TNM Classification, CTCAE, RECIST

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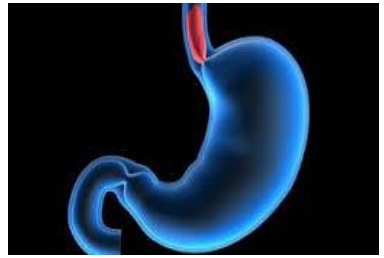
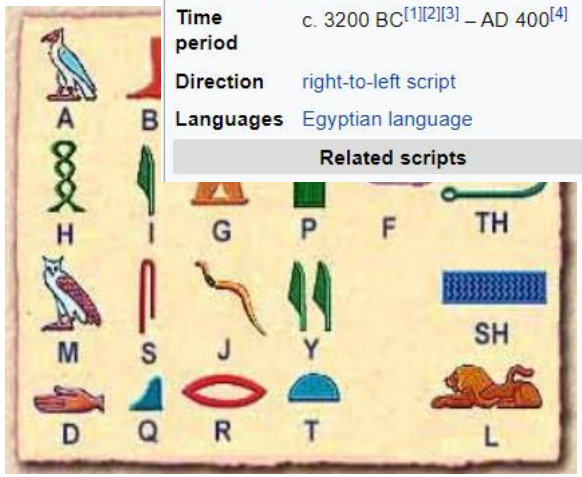
History in the example, why do we need TNM?

- Napoleon Bonaparte died in **1821** at the age of 51
- autopsy performed by Napoleon‘s doctor Francesco Antommarchi
- the reason for his death was gastric cancer



- 7 physicians were invited to confirm and evaluate independently the reason for Napoleon‘s death
- each reached a slightly different conclusion

There is a need to have one mean of communication…



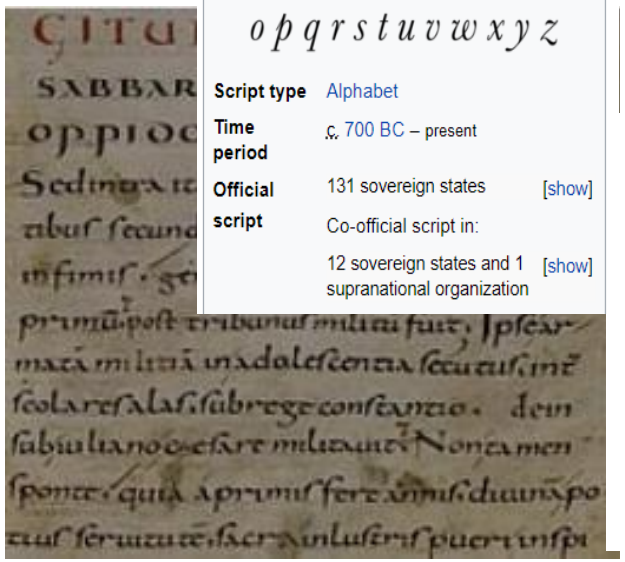
Egyptian hieroglyphs

Hieroglyphs from the tomb of Seti I (KV17), 13th century BC

Script type	Logography usable as an abjad
Time period	c. 3200 BC[1][2][3] – AD 400[4]
Direction	right-to-left script
Languages	Egyptian language

Related scripts

Egyptian hieroglyphs (3200 BC)



Latin

A B C D E F G H I
J K L M N O P Q
R S T U V W X Y Z
a b c d e f g h i j k l m n
o p q r s t u v w x y z

Script type	Alphabet
Time period	c. 700 BC – present
Official script	131 sovereign states [show]
	Co-official script in:
	12 sovereign states and 1 supranational organization [show]

Latin (700 BC)

Korean alphabet
한글 / 조선글
韓孛 / 朝鮮孛
Hangul (Hangeul) / Chosŏn'gŭl

조선글
한글

"Chosŏn'gŭl" (top) and "Hangul" (bottom)

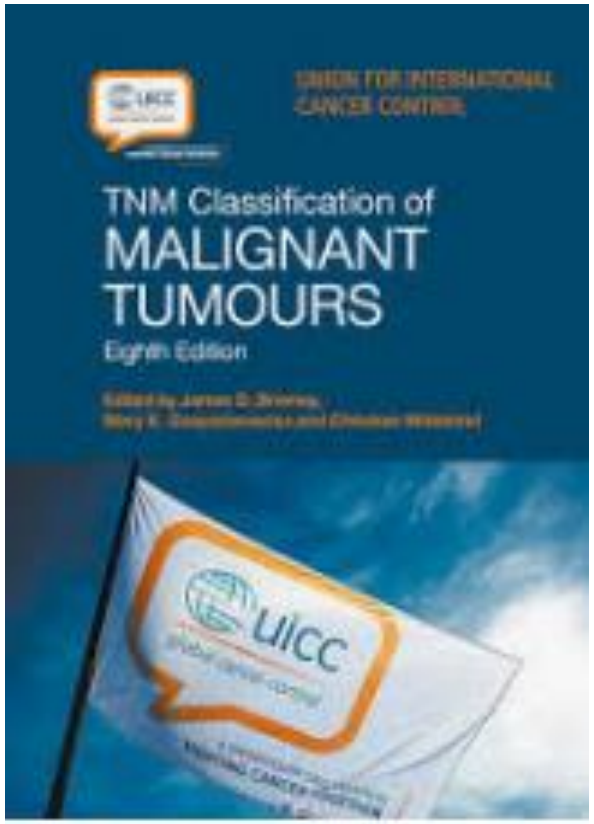
Script type	Featural alphabet
Creator	Sejong of Joseon
Time period	1443–present
Direction	Hangul is usually written horizontally, from left to right and classically from right to left. It is also written vertically, from top to bottom and from right to left.

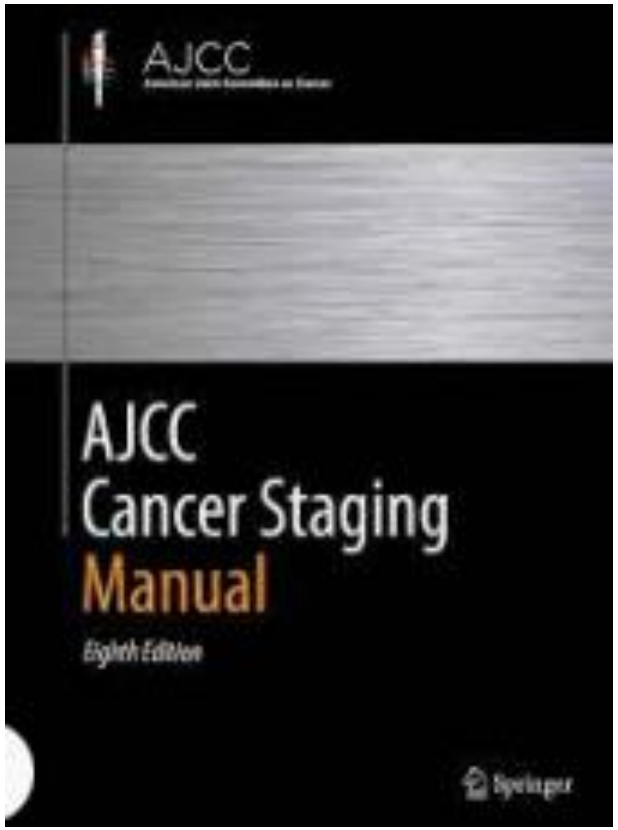
Korean Alphabet (1443)

A ·–	J ·–––	S ···	1 ·————
B –···	K –·–	T –	2 ··———
C –·–·	L ·–··	U ··–	3 ···——
D –··	M ––	V ···–	4 ····—
E ·	N –·	W ·––	5 ·····
F ··–·	O –––	X –··–	6 –····
G ––·	P ·––·	Y –·––	7 ––···
H ····	Q ––·–	Z ––··	8 –––··
I ··	R ·–·	0 –––––	9 ––––·

Morse Code (1830)

TNM Classification: notes from history





- The TNM system for the classification of malignant tumours was developed by Pierre Denoix (France) between 1943 and 1952.
- The International Federation of Gynecology and Obstetrics (FIGO) established the FIGO Classification for Gynecological Malignancies…
- later the American Joint Committee for Cancer (AJCC) published a separate classification in 1987 the UICC and the AJCC TNM classifications were unified

Classification ICD-O

- ICD – International Classification of Diseases

- Codes C00 - C97 Malignant tumours
- Codes D00 - D09 neoplasms in situ
- Codes D10 - D36 benign tumours
- Codes D37 - D48 tumours of unknown or uncertain behaviour

TNM - staging

- assists the clinician in treatment planning
- provides some indication of prognosis
- assists in the evaluation of treatment outcomes
- facilitates the exchange of information among treatment centres
- contributes to ongoing research on human cancer.

TNM and OS in rectal cancer treated with adjuvant chemoradiotherapy

- 5 years Overall (OS) is dependent on TN
  Three risk groups of patients are identified:

- Intermediate: **T1-2/N1**: 78% to 83%, **T3/N0**: 74% to 80%

- Moderately high (**T1-2/N2, T3/N1, T4/N0**):44%- 80%

- High (**T3/N2, T4/N1, T4/N2**): 29% to 57%

Gunderson LL, Journal of Clinical Oncology 2004 22:10, 1785-1796

TNM Basic Rules

- **T** – the extent of the primary tumour
- **N** - absence or presence and extent of regional lymph node metastases
- **M** - absence or presence of distant metastases

Assigning a digit to these three components indicates the extent of the disease:

T0, T1, T2, T3, T4; N0, N1, N2, N3; M0, M1

Once TNM has been established, it no longer changes

TNM Clinical Classification

The following general definitions are used on an ongoing basis:

T - Primary tumour

TX Primary tumour cannot be evaluated

T0 No evidence of primary tumour

Tis carcinoma in situ

T1, T2, T3, T4 increasing size and/or local extent of primary tumour

N - Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 no metastases in regional lymph nodes

N1, N2, N3 increasing the involvement of regional lymph nodes

M

- Distant metastases
- MX distant metastases cannot be evaluated
- M0 not distant metastases
- M1 distant metastases
- The M1 category may be further specified by designation:
- pulmonary PUL (C34) bone marrow MAR (C42.1)
- bone OSS (C40, C41) pleural PLE (C38.4)
- hepatic HEP (C22) peritoneal PER (C48.1,2)
- cerebral BRA (C71) adrenal ADR (C74)
- nodal LYM (C77) cutaneous SKI (C44)
- other OTH

pTNM Pathologic Classification … after surgery

- pT - Primary tumour
- pTX primary tumour cannot be histologically evaluated
- pT0 without histological evidence of primary tumour
- pTis carcinoma in situ
- pT1, pT2, pT3, pT4 increasing size and/or local extent of primary
- tumour histologically
- pN - Regional lymph nodes
- pNX regional lymph nodes cannot be assessed histologically
- pN0 no metastases in regional lymph nodes histologically
- pN1, pN2, pN3 increasing involvement of regional lymph nodes
- pM1 - histologically verified distant metastasis

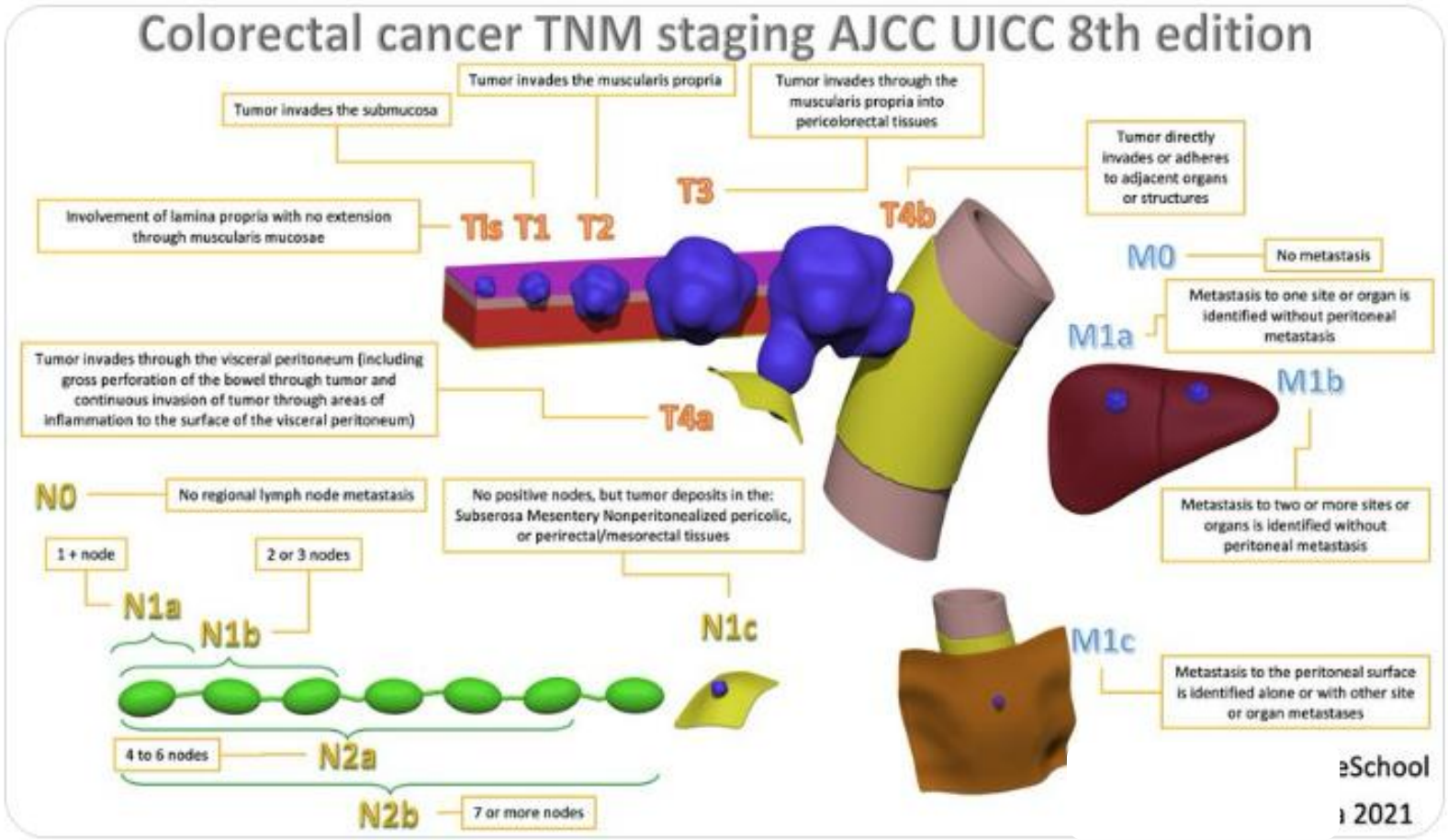
Histopathologic Grading

- G - Histopathological grade of differentiation (grading)
- GX grade of differentiation cannot be assessed
- G1 well differentiated
- G2 moderately differentiated
- G3 poorly differentiated
- G4 undifferentiated

What else can we find in medical records?

- yTNM- after preoperative or neoadjuvant or induction treatment
- ypTNM- after preoperative or neoadjuvant or induction treatment and after surgery
- rTNM- relapse – only moment when we can change TNM
- R0,R1,R2- negative or positive margine

Clinical Stages



Category	Descriptor
T category	
Tx	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1	Submucosa
T2	Muscularis propria
T3	Subserosa and perirectal tissue
a*	<1 mm
b*	1–5 mm
c*	5–15 mm
d*	>15 mm
T4	
a	Tumor penetrates to the surface of the visceral peritoneum
b	Tumor invades or is adherent to other organs or structures
N category	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	
a	1 lymph node
b	2–3 lymph nodes
c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized perirectal tissues
N2	
a	4–6 lymph nodes
b	7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
a	Metastasis confined to one organ or site (eg, liver, lung, nonregional lymph nodes)
b	Metastasis in more than one organ and/or site or in the peritoneum

Glimelius B, **Ann Oncol** 2013;24(suppl 6):vi81–vi88

Clinical Stages

- 0 – IV
- Each stage is more or less homogeneous

with respect to survival

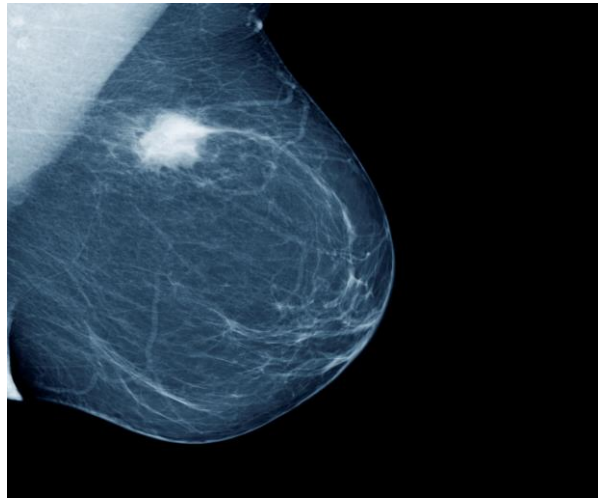
- Different therapies for different stages

0	Tis N0 M0
IA	T1 N0 M0
IB	T2 N0 M0 T1 N1 M0
IIA	T3 N0 M0 T2 N1 M0 T1 N2 M0
IIB	T4a N0 M0 T3 N1 M0 T2 N2 M0 T1 N3 M0
IIIA	T4a N1 M0 T3 N2 M0 T2 N3 M0
IIIB	T4b N0–1 M0 T4a N2 M0 T3 N3 M0
IIIC	T4a N3 M0 T4b N2–3 M0
IV	jakékoli T jakékoli N M1

Gastric Cancer

Case Report: Breast Cancer

- 30-year-old patient diagnosed with breast cancer
- Positive family history
- BRCA1 mutation
- cT2N1M0, clinical stage IIIB
- invasive ductal carcinoma G3, SR negative, HER 2 negative (triple negative), Ki67 93%



Treatment

- Neoadjuvant chemotherapy- **yT0yN0**
- Bilateral mastectomy and tailored axillary surgery– **ypTypN0**
- **- effect of neoadjuvant therapy: pathologic complete response (pCR)**
- Reconstruction with implants
- Adjuvant radiotherapy
- Follow-up

WHO and RECIST assessment of tumour response

Development of treatment response assessment

1960 Zubrod :

"Treatment is considered effective if there is a reduction in the total measured mass of the tumour, provided that there is no progression of any of the individual lesions and no new lesion appears at the same time".

Zubrod CG, Schneiderman M, Frei E III, et al. : Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylen thiophosphoramide. J Chron Dis,1960, 11: 7-33

WHO criteria

- 1977-1979 Consensus in the evaluation of response to treatment and the evaluation of adverse effects of treatment

- Based on two-dimensional measurements of tumour: longest axis and perpendicular dimension
- Precise and time-consuming measurements

WHO criteria

Lesion = metastasis, unambiguous tumour image

Measurable lesions

Measurement in 2 perpendicular dimensions, dimensions must be at least 20mm in one dimension and 10mm in the other dimension

Non-measurable lesions = All other smaller lesions

Evaluable lesions (evaluable)

Ascites, fluidothorax, peritoneal seeding

WHO criteria of disease response

- Complete remission (CR)

- Clearance of all lesions

- Partial remission (PR)

- ≤ 50% compared to the initial examination

- Stabilization (SD/non-PD)

- Failure to meet criteria for CR, PR, PD

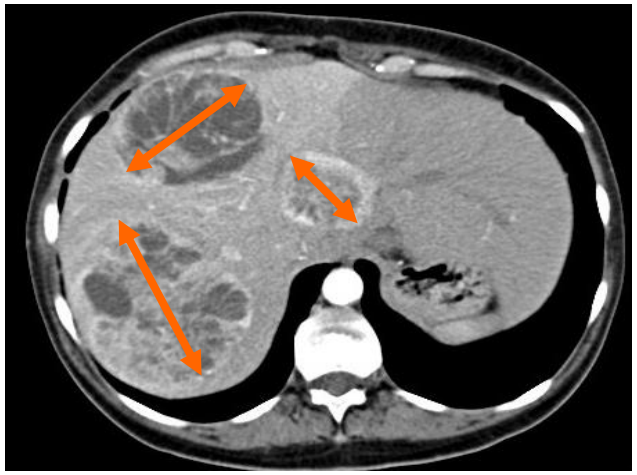
- Progression (PD)

- > 25% compared to the initial examination

RECIST criteria

In the late 1990s, a number of cooperative groups proposed to modify the criteria for measuring cancer - to simplify it.

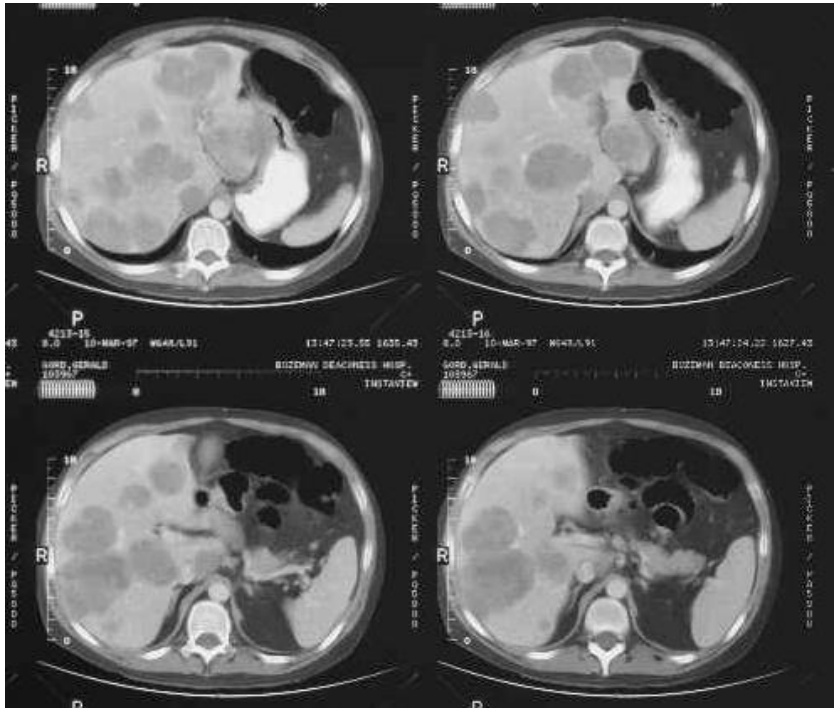
- Response Evaluation Criteria In Solid Tumors
- Clearer than other criteria
- Maintain the basic definition of complete remission, partial remission, stabilization and disease progression.
- Unidimensional measurement.



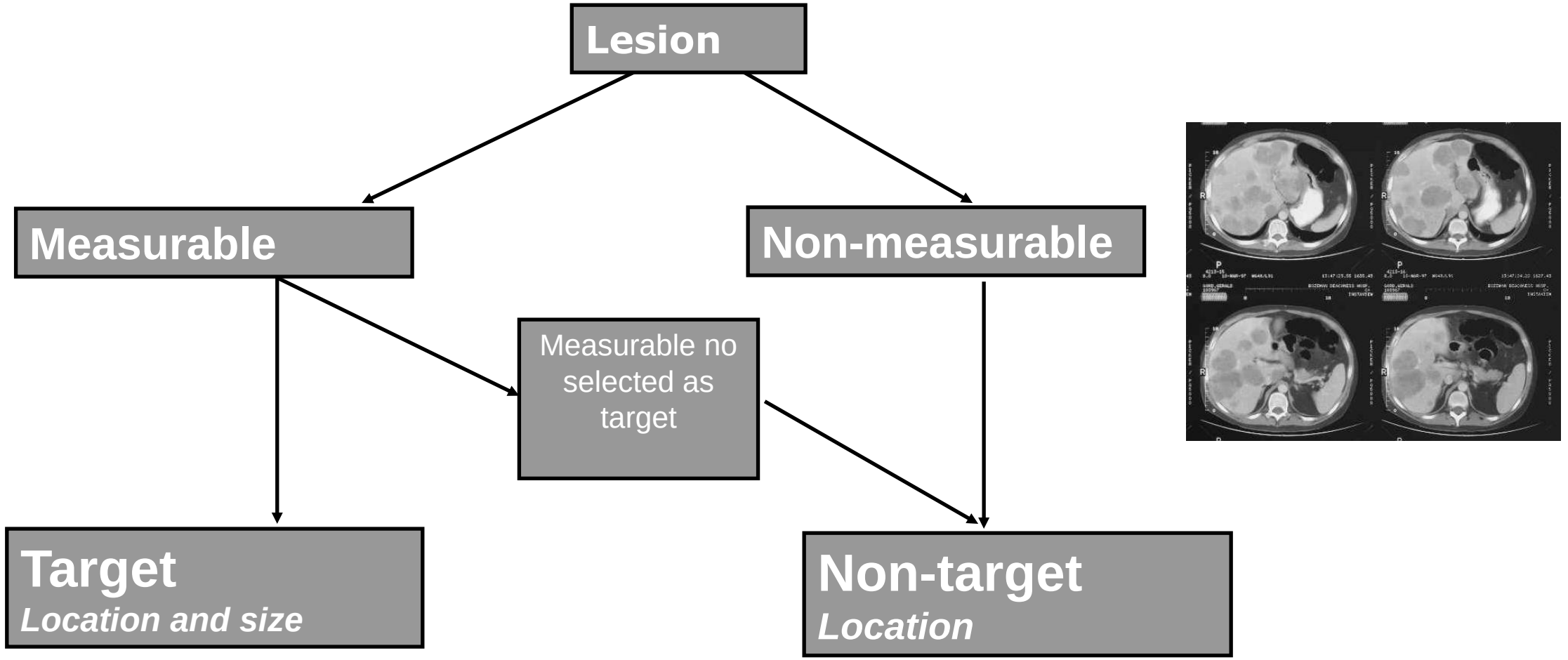
Therasse, P. et al.
New guidelines to evaluate the response to treatment in solid tumors.
J Natl Cancer Inst 2000;92:205-216

RECIST criteria

- Target Lesions
- All measurable lesions up to a maximum of 5 lesions per organ
- 10 lesions total in the body
- Accurately measurable in one dimension
- ≥1.0 cm on spiral CT
- RECIST is evaluated by **RADIOLOGIST**



RECIST, RECIST 1.1 from 2009



Target Lesions: **All measurable lesions up to a maximum of 5 lesions per organ, 10 lesions total in the body**

RECIST criteria for disease response

- Complete remission (CR)

- Clearance of all lesions

- Partial remission (PR)

- ≥30% reduction of the sum of the maximum dimensions of the target lesions compared to the initial examination

- Stabilization (SD/non-PD)

- Failure to meet criteria for CR, PR, PD

- Progression (PD)

- > 20% compared to the initial examination, progression of a non-target lesion

Any new lesion

PR and CR must be verified by a new scan in ≥4 weeks.

Terminology: treatment response

- **Overall Survival time** - expressed by survival curves

- **Disease-free survival** – symptom-free period

= interval from the time of reaching CR to the first signs of relapse

-
- **Progression-free survival**

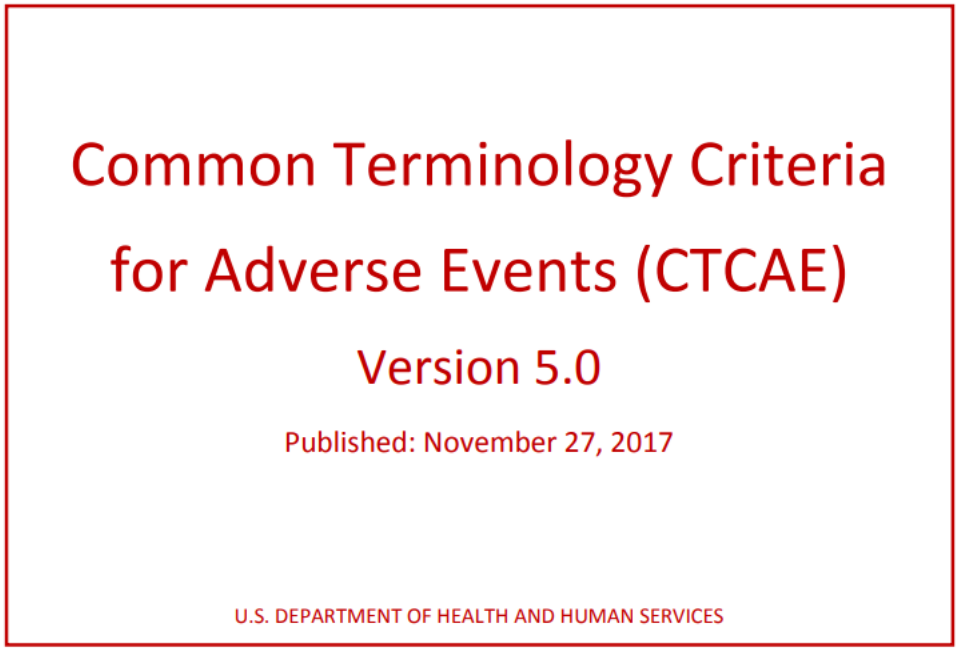
= from initiation of treatment to signs of progression

- Common Terminology Criteria for Adverse Events (CTCAE)
- Quality of life assessment (QoL- EORTC questionnaires, PRO)

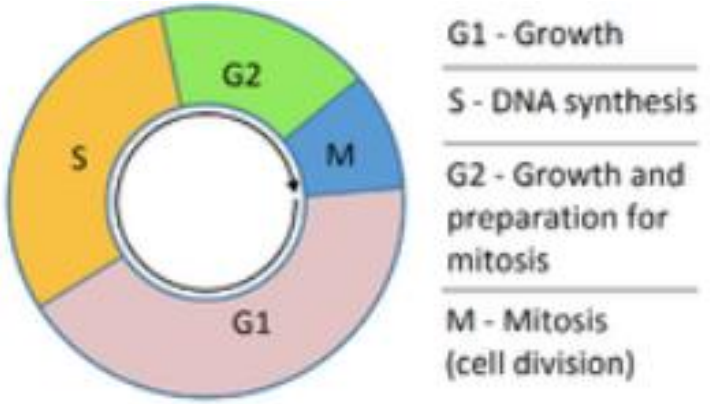
Common Terminology Criteria for Adverse Events (CTCAE)

- Version 5.0, fall 2022 version 6.0 is expected

= list all side effects of cancer treatment



Principles of cytotoxic treatment



- The goal: To eliminate all cancer population

- Problems: heterogeneous population in different period of the cell cycle at the time of chemo application

  non-selective effect (also on healthy tissues, organs…)

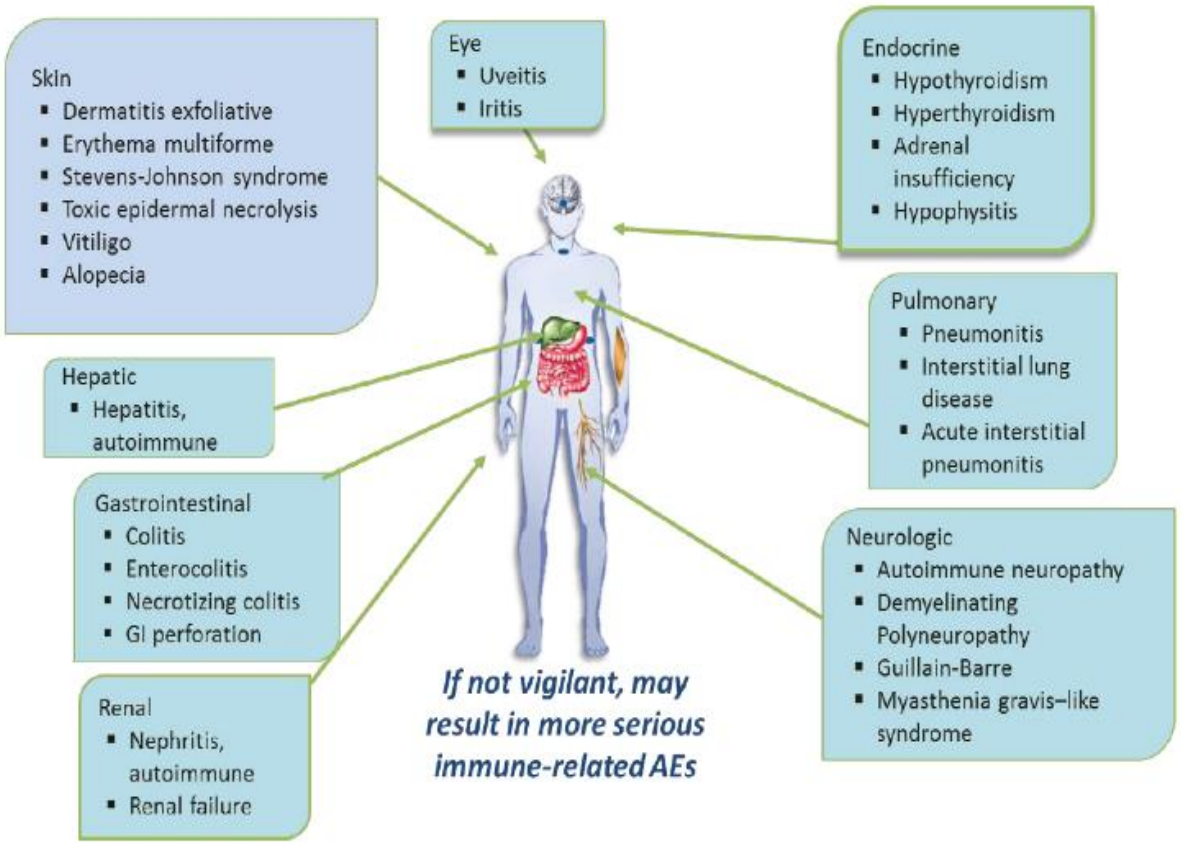
- What can we do?

  Waiting for resolving and being aware of the type side effects and its length

CTCAE- blood and lymphatic system disorders

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements. **Navigational Note:** -					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. **Navigational Note:** -					
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. **Navigational Note:** -					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction. **Navigational Note:** -					

Immunotherapy RECIST and IO side effects



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Lancet Oncol. 2017 March ; 18(3): e143–e152. doi:10.1016/S1470-2045(17)30074-8.

iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

Prof Lesley Seymour, MD,
Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada

https://primarycarenotebook.com/simplepage.cfm?ID=x20191201180561935 87

Summary

Staging

- cTNM evaluated by a clinician
- yTNM evaluated by a radiologist
- ypTNM or pTNM evaluated by a pathologist

Response evaluation

- RECIST evaluated by radiologists
- RECIST 1.1 included also PET…
- iRECIST

Side effects

- CTCAE- evaluated by a clinician

Thank you for your attention.

MUNI