.0000000000001763
FIGURE 4 . Overall survival by number of positive nodes for all patients who underwent a R0 resection (training set, n = 1551) stratified by proposed AJCC 8th edition criteria.

Allen, Peter; Kuk, Deborah; Castillo, Carlos; Basturk, Olca; Wolfgang, Christopher; MD, PhD; Cameron, John; Lillemoe, Keith; Ferrone, Cristina; Morales-Oyarvide, Vicente; MD, MPH; He, Jin; MD, PhD; Weiss, Matthew; Hruban, Ralph; Gonen, Mithat; Klimstra, David; Mino-Kenudson, Mari

Treatment Effect – Tumour Regression Score – Similar to Rectum

Modified Ryan Scheme

• Present
• 0 No viable cancer cells (complete response)
• 1 Single cells or rare small groups of cancer cells (near complete response)
• 2 Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)
• Absent
• 3 Extensive residual cancer with no evident tumor regression (poor or no response)
Pre-op Pancreas

• 69 yo M presenting with back pain
• Pancreatic duct stricture found on ERCP,
• Adenocarcinoma
• Work up demonstrates SMA involvement
Then 4 cycles of Folfirinox
Pre-op Pancreas
Pre-op Pancreas

2.4 cm
Margins negative
0/42 nodes
evidence of treatment related changes
treatment response-
moderate (grade 2)
ypT2N0
Neuroendocrine tumours of the Pancreas
Previous all staged the same way

Only Well Differentiated

G1  <2 Mitosis/10 HPF       Ki -67 < 3%
G2  2-20 Mitosis/10 HPF      Ki -67 3-20%

Not poorly differentiated which are staged as adenocarcinoma
G3  >20 Mitosis/10 HPF       Ki -67 >20%
<table>
<thead>
<tr>
<th>T1</th>
<th>Tumour 2 cm or less</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but no more than 4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension or invading duodenum or bile duct</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades visceral peritoneum or other organs</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>N0</th>
<th>No nodal metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Nodal Metastases</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>M1a</th>
<th>Confined to Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1b</td>
<td>At least one extrahepatic site</td>
</tr>
<tr>
<td>M1c</td>
<td>Both hepatic and other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2 T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Intrahepatic Bile Ducts

• Changes in definitions of T1
  – T1a ≤ 5cm, T1b >5cm
• T2 no longer subdivided
• Changes in Stage Group

Gallbladder

• Changes in definitions of T2 category - perimuscular connective tissue invasion
  – T2a peritoneal side
  – T2b hepatic side
• N categories
  – N1 <4 nodes
• Change in Stage group
Perihilar Bile Ducts  No Changes

Distal Extrahepatic Bile Duct
- Changes in definitions of T1,T2,T3 categories and N categories
- Changes in Stage

Ampulla of Vater
- Changes in definitions of T1,T2 and T3 categories and N categories
- Changes in Stage
Information on anatomical extent of disease at presentation is often not available for cancer registries in low and middle income countries either because of inability to perform necessary investigations or because of lack of recording of information.

The UICC TNM Project has with the International Agency for Research in Cancer and the National Cancer Institute developed “Essential TNM” that can be used to collect stage data when complete information is not available.

When the T, N, and M categories have not been the cancer registrar can code the extent of disease according to the Essential TNM scheme.

The schema for breast, colorectal cancer, prostate and cervix cancer published in the 8th edition TNM Classification and are available on the website.
Stage data is central to determine cancer burden as it provides information regarding incidence, mortality, and stage distribution of major cancer types.

But globally often not available
Prostate Cancer Incidence
Essential TNM

- An example of adaption stage to facilitate collection in LIC and MIC
- Information on anatomical extent of disease is often not available for cancer registries in because of inability to perform necessary investigations or because of lack of recording of information.
COLON and RECTUM and CERVIX

Metastases?  
[Excl distant nodes, para-aortic, sup. mesenteric, retroperitoneal, exc. iliac]

Yes \( \rightarrow \) M+

No (M−)

Regional nodes?

Yes \( \rightarrow \) R+(N2/2)

No (R−)

Through the bowel wall?

Yes \( \rightarrow \) A (T3/T4)

No \( \rightarrow \) L (T1/T2)

IV Distant

III Regional

II Localized

I Localized

Subserosa  Serosa

Muscular propria

T4: Invasion into rectum and bladder

T3: Invasion to lower 1/3 vagina

Invasion to pelvic side wall

1 Paracervical
2 Parametrial
3 Hypogastric
4 External iliac
5 Common iliac
6 Presacral

Gruppe de grade TNM

In-distant

Il Regional

I Regional

Localized advance

Localized limita

Note: distension limita as collateral

L3 (T1)

L2 (T1)

L1 (T1)
Comparability of stage data in cancer registries in six countries: lessons from the International Cancer Benchmarking Partnership

• UK, Sweden, Norway, Denmark, Canada and Australia.
• Survival differences for patients diagnosed during 1995-2007 (14).
• One-year and five-year relative survival were lowest in the UK and Denmark, highest in Sweden, Canada and Australia, and intermediate in Norway.
Comparability of stage data six countries

• The second phase of analysis is to consider whether these differences are explained by stage at diagnosis and stage-specific survival – arising from delayed diagnosis and stage-specific treatment variation.

• The ICBP protocol specified stage data according to TNM
Comparability of stage data six countries

• Editions TNM Used: 5, 6 and 7th
• Other classifications used:
  – Dukes
  – FIGO
  – Norway  - Localized, Regional, Distant
  – New South Wales - Localized, Regional, Distant
• In the UK TNM 5th Edition is used by pathologist for colorectal cancer

• In Japan some organ site committees recommend UICC TNM (ie gastric cancer)
Other organ site committees use their own staging system
Comparability of stage data six countries

• Comparative research would be facilitated if all clinicians adhered to a common staging system, such as TNM.
• TNM should remain simple enough for epidemiological research.
• The UICC should examine how mapping from TNM to “localised, regional, distant” systems could be made explicit and standardised for all cancers.

S Walters et al Int J Cancer. 2013 Feb 1;132
Breast cancer

Future of TNM?

• For the individual patient/physician in regard to prognosis and treatment decision, TNM is redundant

• Identification of other important prognostic factors
  – ER, PR, Her2-neu Status
  – PSA, Gleeson
  – HPV
  – Gene expression profiling
Breast

- Stage IIb ER & PR negative, Her2-neu negative
- But in US everyone has early stage cancer
- Markers more important than stage
- Combine TNM with ER, PR, Grade, Her 2 Neu status
## Breast- STAGE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</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>T0, T1</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0, T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

| Stage IIIA| T0, T1, T2 | N0  | M0  |
| Stage IIB| T3  | N1, N2 | M0  |
| Stage IIIC| T4  | N0, N1, N2 | M0  |
| Stage IV| Any T | N3  | M0  |
| Stage V| Any T | Any N | M1  |
Breast- Prognostic Stage Groups

AJCC Cancer Staging Manual
Amin et al
Springer 2016
• Locally advanced low grade, marker positive and small high grade marker negative may be same stage group

  ? Useful for prognosis but not treatment decision making or surveillance

• Important to keep (anatomical) stage separate from prognostic factors but they need to be identified
Breast

- Locally advanced low grade, marker positive and small high grade marker negative may be same stage group
  - Useful for prognosis but not treatment decision making or surveillance
- Important to keep (anatomical) stage separate from prognostic factors but they need to be identified
Breast

- 42 year old woman, excellent performance status
- pT2N1aM0
- Triple negative
Extent of Disease

• Even in tumours in which tumour profile has proven benefit anatomical extent of disease is still essential
• Extent of disease an essential component of normograms/descision tools
For Medical Professionals

Cancer prediction tools

Stage III colon cancer

Patient Details  (edit details)
White Male, 55 years old with a BMI of 50

ECOG/WHO Performance Status
PS1

Tumor Grade
Moderately differentiated (intermediate grade)

Number of Lymph Nodes Examined vs Positive
Examined: 15  Positive: 3

Tumor Number / Location
Single / Right

Tumor Stage
T3

Treatment Type
S-FU with Oxaliplatin (e.g., FOLFOX)

Calculate Results

Details regarding the development and validation of this tool are provided in the manuscript titled "ACCENT-Based Web Calculators to Predict Recurrence and Overall Survival in Stage III Colon Cancer" (L.A. Mantlo et al., JNCO 106(10), 2014).
Future of TNM

• Remains relevant
• Essential for patient care
• Important component of Cancer Registry
• Facilitates cancer control
• Allows cross jurisdiction comparisons
• In many parts of the globe may be all you have is some description of the extent of disease
• Rolling Updates