Stage: The Language of Cancer

American Joint Committee on Cancer
American College of Surgeons
Chicago, IL

AJCC

American Joint Committee on Cancer

Validating science. Improving patient care.

Outline

- History of staging
  - UICC and AJCC
- What is staging?
- Why do we stage?
- Who does staging ?
- What is the role of the cancer registry/registrar?
- How are imaging and pathology used in staging?
- Why does stage evolve?
- An introduction to the 8th edition?

Historical Perspective 1

Staging based on the TNM concept was first championed by Dr. Pierre Denoix a surgical oncologist from Insitut Gustave-Roussy, Paris (1943-52)

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Historical Perspective 2

- North American effort first organized as the American Joint Committee for Cancer Staging and End Results Reporting (AJC) (1959)
- Jointly formed by the *American College of Surgeons, American College of Radiology, College of American Pathologists, College of Physicians, American Cancer Society & the National Cancer Institute*
- AJC (1970) – adopted "objectives, rules & regulations of the AJC" – resulted in formulation and publication of systems of classification of cancer
- First Edition of AJC staging manual published in 1977

Historical Perspective 3

Union for International Cancer Control – UICC

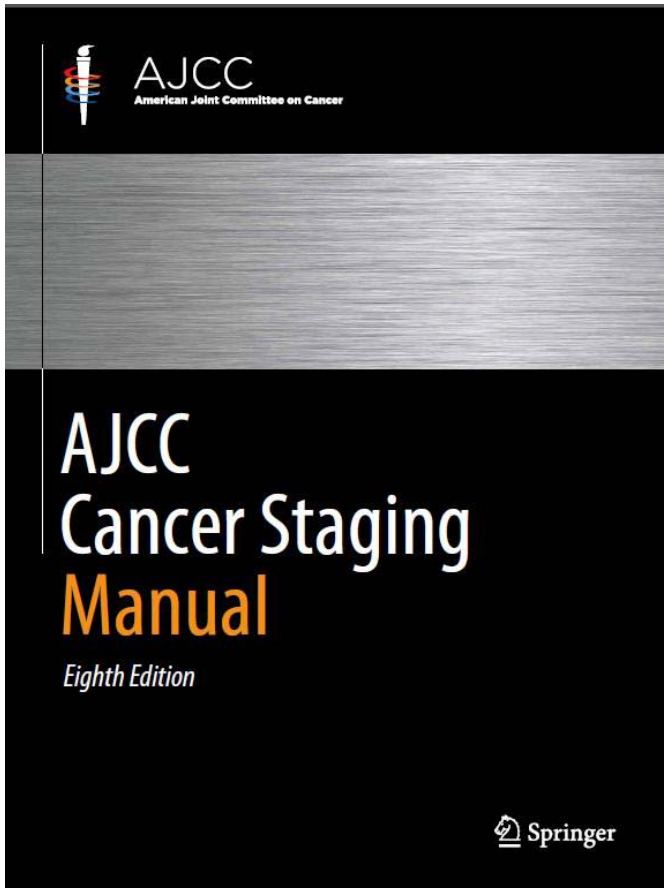
- 1943-52 TNM system proposed by Pierre Denoix
- 1968 First UICC publication, Editor Pierre Denoix
- 1987 Unified UICC/AJCC TNM

  Later incorporated FIGO and ANN ARBOR
- 2016 AJCC and UICC 8th editions published

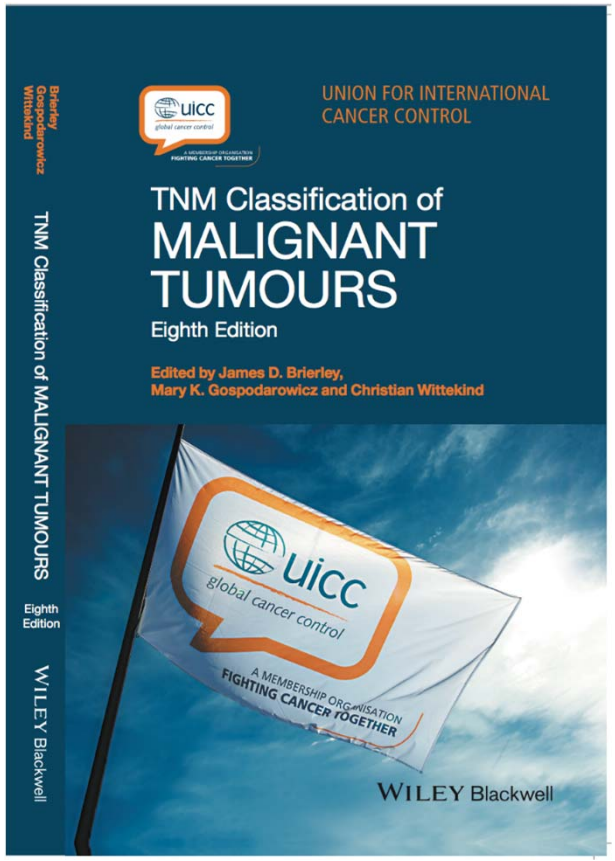
- The UICC aim to ensure there is a common language used to stage patients and that common language can be used across the globe

Publications 2016

AJCC: Cancer Staging Manual



UICC: TNM Classification System



Cancer Staging

To effectively care for any patient with cancer it is essential to consider three factors:

- The site of origin of the cancer
  - e.g. lung, a prostate cancer, or a breast cancer
- The histologic and biologic characteristics
  - if lung cancer is it non small cell or a small cell cancer
  - if prostate cancer what is the Grade score
  - if breast cancer what is its receptor status
- The extent of the cancer - The globally accepted method of describing anatomical extent of cancer is the TNM Classification.

Use of Stage

- To determine treatment
- To determine prognosis
- To facilitate clinical research and evaluate the results of treatments and clinical trials
- To facilitate the exchange and comparison of information between treatment centers, both nationally and internationally.

The original approach to stage was predicated on a sequential process

- Cancer starts in the organ of origin (T)

THEN

- It spreads to local tissues

THEN

- It invades lymphatics or blood vessels (N)

THEN

- It colonizes lymph nodes or other organs (M)

The original philosophy behind "stage"?

- Stage I: tumour in the organ of origin only
- Stage II: involvement of regional lymph nodes
- Stage III: locally advanced disease or non-regional lymph node involvement
- Stage IV: distant metastatic disease

…but things have changed with increasing knowledge about cancer behaviour and cancer prognosis.

Biology of Cancer

Halsted

- Tumors begin in an organ
- They spread locally
- They spread regionally
- They then spread systemically
- Therefore a big enough operation will cure cancer
- Size matters

Fisher

- Cancers spread early in their development
- Cancer is a systemic disease from the time the diagnosis is made
- Local treatments mean little without effective systemic therapy
- Biology matters

So....

- Small tumours with involvement of some regional lymph nodes may have a better prognosis than large local tumours without obvious nodal disease

- Factor other than anatomical extent of disease have an important effect on prognosis and they may be combined with anatomical extent of disease to form prognostic stage groups

Non-anatomic factors

- Generally available in the West
- Often not available in the developing world
- Therefore the staging system has to maintain anatomic staging for universal applicability
- Prognostic staging includes non-anatomic factors (ER/PR, MSI, etc.) to better inform prognosis and treatment

Basic Concepts of Staging

- T-, N-, M- are categories, NOT "T-stage, N-stage, M-stage"
- Clinical and Pathological staging
  - Clinical stage is based on physical examination, biopsy and imaging
  - Pathologic stage is done after removal of the primary tumor
- cTNM Stage applies to the initial presentation ONLY

General Rules

T Extent of the primary tumour

N Absence or presence and extent of regional lymph node metastasis

M Absence or presence and extent of distant metastasis

Fundamentals

- Please read Chapter 1
- Assigning stage means:
  - T category
  - N category
  - M category
  - Non anatomic factors
- These are used to assign a Prognostic Stage Group
- Both TNM and Prognostic Stage grouping are required

Some concepts - c and p

“Clinical classification” (cTNM):

Clinical stage classification is based on patient history, physical examination, and any imaging done before initiation of treatment.

- No specific imaging is required to assign a clinical stage for any cancer site.
- Imaging study information may be used for clinical staging
- Biopsy information on regional lymph nodes and/or other sites of metastatic disease may be included in the clinical classification.

Some concepts - c and p

“Pathological classification” (pTNM):

This classification is applicable when surgery is performed before initiation of adjuvant radiation or systemic therapy.

- It is composed of information from diagnostic workup from clinical staging combined with:
  - operative findings
  - pathology review of resected surgical specimens

INTRODUCTION TO STAGE
General Rules

cTNM

Clinical Classification

Determined

before any treatment

pTNM

Pathological Classification

Determined

after surgical treatment

INTRODUCTION TO STAGE
General Rules - Primary Tumor

- **TX** Primary tumour cannot be assessed
- **T0** No evidence of primary tumour
- **Tis** Carcinoma in situ
- **T1-T4** Increasing size and/or local extent of the primary tumor

INTRODUCTION TO STAGE
General Rules – Regional Nodes

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1-N3** Increasing involvement of regional lymph nodes

INTRODUCTION TO STAGE
General Rules - Metastases

- **M0** No distant metastasis
- **M1** Distant metastases

- Note: the cMX category should never be used because clinical assessment of metastasis can be based on physical examination and imaging alone.

Prognostic Stage Grouping

- Prognostic stage groups are based on combinations of T, N, M, and relevant prognostic factors
- They are identified by roman numeral as I, II, III or IV
- They usually define groups of patients with similar outcomes to help to:
  - define prognosis and appropriate treatment,
  - enable comparisons of similar groups of patients between institutions and over time

Anatomical Stage Groups

- Some stage groups depend only on anatomical extent of disease
  - Examples are lung cancer and colorectal cancer

For example:

- 65 year old man presents with rectal bleeding, examination shows a rectal carcinoma
- Biopsy confirms adenocarcinoma
- MRI is performed

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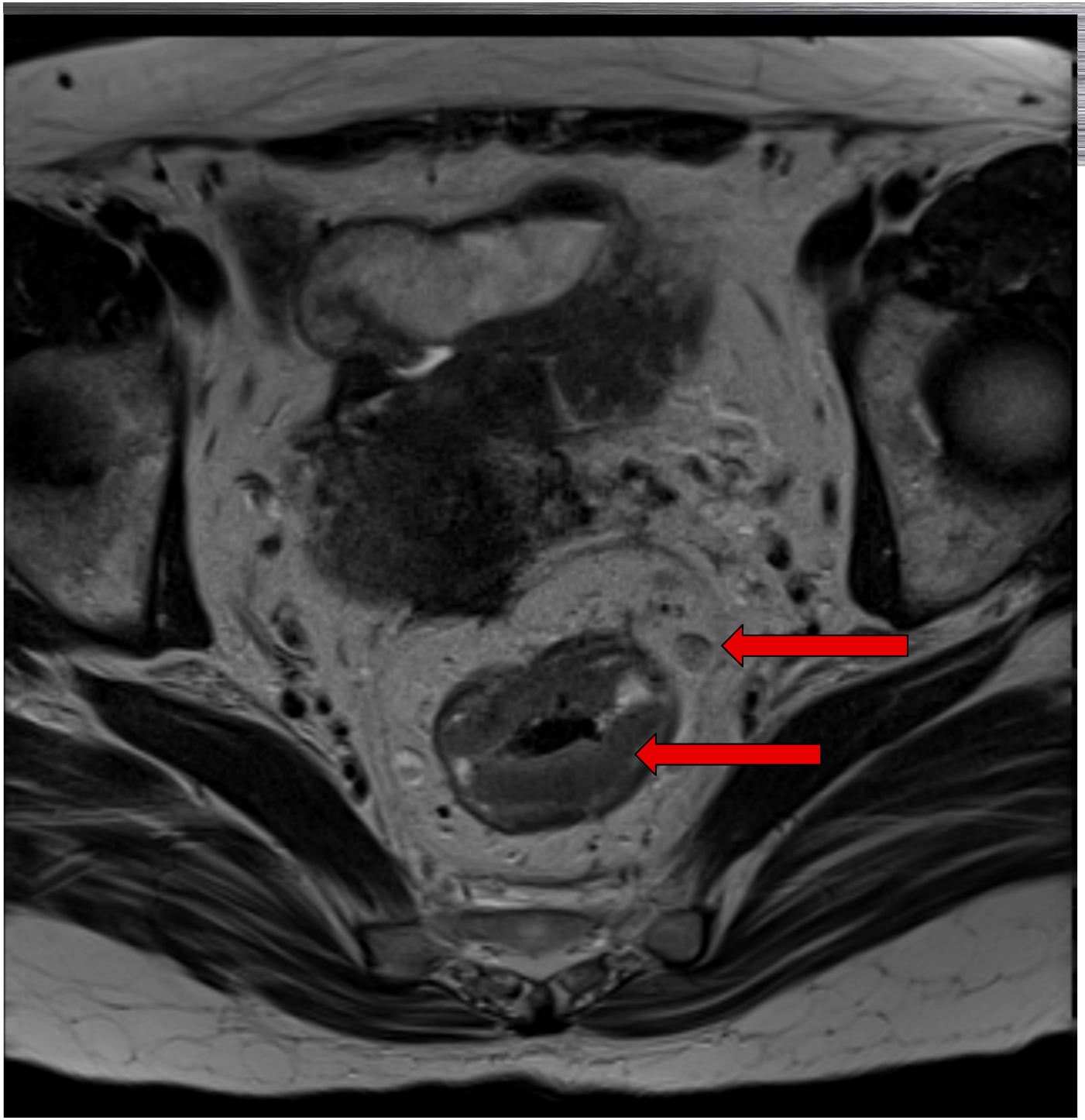


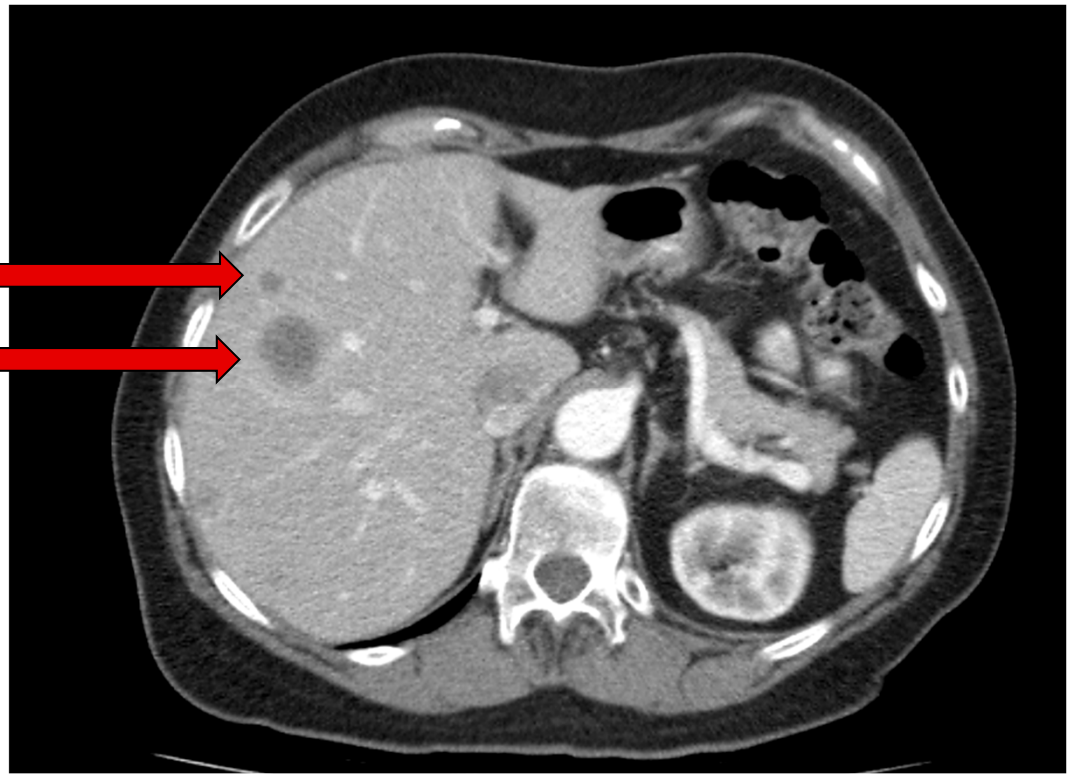
cT3N1a
Rectal cancer

Lymph Node

T3 Rectal Cancer

Staging Workup

- CT scan thorax, abdomen and pelvis is performed
- Multiple liver metastases are identified
- cM1a



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Therefore the Stage Grouping is:

- T3N1aM1a
- Which is Stage IVa

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0, NX	M0	0
T1 , T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
any T	N1-N2	M0	III
T1 –T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1	IV
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

Assigning Stage: The Role of the Managing Physician Chapter 1

- Staging requires the collaborative effort of many professionals, including the managing physician, pathologist, radiologist, cancer registrar and others

- While the pathologist and the radiologist provide important information, stage is defined ultimately by the managing physician from the synthesis of all available information some of which the other physician may not have

Assigning Stage: The Role of the Managing Physician

The managing physician is therefore responsible for:

- ensuring all appropriate staging investigations have been performed
- assigning the patient's stage.

RULES ABOUT STAGE

- Stage at diagnosis does not change.
- Patients do change; the extent of disease can change after treatment and after follow up
- But the original stage “sticks.”

Modifiers of Stage “y”

- If however there are no liver metastases in the case described above
- The stage at diagnosis is:
  - cT3N1aM0
  - Stage IIIB
- Preoperative chemoradiation is given

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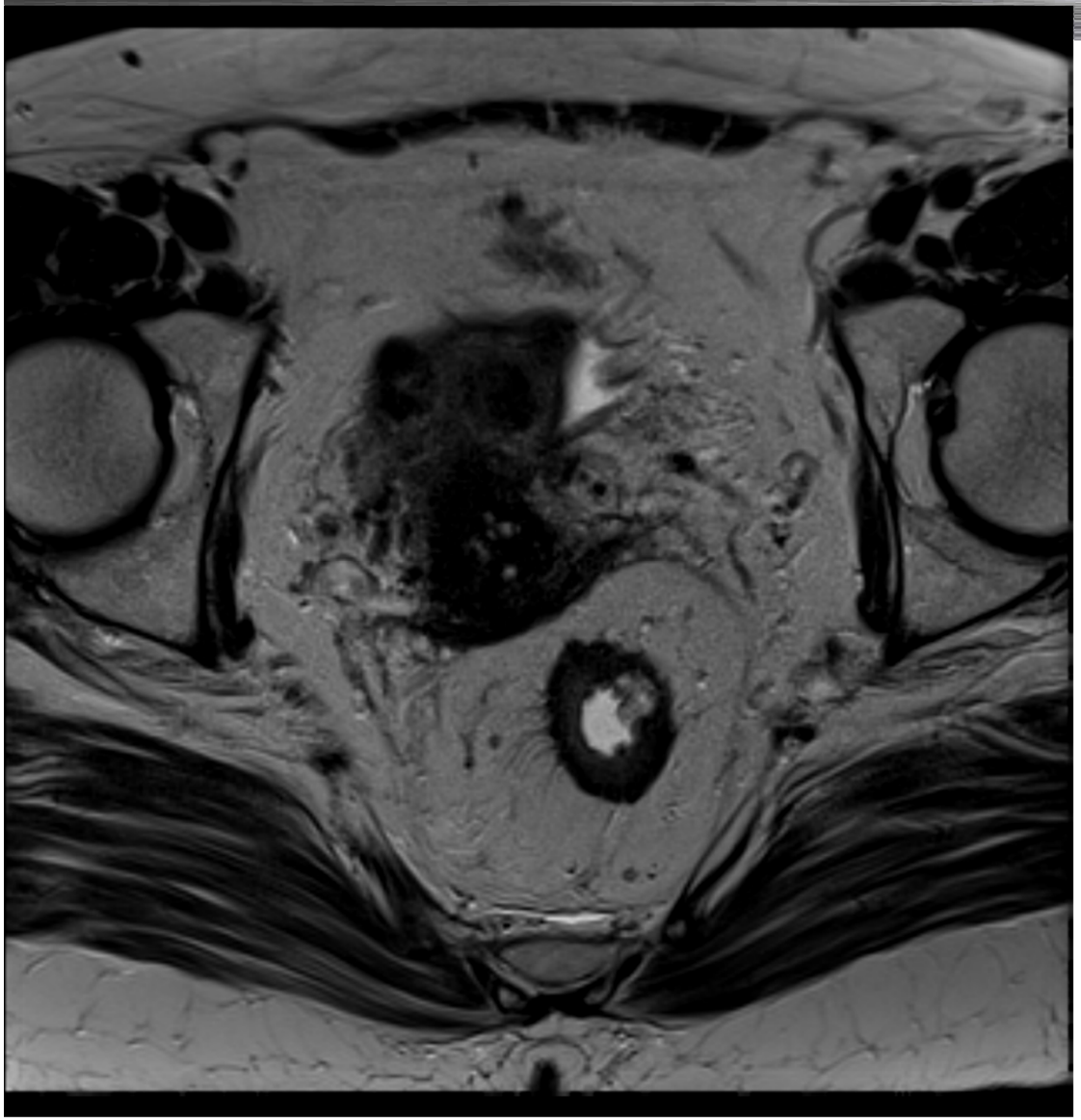
Preoperative chemoradiation is



The tumor reduces in size - Downsizing

The tumor is now staged as T2 and no involved nodes N0- Downstaging

Surgery is performed. There is residual tumor invading the muscularis propria -T2 and no evidence of node involvement but mucin seen in three lymph nodes- N0

Stage y

- At surgery no residual tumour cells.
- Mucin is seen in 3 lymph nodes
- The stage is
  - ypT2N0M0
- y is used as a prefix to indicate that the stage has been determined after preoperative treatment
- P is used to identify that this is the pathologic stage

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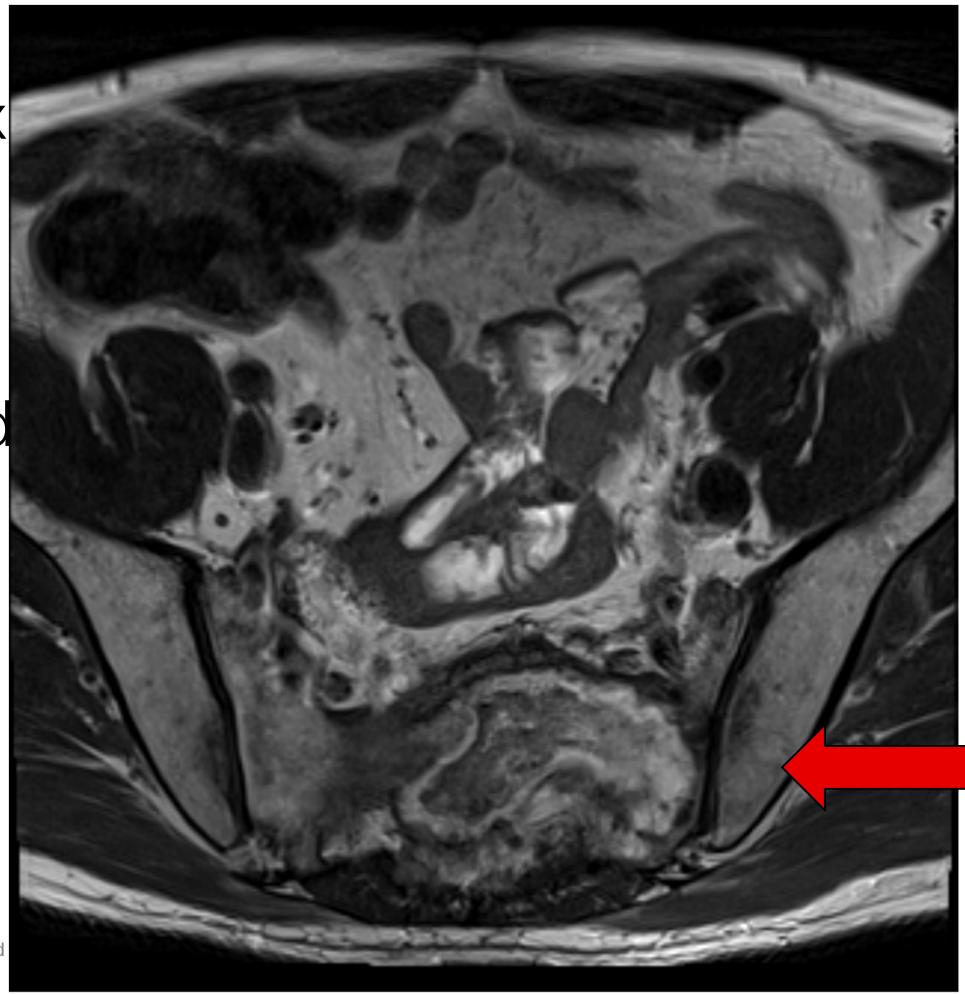
Modifiers of Stage “r”

Five years later has pelvic pain

Stage Modifier “r” rT4N0M0

r is used as a prefix to indicate that the stage has been determined after initial treatment and at recurrence or after a period of surveillance



MRI reveals a sacral mass. Biopsy shows recurrent rectal cancer

Prognostic Stage Groups

- For some cancers the stage groups depends on anatomical extent of disease **and** additional prognostic factors
- Examples are:
  - Thyroid Age
  - Prostate PSA and Grade Score
  - Breast Grade, ER/PR, Her-2-neu, Genomic assays

Anatomical and Prognostic Stage Groups

- For some cancers there are clinical, pathological and prognostic stage groups
- Some prognostic factors may not always be available, especially in low and middle income countries
- Therefore in some tumor sites such as breast there are both anatomical stage groups and prognostic stage groups.

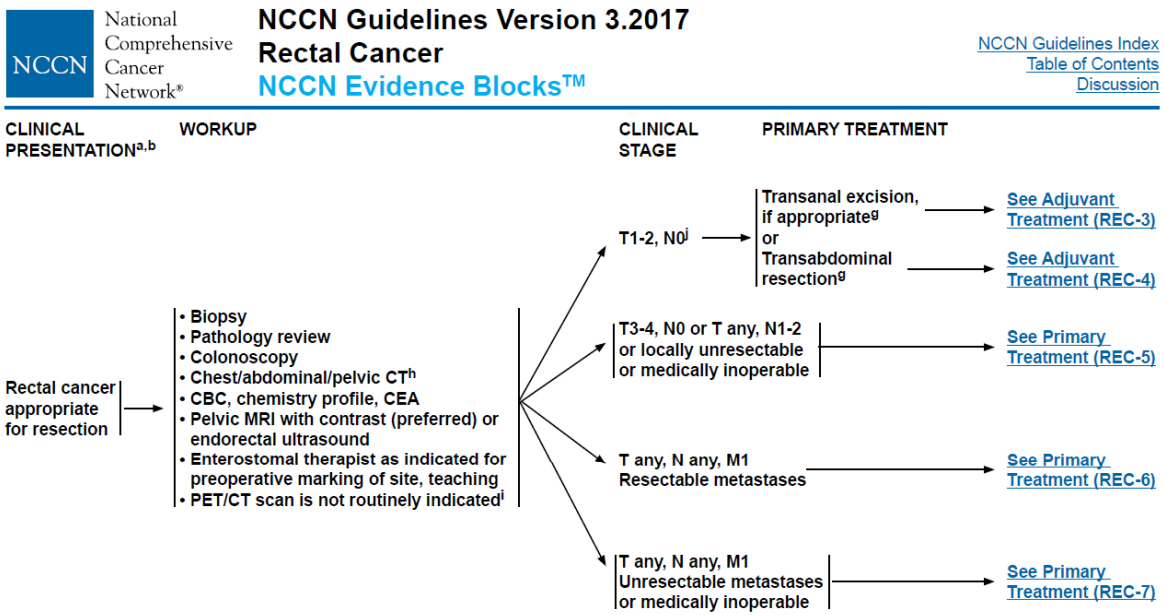
How to Record the Stage

Stage at Diagnosis. Recorded in the chart and remains unchanged

Use of modifiers:

- After neoadjuvant therapy –
  - use y
- After period of freedom from disease or after surveillance –
  - use r

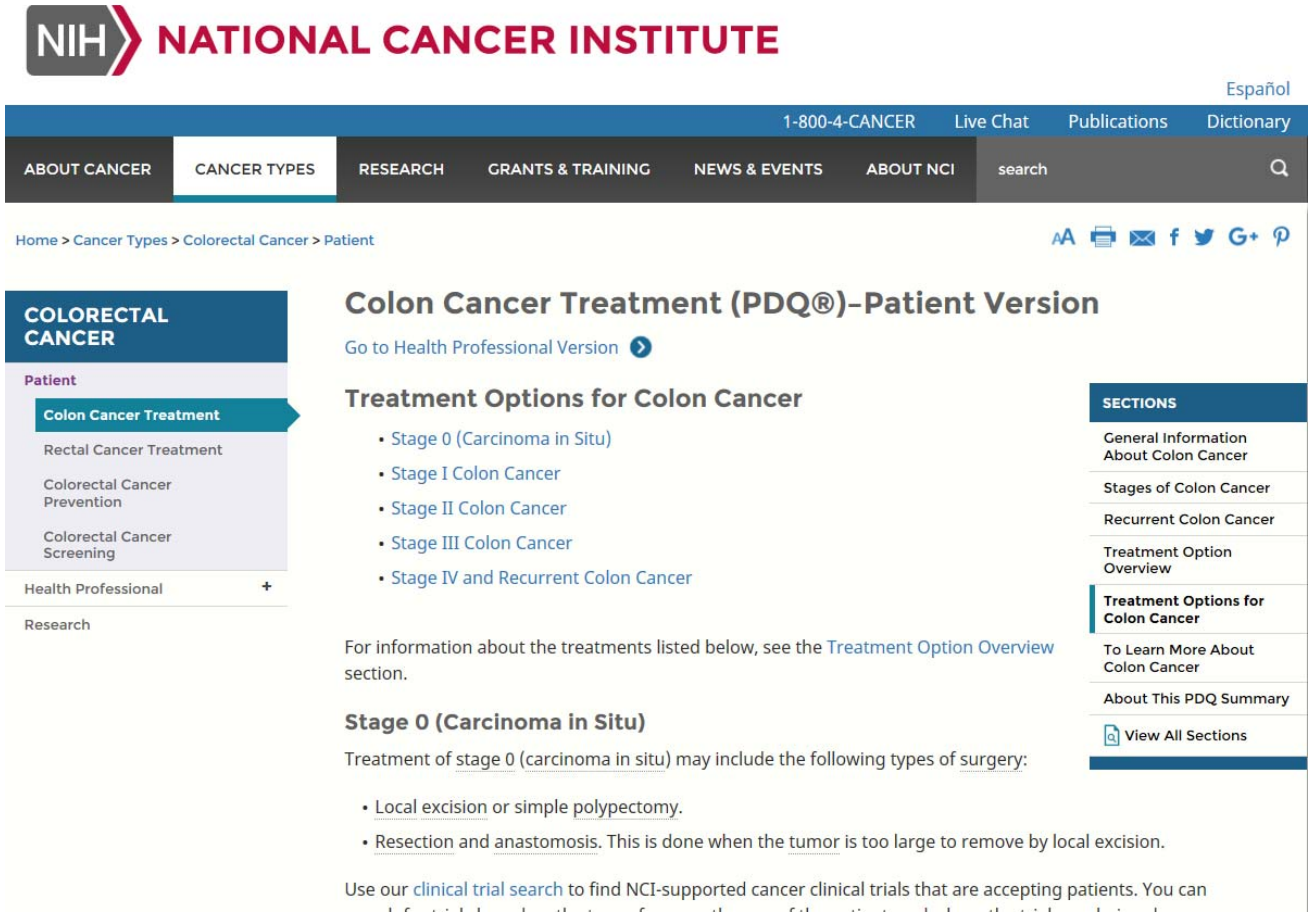
Stage is used in treatment decision making



Knowing stage at diagnosis is essential in choosing appropriate treatment.

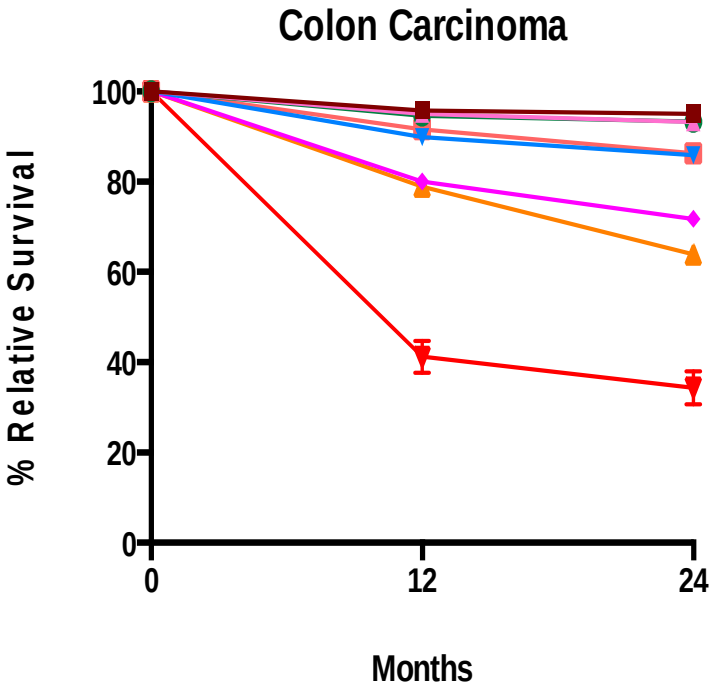
For instance in the NCCN guideline for the management of rectal cancer the primary treatment recommendations differ for different stages

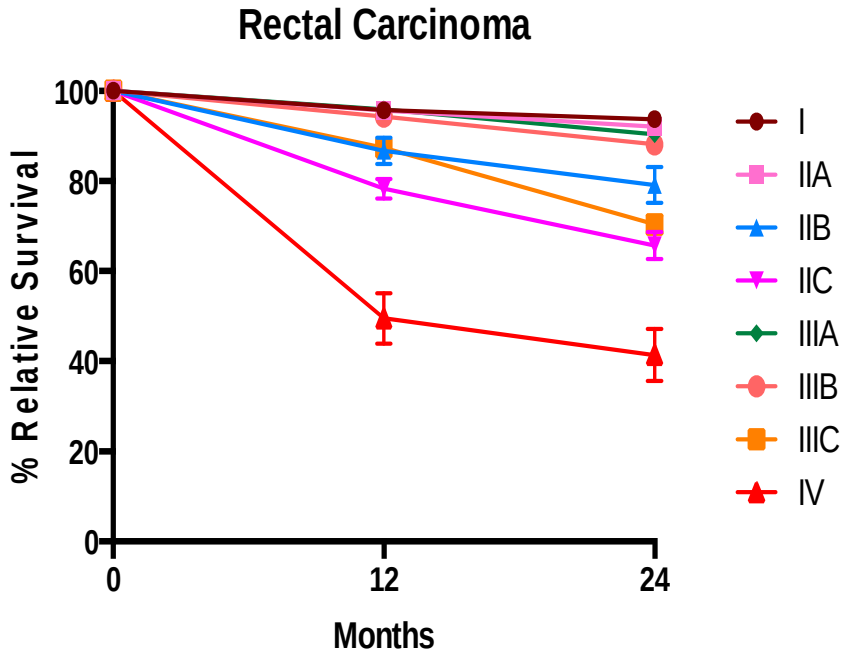
Stage is important in patient education



Patients with cancer are encouraged to ask the stage of their cancer if they have not been told.
It helps in looking up information about their cancer and treatment options as seen in this page from the NCI website for patients

Stage gives an indication of prognosis





Staging in Population Health 1

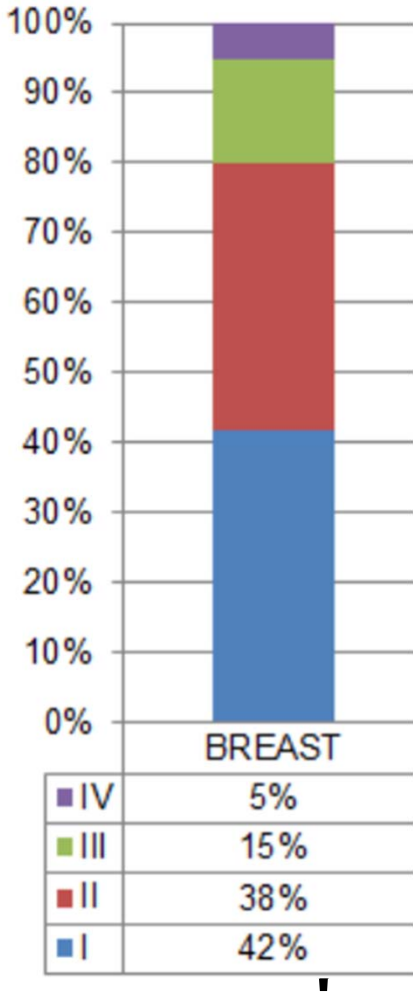
If stage is known as well as incidence the data can be used for:

Screening

- Assess the need
- Assess effectiveness
  - After introduction of an effective screening program we would expect change in distribution with fewer stage IV and more stage I cancers

Treatment guideline concordance

- If treatment is known can assess if treatment give is concordant with guidelines that incorporate stage

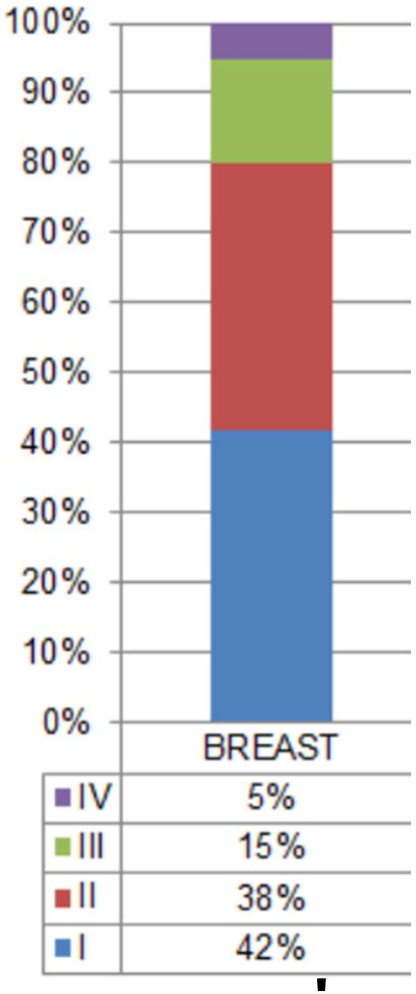


Staging in Population Health 2

If stage is known as well as incidence the data can be used for:

Resource Planning

- Different resources are needed depending on at which stage patients present
- The more patients presenting with advanced stage the greater the need for systemic therapy and/or palliative care facilities



Comparisons of survival by stage

- The survival by stage can be compared between different countries

Staging terms that cause confusion - 1

- Stage Migration
  - describes a change in the proportion of T, N or M categories following introduction of new means of assessing disease extent, such as PET scan.
- Stage Shift
  - describes a change in the pattern of stage distribution within a population to a lower stage following the introduction of early detection or screening programs, or to higher stage when access to care becomes limited.

Staging terms that cause confusion - 2

- Downstaging
  - describes a reduction in T or N category after neoadjuvant therapy
- Downsizing
  - describes a reduction in size of tumor after neoadjuvant therapy

Remember though, the stage at diagnosis remains the patient's clinical stage even if the tumor shrinks

The need to change and remain relevant

- New Knowledge. For example:
  - Breast prognosis
    - Genomics are a more powerful an indicator of outcome than anatomic features
- New disease. For example:
  - HPV Oropharynx

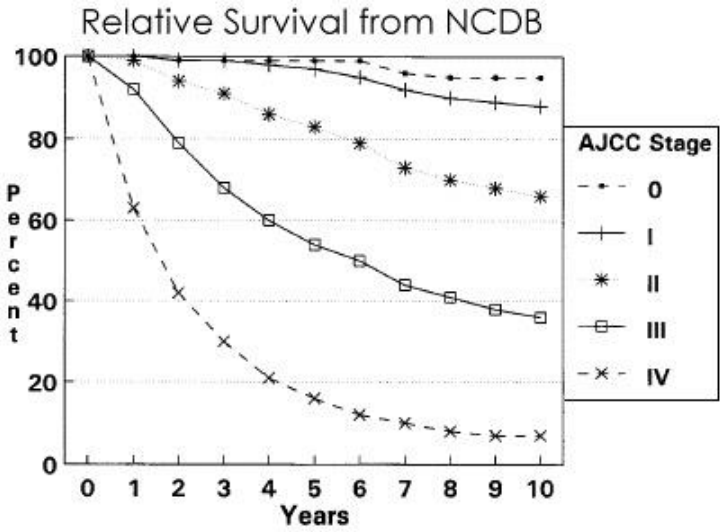
BREAST CANCER
Anatomical and Prognostic Stage Groups

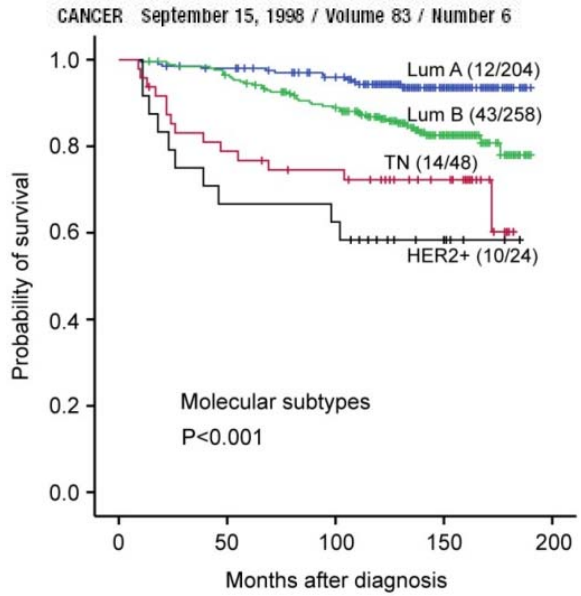
Breast cancer is now understood to be a group of diseases with different molecular characteristics (*identified by gene expression profiling, IHC, proteomics, NGS, and other molecular techniques)* that originate in breast epithelial tissue

- *different prognoses*
- *different patterns of recurrence*
- *different patterns of metastasis*
- *different sensitivities to available therapies*

Breast: Anatomy is Not Enough

- Anatomy provides some prognostic information to support treatment planning
- But anatomy is insufficient to define prognosis and therapy
- Including non-anatomic factors is necessary to define prognosis and treatment





BREAST CANCER Prognostic Group

- Addition of tumor factors such as
  - Grade
  - HER2 status
  - Estrogen receptor (ER), progesterone receptor (PR) Status
  - Genomic assays

- In conjunction with anatomic information on the tumor (T), regional nodes (N), and distant metastases (M) categories

BREAST CANCER (8th Ed.)
Anatomical and Prognostic Stage Groups

- Anatomic Stage table. Based solely on anatomic extent of cancer as defined by the T, N, and M categories.
  - Intended for use in settings around the world where biomarker analysis is not available.
- When biomarkers are available, cancers are staged using the Clinical and Pathological Prognostic Stage tables.

BREAST CANCER 8th Ed.
Anatomical and Prognostic Stage Groups

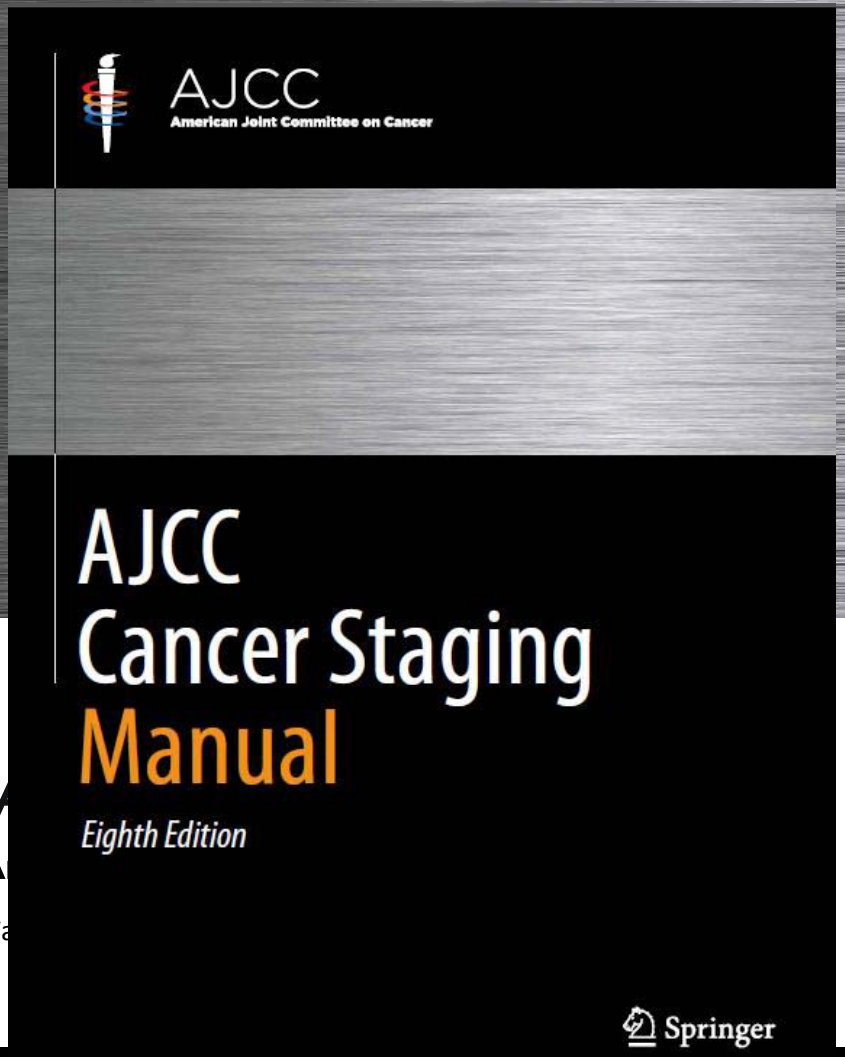
- Stage Groups reflect survival outcome for that TNM
- Stage group does not directly drive treatment
- But there is the expectation that treatment will be appropriate for the TNM

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T2 N1 M0 T3 N0 M0	1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

A New Disease

- HPV related squamous cell oropharyngeal carcinoma behaves differently from squamous cell oropharyngeal cancer related to smoking.
- TNM was developed for smoking related oropharygngeal cancer
- When applied to HPV cancer the survival curves for stage I and II and III and IV overlap.
- The 7th edition TNM does not work for HPV related disease so a new separate classification has been developed for HPV oropharyngeal cancer for the 8th edition

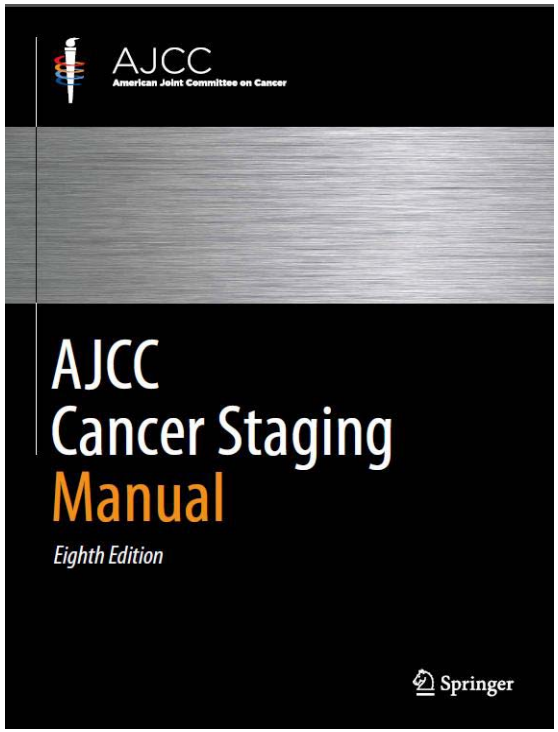
The 8th Edition



AJCC 8th Edition

- **Bridge from a Population Based to a More Personalized Approach**
  - require integration of a wide variety of information based on patient history and physical examination findings supplemented by imaging, intraoperative findings, and pathologic data

- **What's New?**
  - Data Element Review Form and Levels of Evidence
  - Precision Medicine Core with relevant genomic markers
  - Chapter Templates
  - New Chapter Headings
  - Tabular format for TNM Definitions and Stage Group



AJCC 8th Edition

- Published October 6, 2016
- Effective for all cased diagnosed on or after January 1, 2018
- **Read Chapter 1**
  - Principles of Cancer Staging
- Chapter Outline
  - Definitions of AJCC TNM
  - AJCC Prognostic Stage Groupings
  - Registry data collection variables
  - Histologic Grade
  - Survival Data
  - Illustrations
  - Bibliography

AJCC 8th Edition

- Involved 450 volunteers
  - X expert panels
  - Editorial Board consisting of y volunteers
  - Countless hours of work by dedicated AJCC staff
- Introduced structured authoring that will allow for editing and publication in a variety of formats
- Created an API; an electronic platform that supports publication, research and translation

Persistent Challenges to TNM Staging

The 8th Edition recognizes that :

TNM is largely limited to anatomic information

- –Lacks biologic data and impact of response
- –Creates ‘bins’ of like patients and not individualized

TNM does not always meet needs of clinicians and patients – but is it still relevant for many disease sites

- –Individualized prognosis
- –Predict value of therapy
- –But TNM risks marginalization

- TNM should maintain anatomic base because of its value in:
  - –Population incidence and impact
  - –Longitudinal changes
  - –World wide use

What's Changing Since the Last Edition - *The Evolving Landscape (2008 - 2013 ….)*

- Advances in molecular underpinnings of cancer - oncogenesis, progression, resistance – molecular classification of cancer
- Increasing availability of high throughput testing, mutational analysis (sequencing), microarrays (RNA, mi RNAs, SNPs, etc)
- Advances in informatics & computational biology; increased adoption of EHRs, data interoperability, real time risk calculating strategy apps (nomograms, tables, etc)
- Maturing data is gradually becoming available on prognostic and predictive factors that allow evidence-based decision making

Updates

AJCC and UICC periodically modify the system in response to newly acquired clinical and pathological data and improved understanding of cancer biology and other factors affecting prognosis.

Revision cycles are historically every 5-7 years

But rolling updates will be introduced

Summary

The 8th Edition of the AJCC Cancer Staging System is the “language of cancer”

It is used to classify extent of disease, help define treatment strategies and to analyze and compare results of clinical trials.

The 8th Edition is now in effect.