TNM Classification of Malignant Tumours 8th edition

Changes between the 7th and 8th editions With focus on Pancreas and Biliary Tracy Carcinomas

AJCC
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A MEMBERSHIP ORGANISATION
FIGHTING CANCER TOGETHER

CANADIAN PARTNERSHIP AGAINST CANCER
PARTENARIAT CANADIEN CONTRE LE CANCER

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:

Site

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

Characteristics

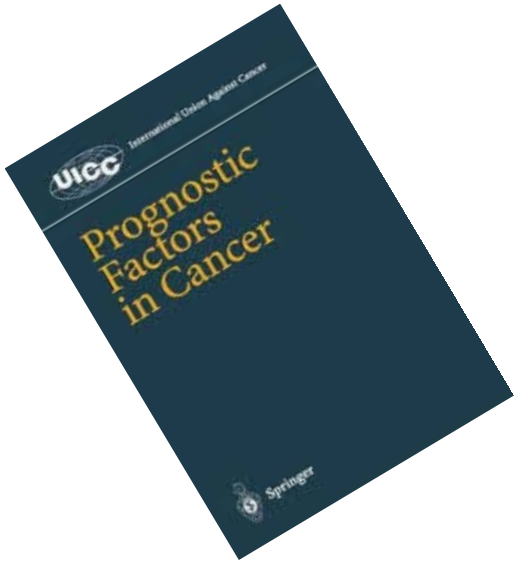
- Histologic/biologic characteristics
- E.g. Gleason 8 adenocarcinoma, HER2/neu positive adenocarcinoma – Blue Book

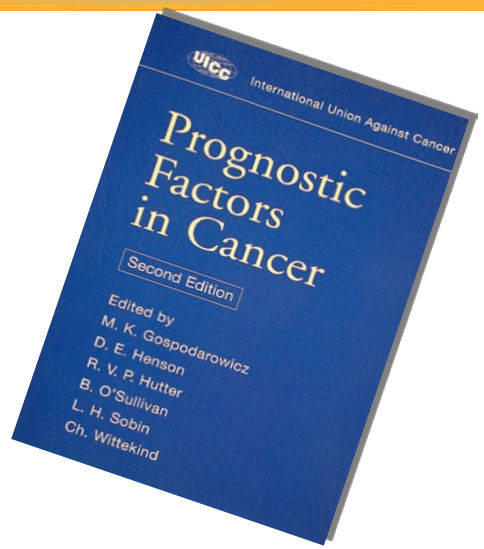
Extent

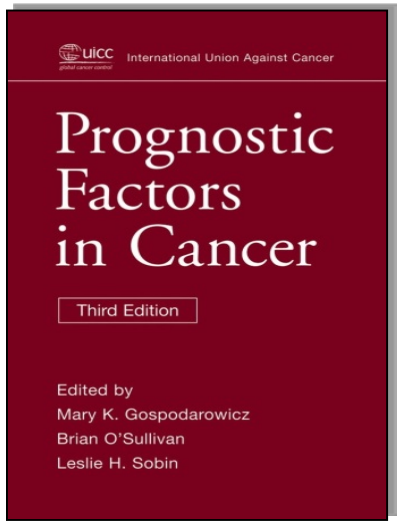
- Anatomical extent of the cancer or its **stage**
- E.g. Stage groupings (I, II, III, IV). TNM

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







AJCC

Validating science. Improving patient care.

- 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 UICC

- 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 8th 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

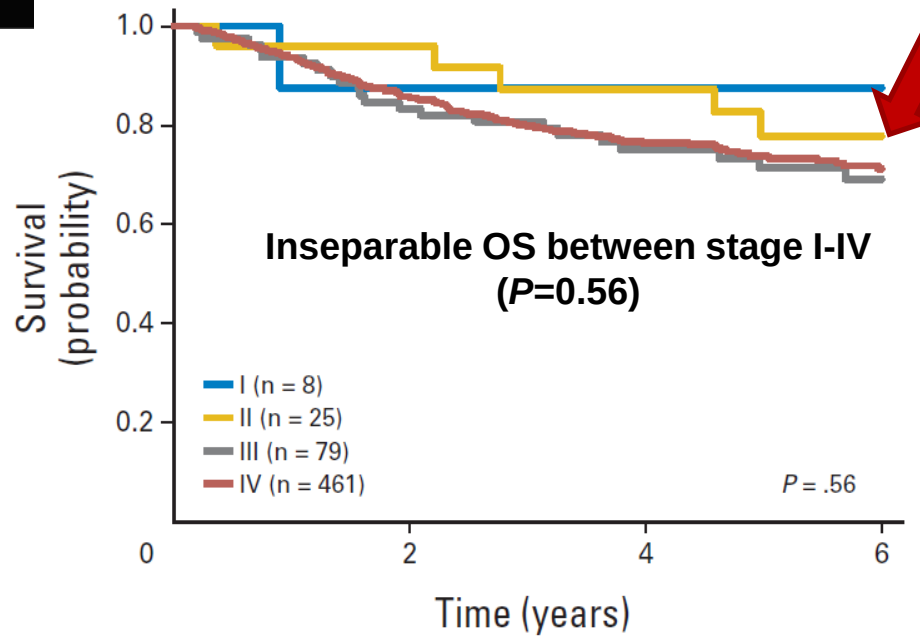
Head and Neck Changes

- 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

OS by 7th edition TNM Stage Groups: PMH Data

HPV(+) Stage IV disease does not have the ominous outcome of smoking-related OPC

HPV+ OPC (n=573)

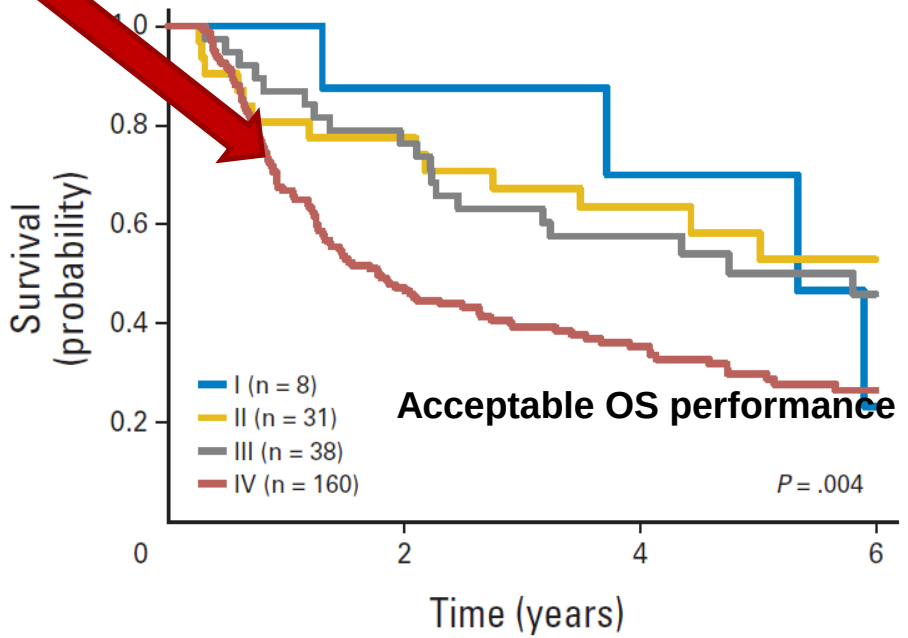


Inseparable OS between stage I-IV (*P*=0.56)

No. at risk				
I	8	7	5	4
II	25	23	19	7
III	79	64	47	27
IV	461	386	273	112

HPV Related	Events/ Total	3 Years Median (%)	3 Years 95% CI (%)	5 Years Median (%)	5 Years 95% CI (%)	*P*
Total	164/573	80	77 to 84	74	70 to 78	
Stage I	1/8	88	67 to 100	88	67 to 100	
Stage II	5/25	87	75 to 100	78	62 to 97	
Stage III	27/79	81	72 to 90	71	62 to 83	
Stage IV	131/461	80	76 to 84	74	70 to 78	.560

HPV– OPC (n=237)



Acceptable OS performance

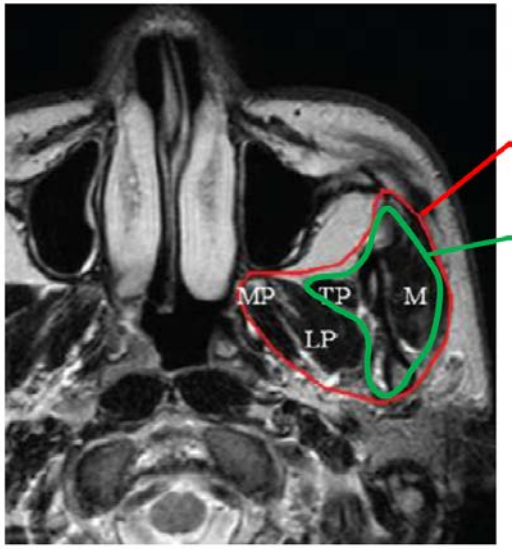
No. at risk				
I	8	7	3	1
II	31	24	16	9
III	38	29	18	10
IV	160	74	42	21

HPV Unrelated	Events/ Total	3 Years Median (%)	3 Years 95% CI (%)	5 Years Median (%)	5 Years 95% CI (%)	*P*
Total	161/237	49	42 to 55	38	32 to 45	
Stage I	4/8	88	67 to 100	70	42 to 100	
Stage II	16/31	67	53 to 86	58	42 to 80	
Stage III	24/38	63	49 to 80	50	36 to 70	
Stage IV	117/160	39	32 to 48	30	23 to 39	.004

INTERNATIONAL UNION AGAINST CANCER

Huang, Xu, Siu, Waldron, O'Sullivan, et al. JCO, March, 2015

- 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

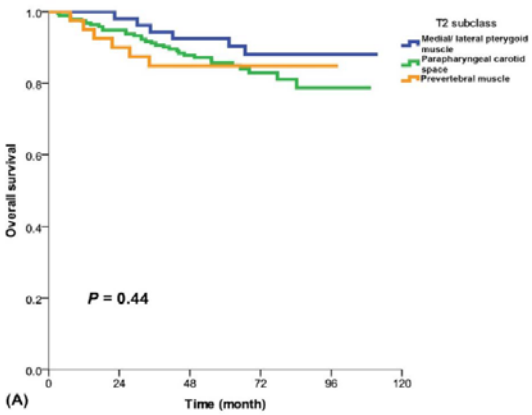


Abbreviations: LP = lateral pterygoid, M = massete
MP = medial pterygoid, T = temporalis.

Redefining infra-temporal fossa / masticator

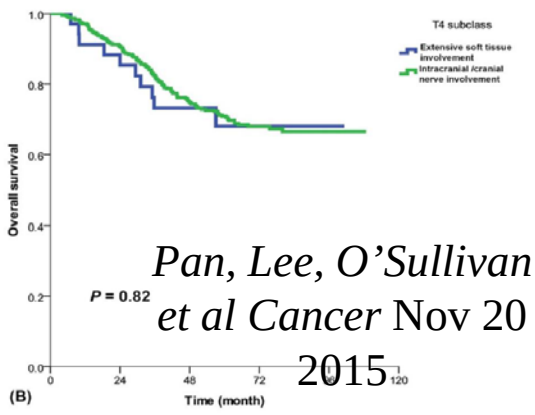
Understanding risk of Medial and Lateral Pterygoid muscle invasion with IMRT

Patients with no other T3-4 criteria:
MP ± LP involvement
No sign. difference in OS from
prevertebral muscle or
parapharyngeal /carotid space alone



Adjacent soft tissue involvement → T2

Infiltration beyond the anterior surface of LP, hypopharynx, orbital structures, parotid gland, but no other T4 criteria
No sign. difference in OS from
intracranial extension and/or cranial nerve

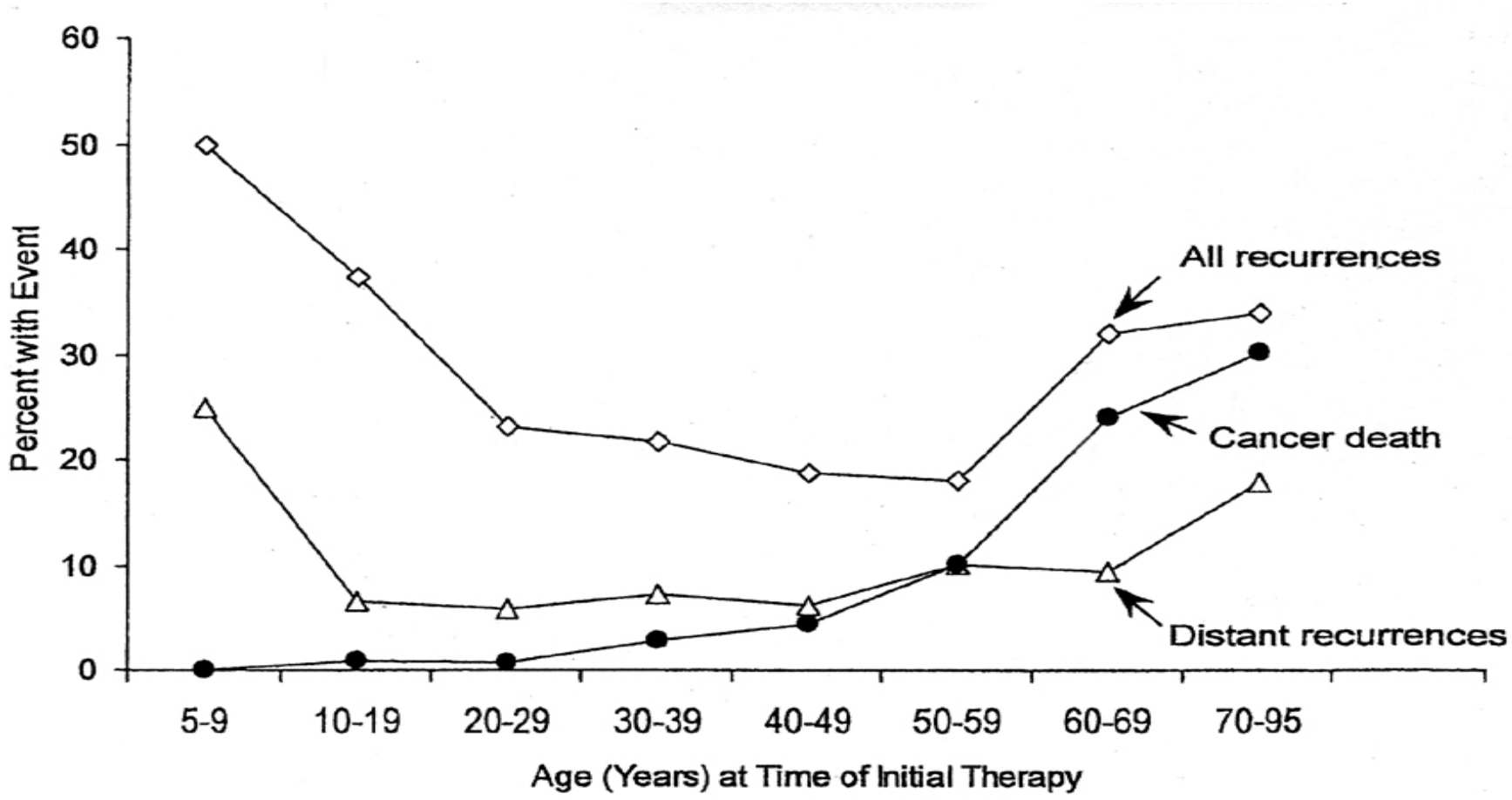


extensive soft tissue involvement → T4

Pan, Lee, O'Sullivan et al Cancer Nov 20 2015

Age

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



Mazzaferri and Kloos. J C E & M; 86: 2001

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.

  Mete et al Ann Surg Oncol (2010)

- 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

T1	Tumour 2 cm or less
	T1a Tumour 0.5 cm or less
	T1b Tumour greater than 0.5 cm and less than 1 cm
	T1c Tumor greater than 1 cm but no more than 2 cm
T2	Tumour more than 2 cm but no more than 4 cm
T3	Tumour more than 4 cm in greatest dimension
T4	Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery
N1	Metastases in 1 to 3 nodes
N2	Metastases in 4 or more nodes

M category unchanged

Stage

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Pancreas

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

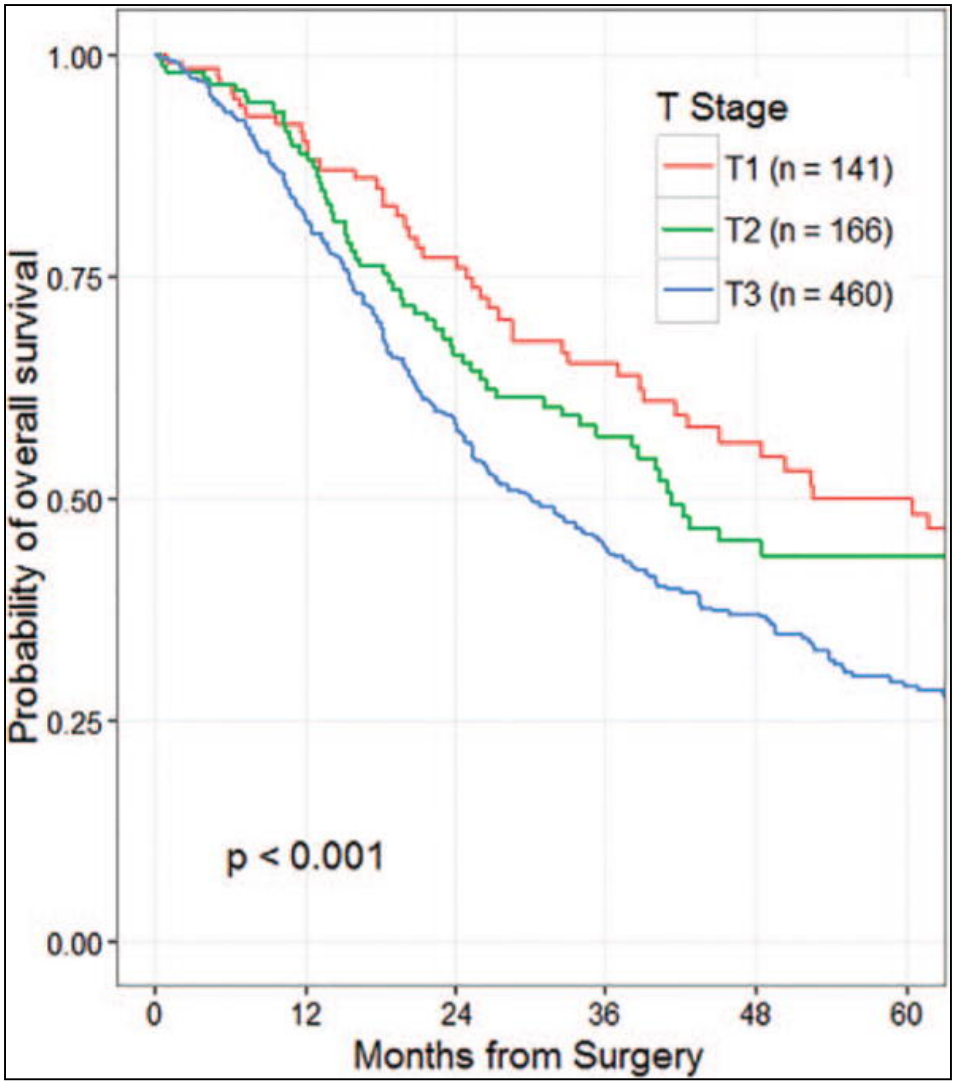


FIGURE 1 . Overall survival by T-stage of 767 patients who underwent resection for node-negative pancreatic cancer. T-stage defined by AJCC 7th edition criteria.

Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma.

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

Annals of Surgery. 265(1):185-191, January 2017.
DOI: 10.1097/SLA.0000000000001763

FIGURE 4

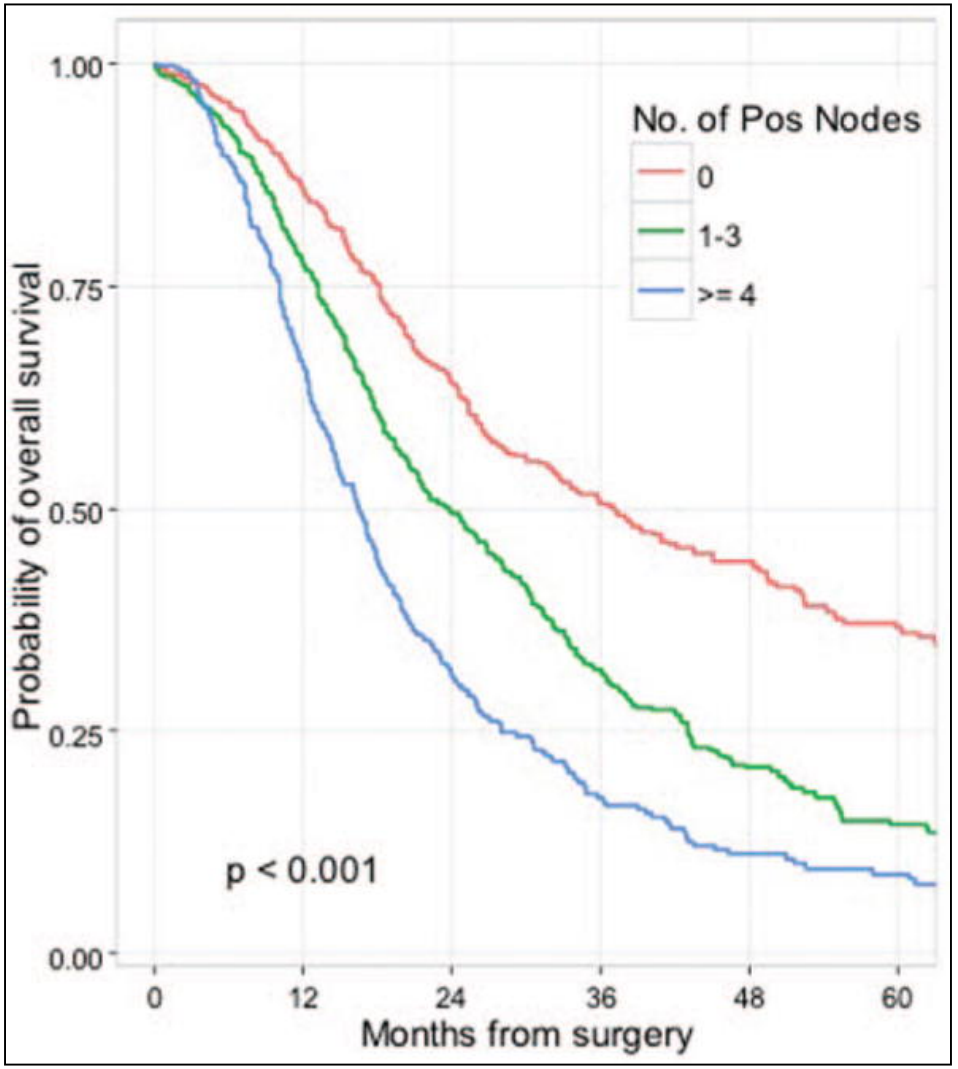


FIGURE 4 . Overall survival by number of positive nodes for all patients who underwent a R0 resection (training set, n = 1551) stratified by proposed AJCC 8th edition criteria.

Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma.

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

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CAP

Treatment Effect – Tumour Regression Score – Similar to Rectum

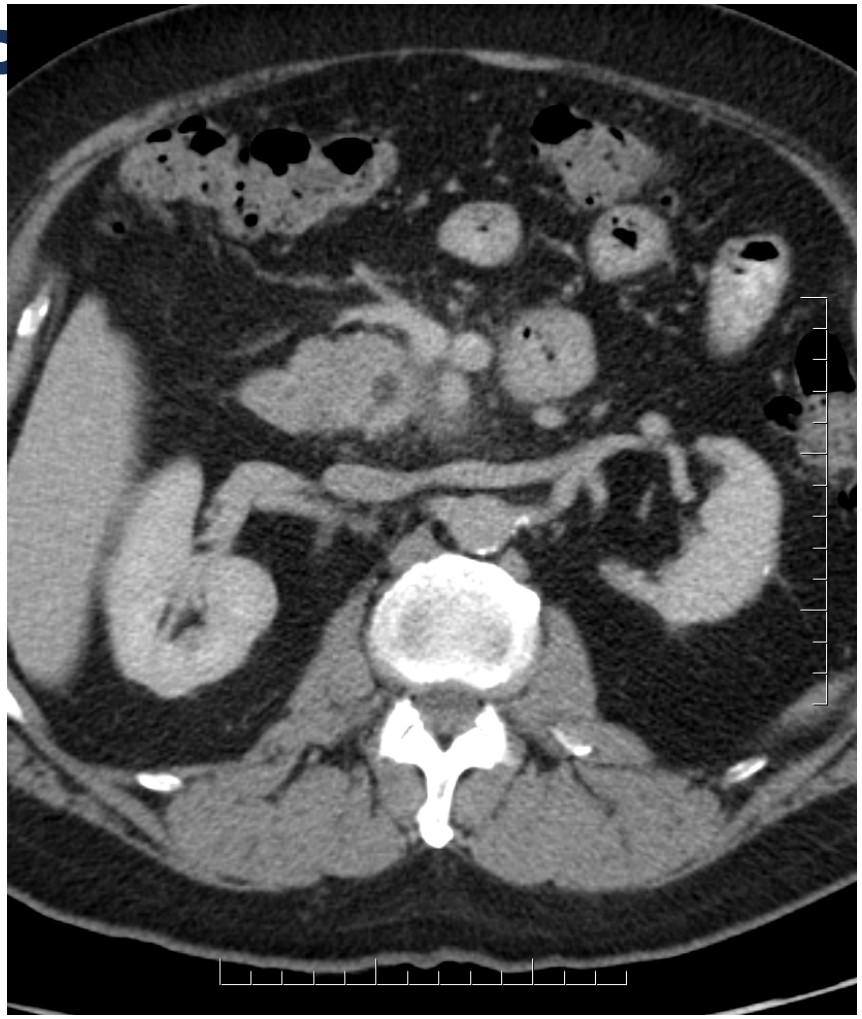
Modified Ryan Scheme

- 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

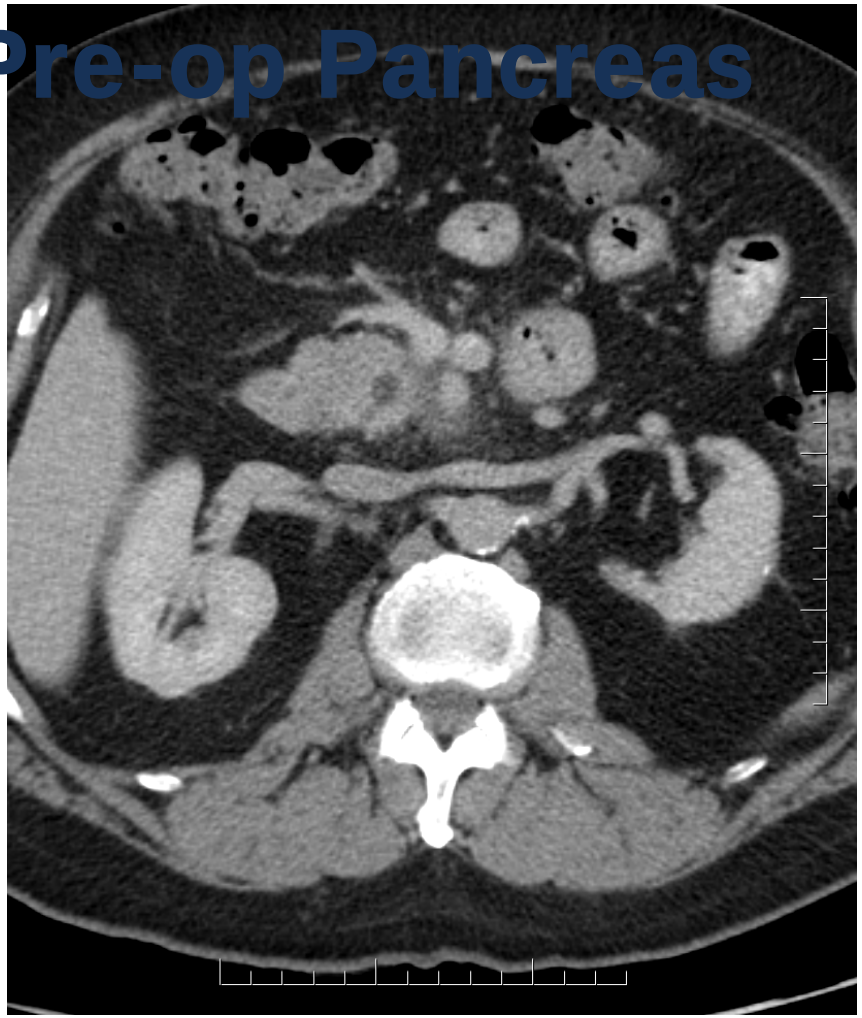
- 69 yo M presenting with back pain
- Pancreatic duct stricture found on ERCP,
- Adenocarcinoma
- Work up demonstrates SMA involvement

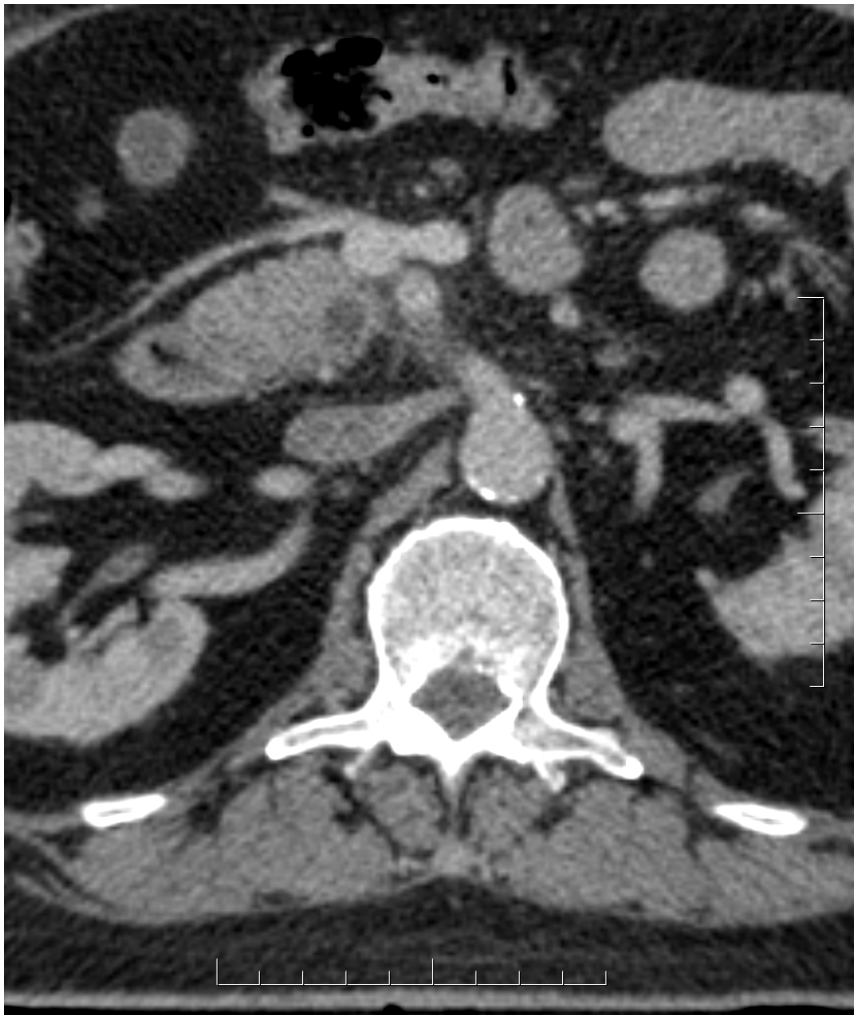
P

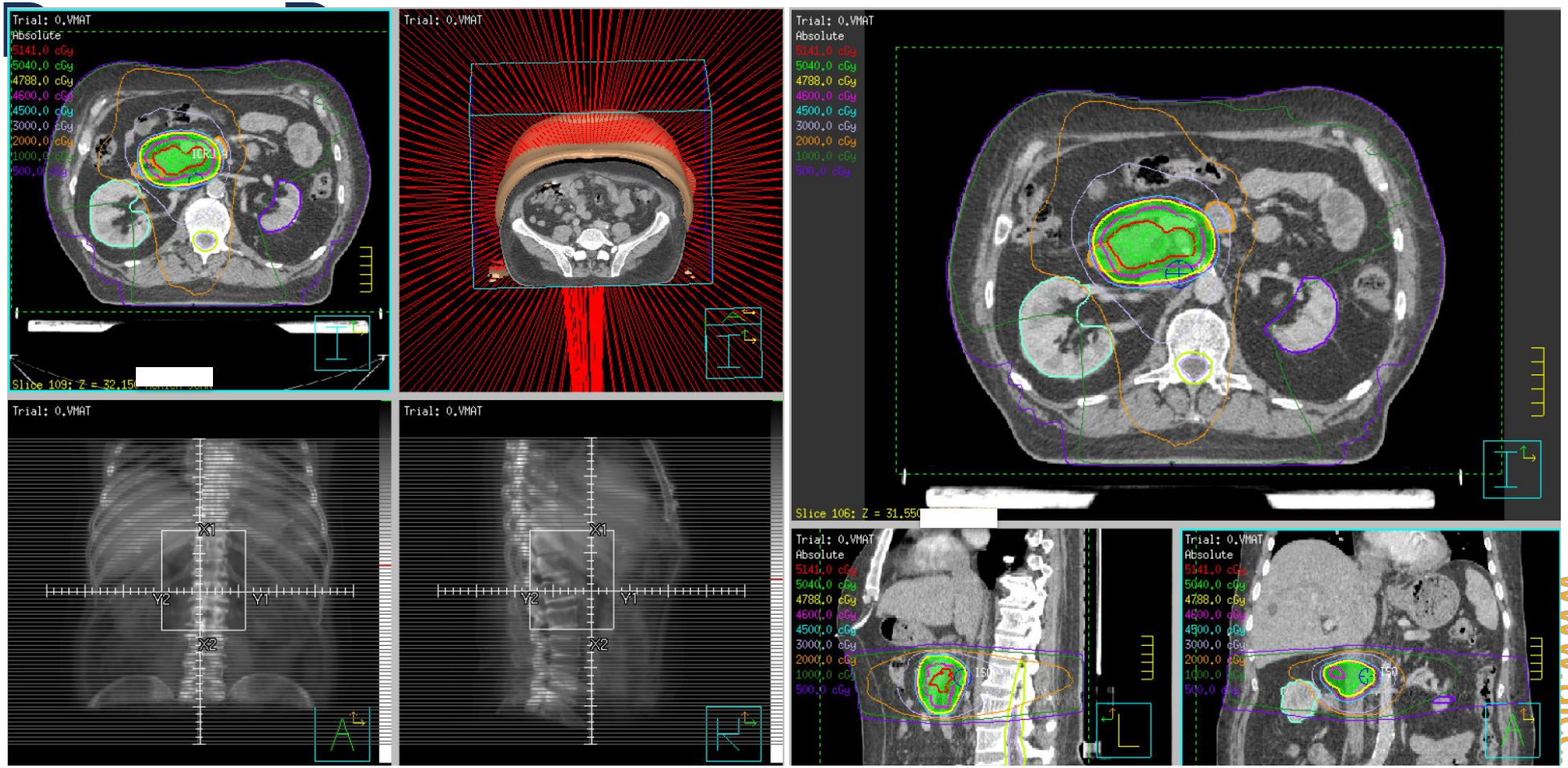


Then 4 cycles of
Folfirinox

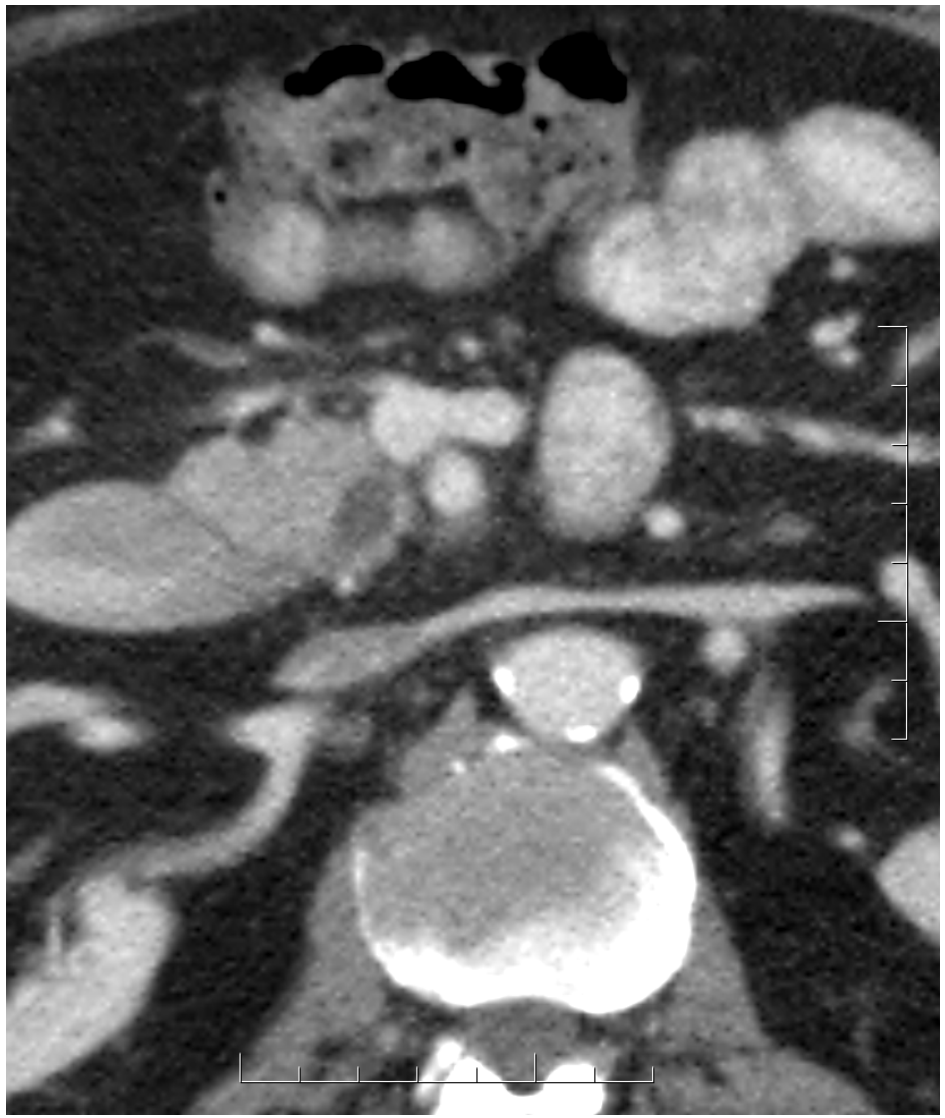
Pre-op Pancreas





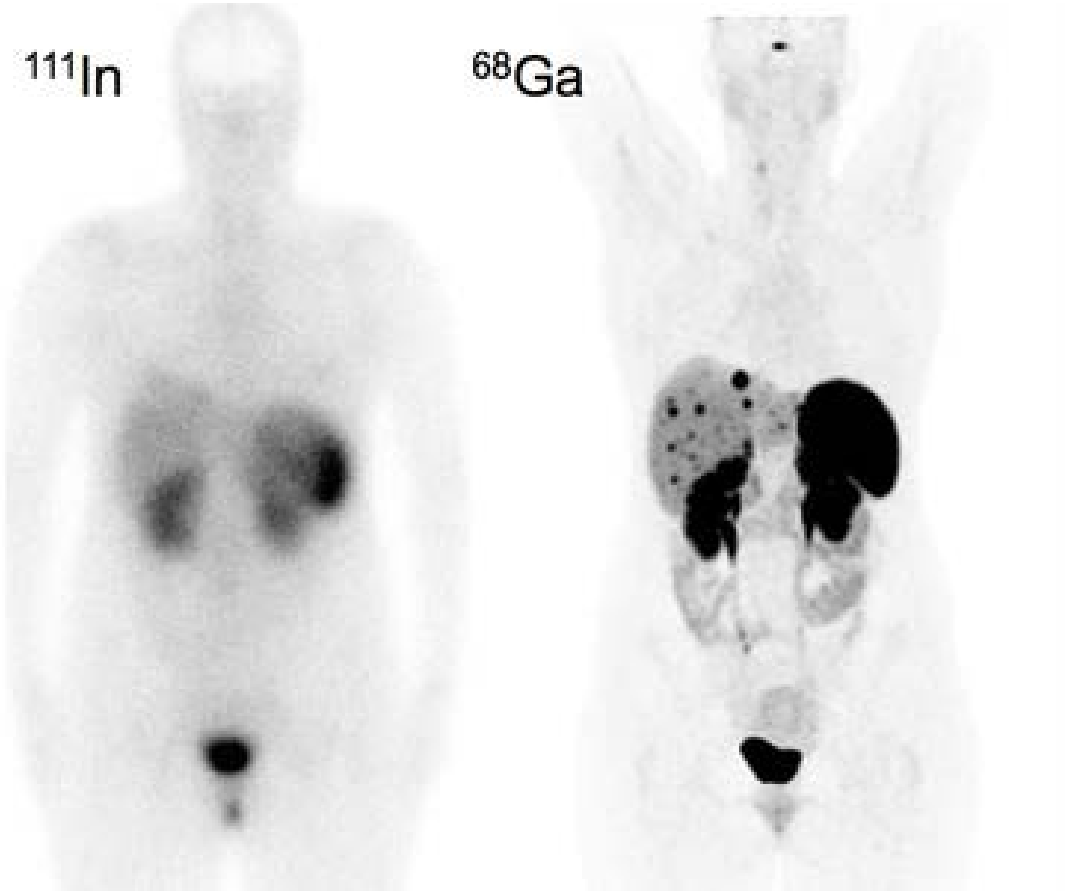


Pre-



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%

Pancreas Neuroendocrine

T1	Tumour 2 cm or less
T2	Tumour more than 2 cm but no more than 4 cm
T3	Tumour more than 4 cm in greatest dimension or invading duodenum or bile duct
T4	Tumour invades visceral peritoneum or other organs
N0	No nodal metastases
N1	Nodal Metastases
M1a	Confined to Liver
M1b	At least one extrahepatic site
M1c	Both hepatic and other

Stage

Stage I	T1	N0	M0
Stage II	T2 T3	N0	M0
Stage III	T4	N0	M0
Stage III	Any T	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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

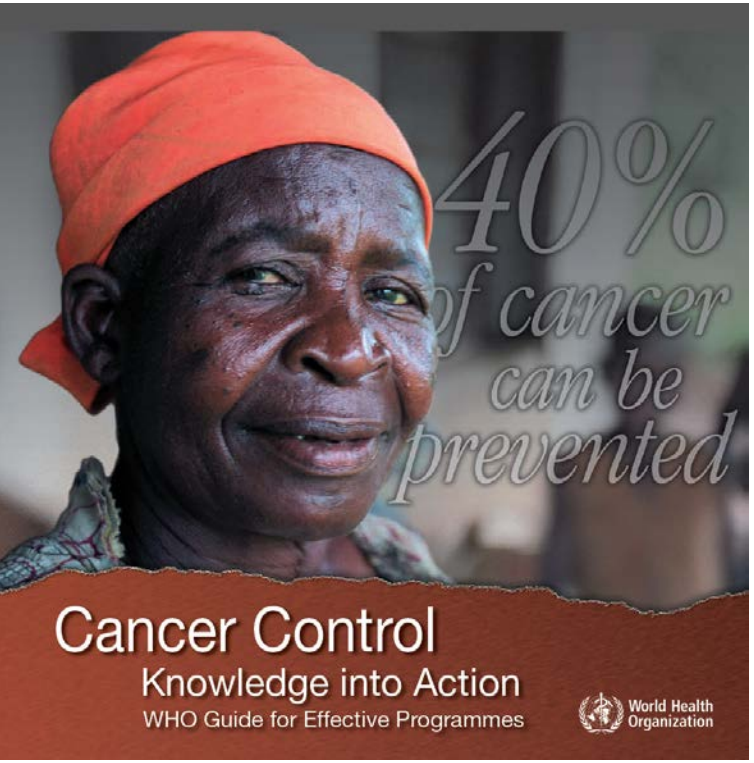
Ampulla of Vater

- Changes in definitions of T1,T2 and T3 categories and N categories
- Changes in Stage

Essential TNM

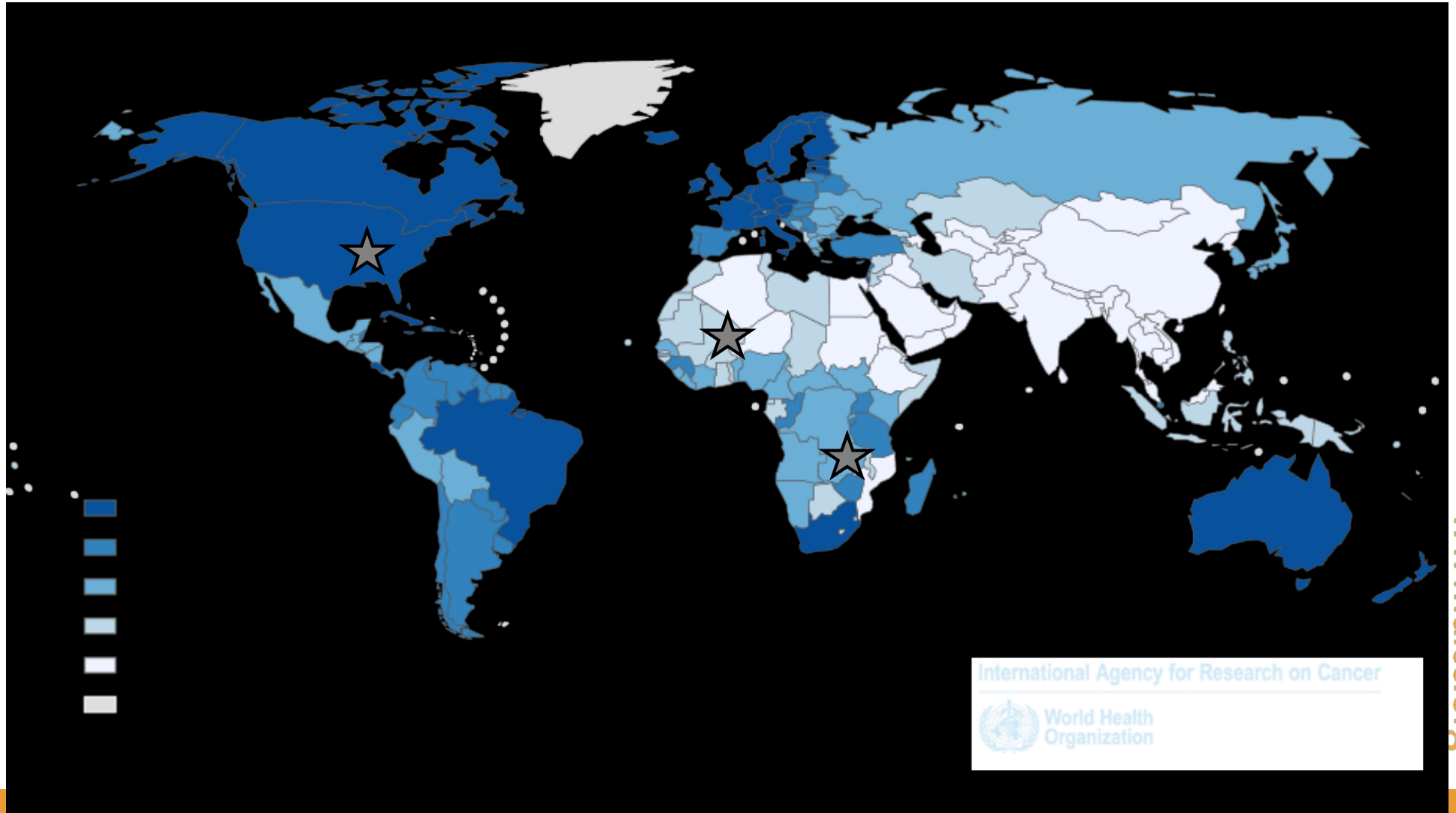
- Information on anatomical extent of disease at presentation is often not available for cancer registries in low and middle income countries either because of inability to perform necessary investigations or because of lack of recording of information.
- The UICC TNM Project has with the International 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

The World Health Organization "Cancer Control Knowledge into Action, Guide for Effective Programs"



- 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

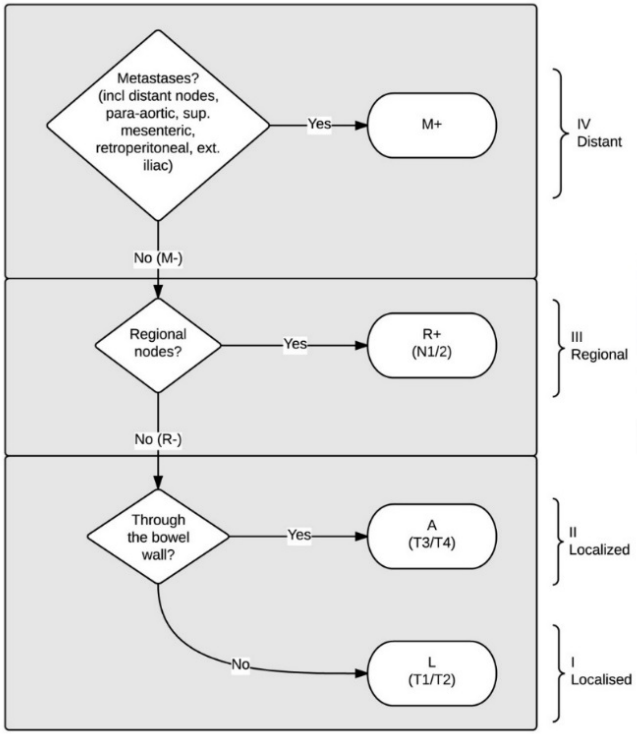
Prostate Cancer Incidence

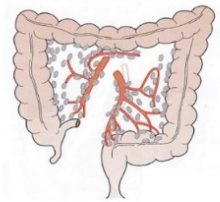


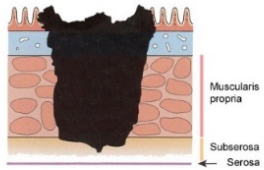
Essential TNM

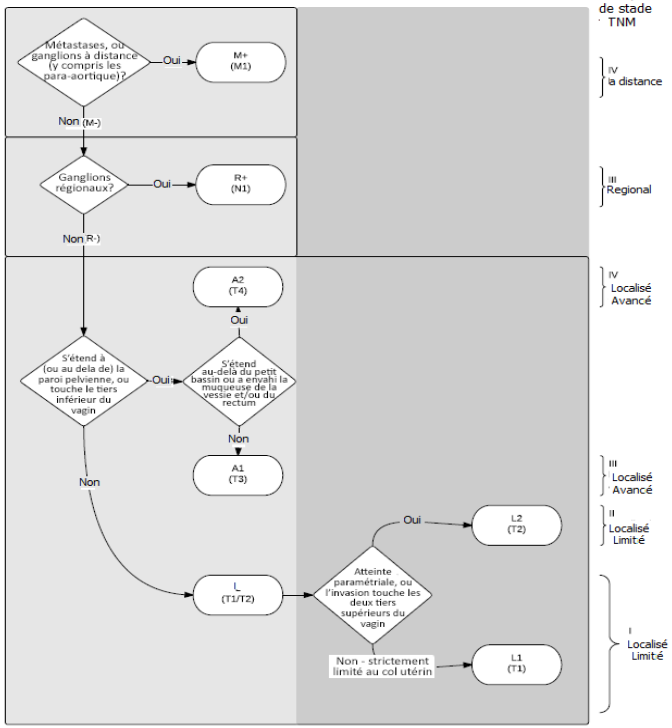
- An example of adaption stage to facilitate collection in LIC and MIC
- Information on anatomical extent of disease is often not available for cancer registries in because of inability to perform necessary investigations or because of lack of recording of information.

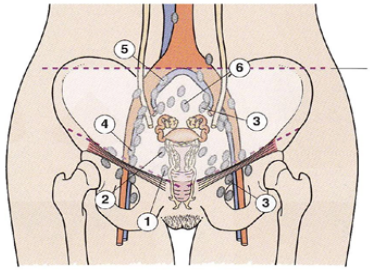
COLON and RECTUM and CERVIX

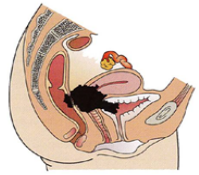




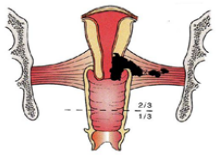




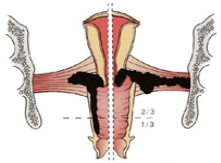




T4: Invasion into rectum and baldder



T2: Parametrial invasion



T3: Invasion to lower 1/3 vagina
Invasion to pelvic side wall

Pieter Bruegel the Elder – The Tower of Babel

Comparability of stage data six countries

- **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.

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

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

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

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

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

- 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)

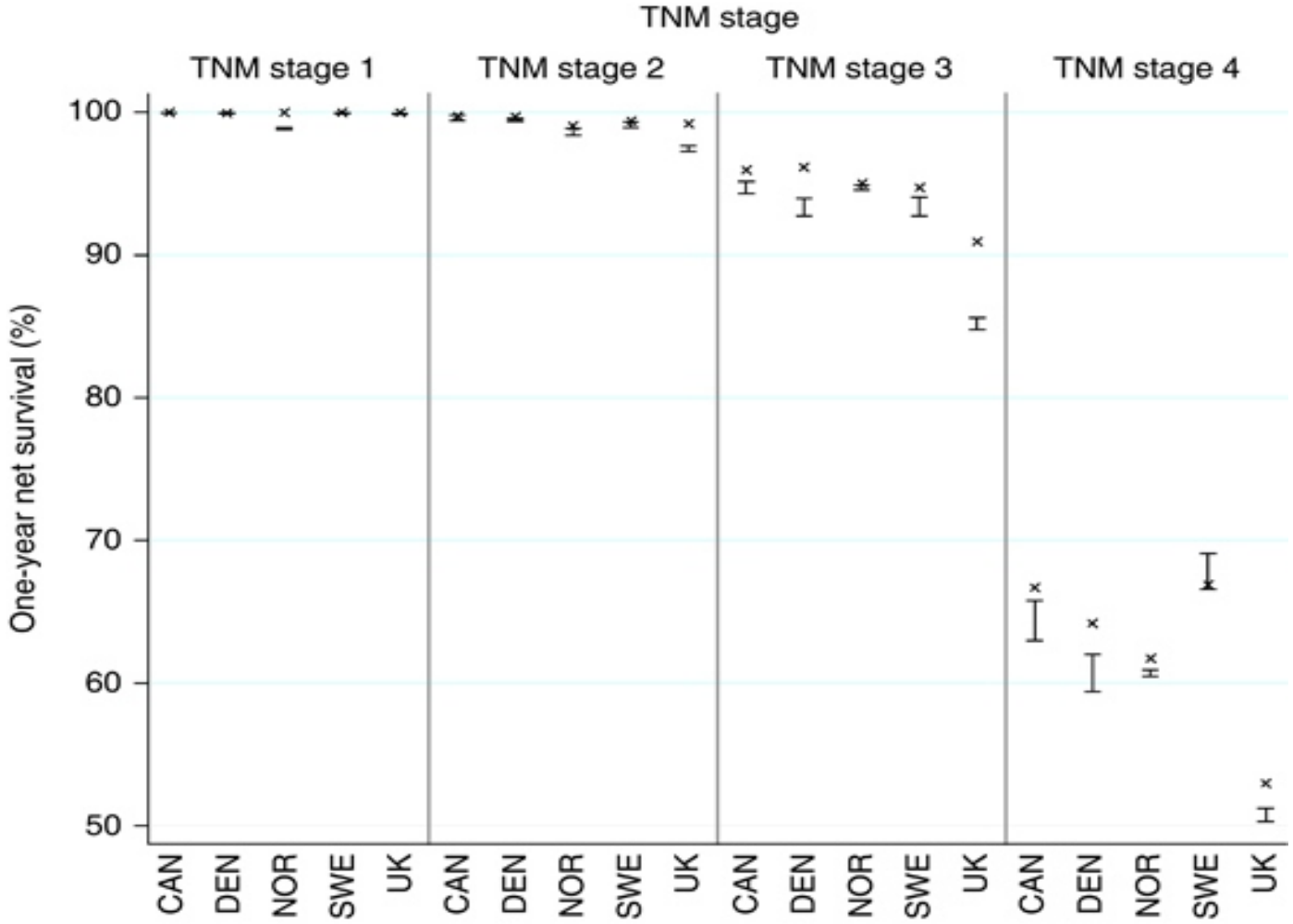
  Other organ site committees use their own staging system

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



S Walters et al *B .J. C.* (2013) **108**, 1195–1208

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

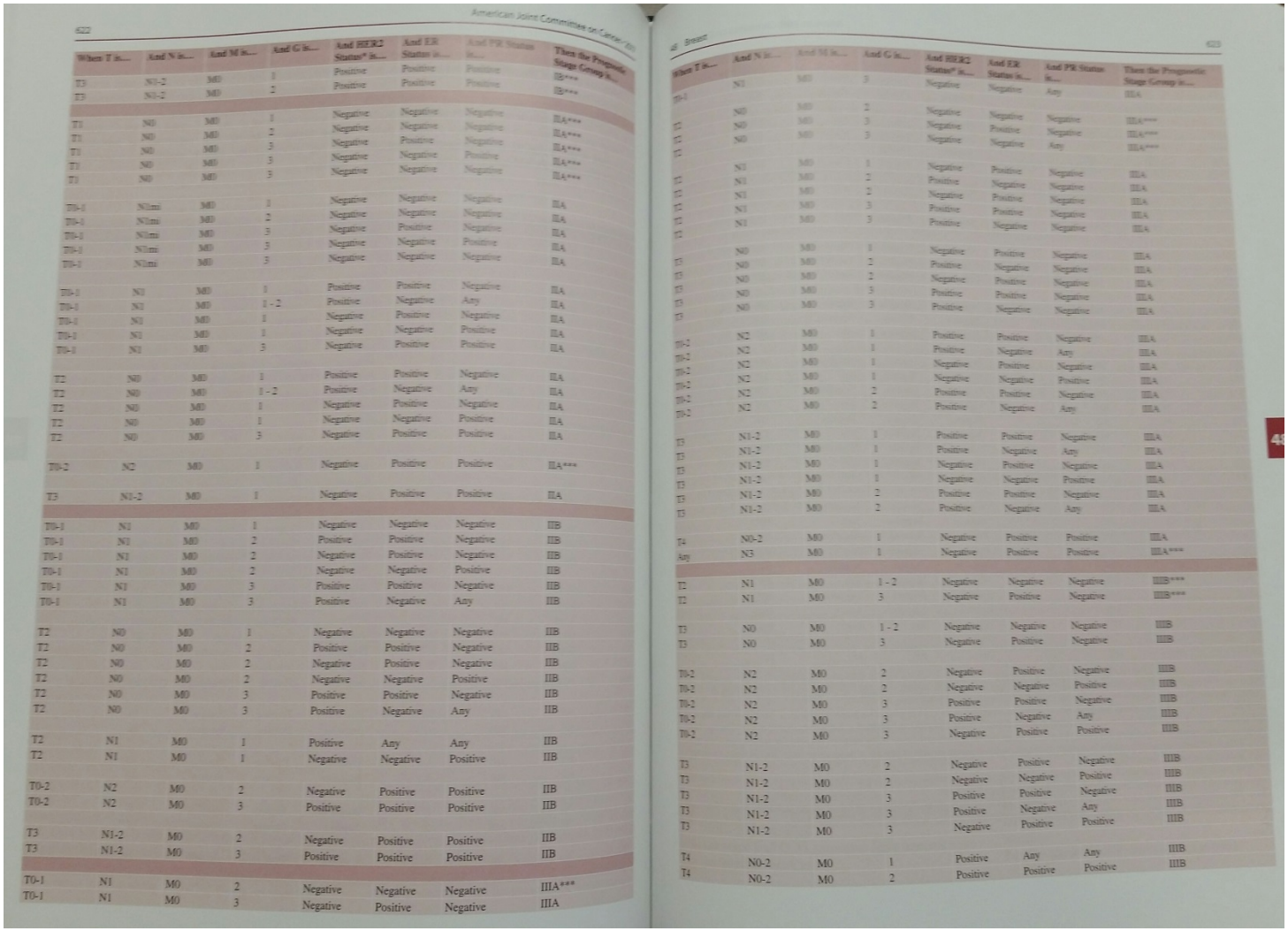
- Stage IIb ER & PR negative, Her2-neu negative
- But in US everyone has early stage cancer
- Markers more important than stage
- Combine TNM with ER, PR, Grade, Her 2 Neu status

Breast- STAGE

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0, T1	N1mi	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0

Stage IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	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

Breast Cancer Risk Prediction | Stage III colon cancer | Adjuvant systemic therapy for melanoma

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: 18 Positive: 3

Tumor Number / Location
Single / Right

Tumor Stage
T3

Treatment Type
5-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. Renfro et al., JNCI 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