Common cancer & Oncologic emergency for medical residents

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  - Breast
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  - SVC syndrome
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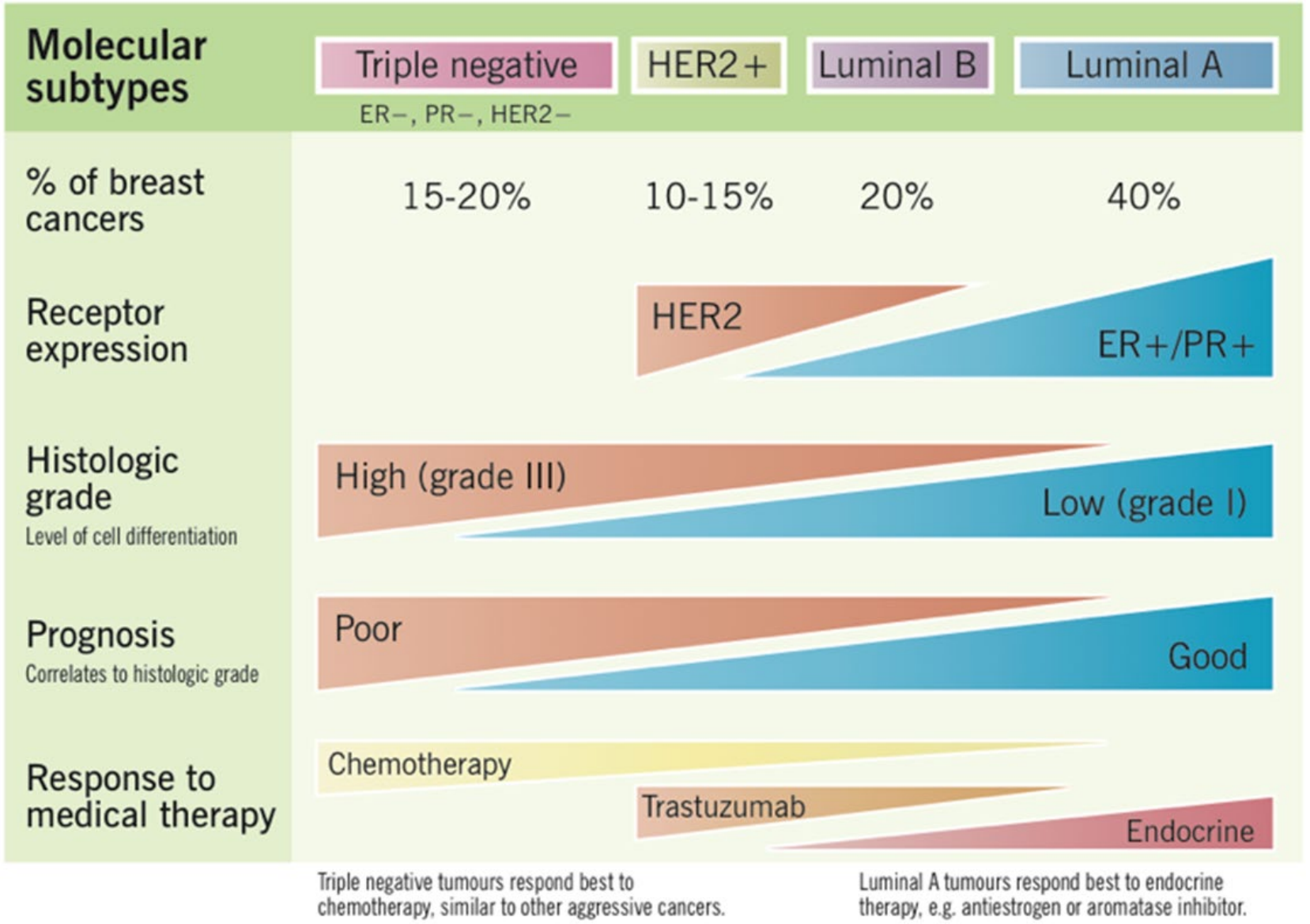
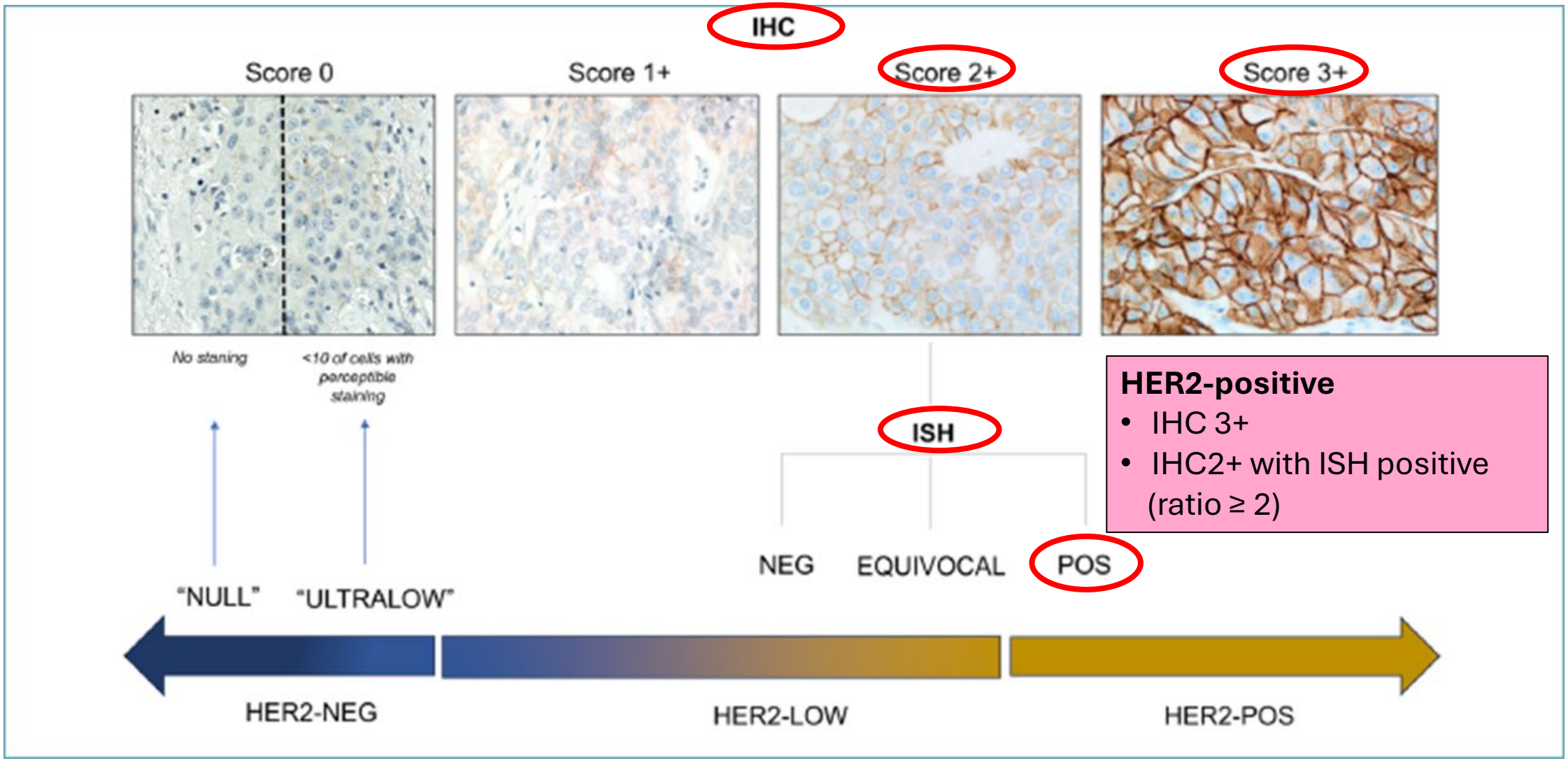
Breast Cancer

Breast cancer: Molecular subtypes



Definition of HER2-positive

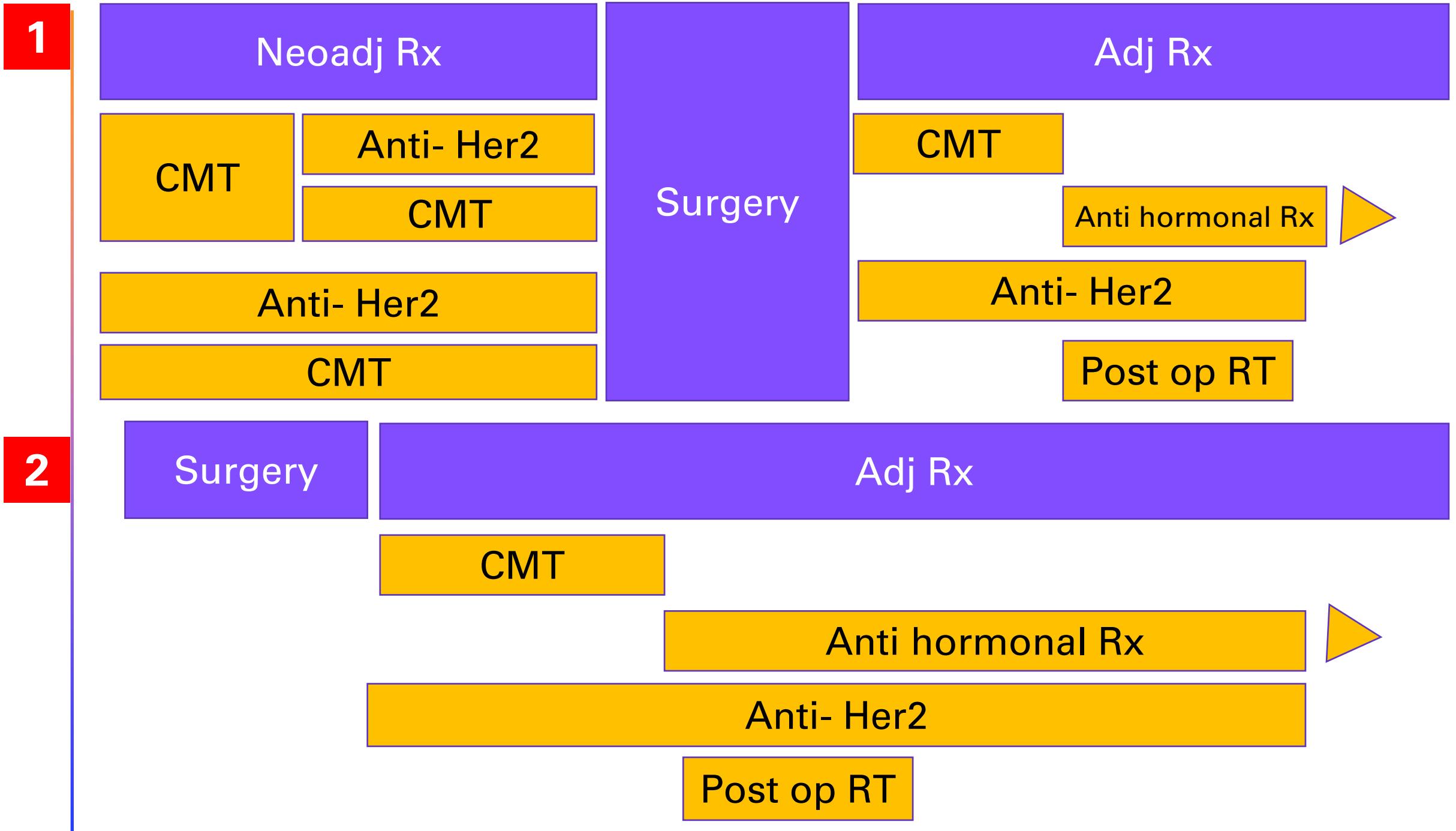


HER2-positive

- IHC 3+
- IHC2+ with ISH positive (ratio ≥ 2)

Marchiò C, et al. Pathologica. 2023 Dec;115(6):292-301.

NON-METASTASIS BREAST CANCER MANAGEMENT


1
Neoadj Rx
Adj Rx
CMT
Anti- Her2
CMT
Surgery
CMT
Anti hormonal Rx
Anti- Her2
CMT
Anti- Her2
Post op RT
2
Surgery
Adj Rx
CMT
Anti hormonal Rx
Anti- Her2
Post op RT

Candidates for neoadjuvant treatment

Candidates for Preoperative Systemic Therapy

- **Patients with inoperable breast cancer:**
  - **IBC**
  - **Bulky or matted cN2 axillary nodes**
  - **cN3 nodal disease**
  - **cT4 tumors**

→ Locally advanced stage

- **In patients with operable breast cancer, preoperative systemic therapy is preferred for:**
  - ◊ **HER2-positive disease and TNBC, if cT ≥2 or cN ≥1**
  - ◊ **Large primary tumor relative to breast size in a patient who desires breast conservation**
  - ◊ **cN+ disease likely to become cN0 with preoperative systemic therapy**
- **Patients in whom definitive surgery may be delayed.**

Breast cancer staging: AJCC 8th edition

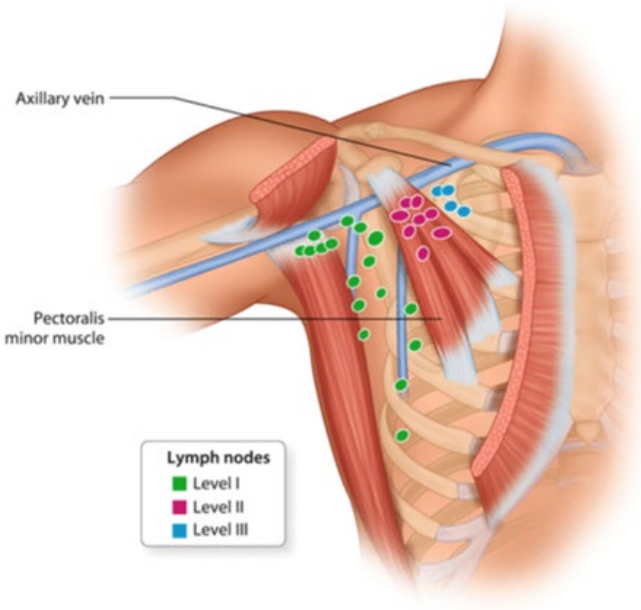
Table 1. **Definitions for T, N, M**

TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis (DCIS)*		Ductal carcinoma *in situ*
Tis (Paget)		Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1		Tumor ≤20 mm in greatest dimension
	T1mi	Tumor ≤1 mm in greatest dimension
	T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm)
	T1b	Tumor >5 mm but ≤10 mm in greatest dimension
	T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2		Tumor >20 mm but ≤50 mm in greatest dimension
T3		Tumor >50 mm in greatest dimension
T4		Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
	T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
	T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
	T4c	Both T4a and T4b are present
	T4d	Inflammatory carcinoma

*Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

[a] IBC is characterized by:
1) Rapid onset (≤6 months) of erythema, edema, p'eau d'orange occupying ≥1/3 of the breast, with or without a palpable mass.
2) Pathologic confirmation of invasive breast cancer.
3) Dermal lymphatic involvement may be seen but is not required for the diagnosis.

Breast cancer staging: AJCC 8th edition



Clinical (cN): location and characters (movable/fixed)

- Axillary LN
- Internal mammary LN (at least N2)
- SPC LN (N3)

Table 1. **Definitions for T, N, M (continued)**

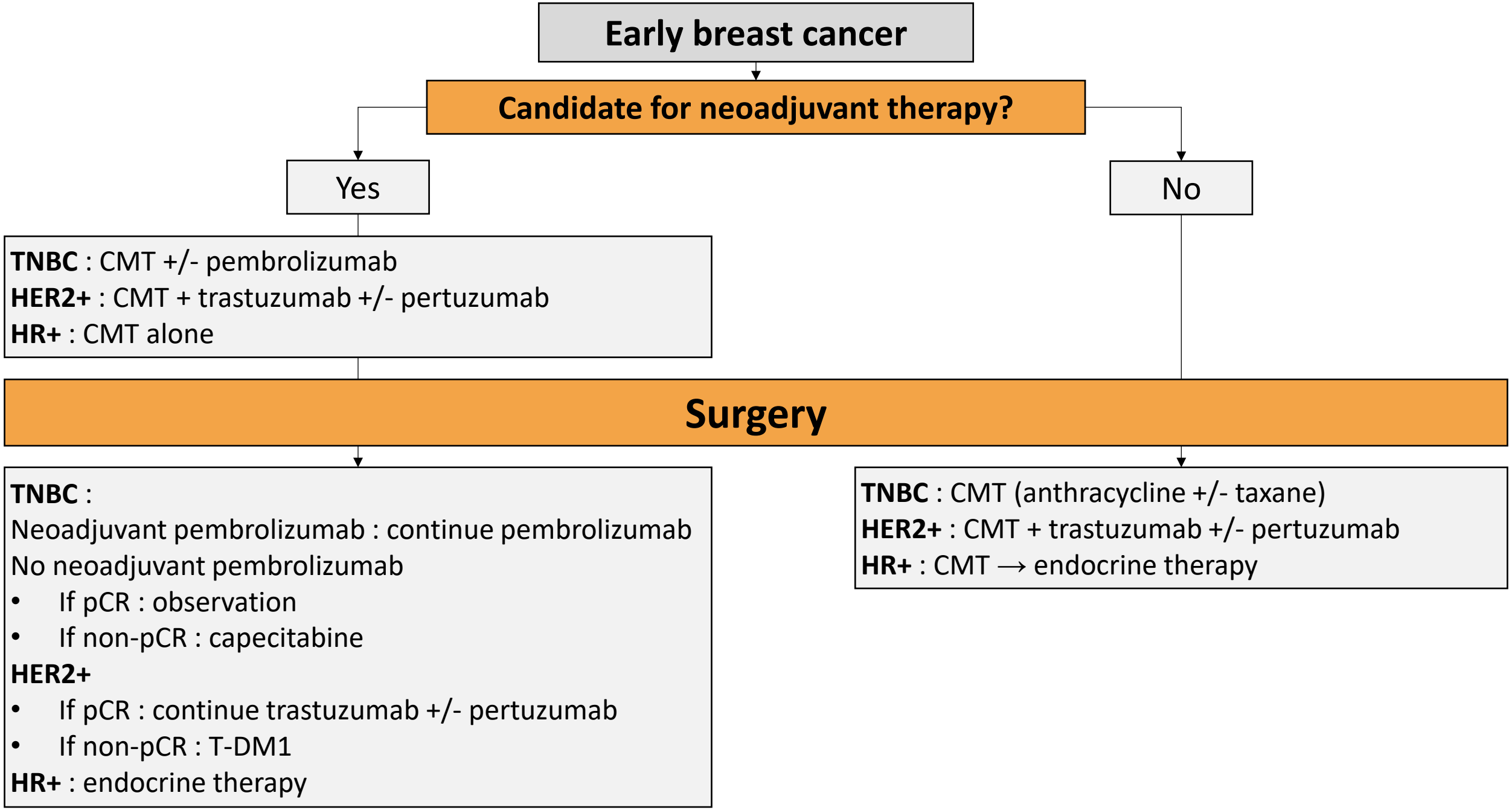
Regional Lymph Nodes (N)

Clinical (cN)	
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; *or* metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Number of +LN

Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cells clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined.
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes


Early breast cancer
Candidate for neoadjuvant therapy?
Yes
No
TNBC : CMT +/- pembrolizumab
HER2+ : CMT + trastuzumab +/- pertuzumab
HR+ : CMT alone
Surgery
TNBC :
Neoadjuvant pembrolizumab : continue pembrolizumab
No neoadjuvant pembrolizumab
• If pCR : observation
• If non-pCR : capecitabine
HER2+
• If pCR : continue trastuzumab +/- pertuzumab
• If non-pCR : T-DM1
HR+ : endocrine therapy
TNBC : CMT (anthracycline +/- taxane)
HER2+ : CMT + trastuzumab +/- pertuzumab
HR+ : CMT → endocrine therapy

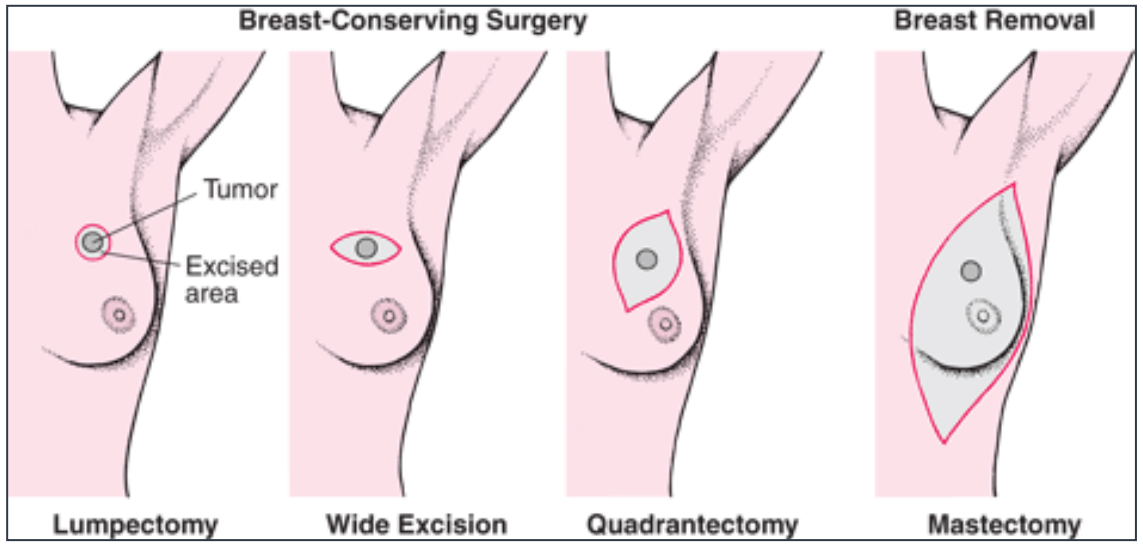
Breast Cancer : Surgery

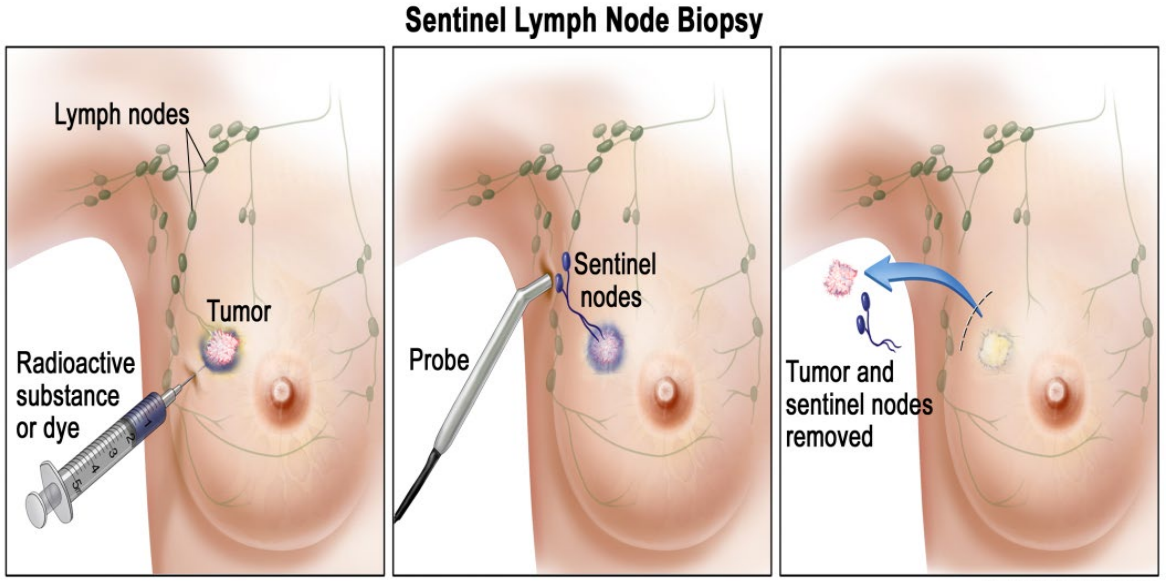
Primary breast tumor management

- Mastectomy
- Breast conserving surgery: WE/lumpectomy + post-op RT

LN management

- Axillary LN dissection
- Sentinel LN biopsy (clinical node-neg)





Adjuvant systemic therapy after preoperative systemic therapy

HER2-POSITIVE DISEASE (ypCR = no residual invasive carcinoma = ypT0/TisN0)

- Complete Trastuzumab +/- pertuzumab 1 yr/ Endocrine therapy if HR+

HER2-POSITIVE DISEASE (non-ypCR)

- Ado-trastuzumab emtansine (T-DM1) for 14 cycles / Endocrine therapy if HR+

HR-POSITIVE – HER2-NEGATIVE

- Endocrine therapy +/- CDK4/6 inhibitor (in high risk LN+)

*high-risk: 1) ≥4 AXLNs, 2) 1-3 AXLNs with tumor size ≥5 cm or grade 3

HR-NEGATIVE – HER2-NEGATIVE (ypCR)

- Continue Pembrolizumab until 1 yr (if received pembro pre-op)
- No further CMT (if no Pembro pre-op)

HR-NEGATIVE – HER2-NEGATIVE (non ypCR)

- Capecitabine

+/- adjuvant olaparib if germline *BRCA1/2 (HR+ or TNBC) with residual disease*

Adjuvant therapy
without preoperative systemic disease

HER2-POSITIVE HR-POSITIVE DISEASE

- Adj CMT/ Trastuzumab +/- pertuzumab (pN+)/ Endocrine therapy

HER2-POSITIVE - HR-NEGATIVE

- Adj CMT/ Trastuzumab +/- pertuzumab (pN+)

HR-POSITIVE – HER2-NEGATIVE

- Adj CMT (T >= 0.5 cm/N+)
- Endocrine therapy +/- CDK4/6 inhibitor (in high-risk LN+)

*high-risk: 1) ≥4 AXLNs, 2) 1-3 AXLNs with tumor size ≥5 cm or grade 3

HR-NEGATIVE – HER2-NEGATIVE

- Adj CMT alone

Adjuvant Endocrine Treatment in EBC

Treatment options

Premenopausal women

- Tamoxifen 5-10 y +/- GnRH blockade
- GnRH blockade + AI

Postmenopausal women

- Tamoxifen 5-10 y
- AI (aromatase inhibitor) alone 5-10 yr
- Sequential/switching
  - AI→Tam total 5-10y
  - Tam→AI total 5-10y

Menopause -> Definition By NCCN [2015v2]

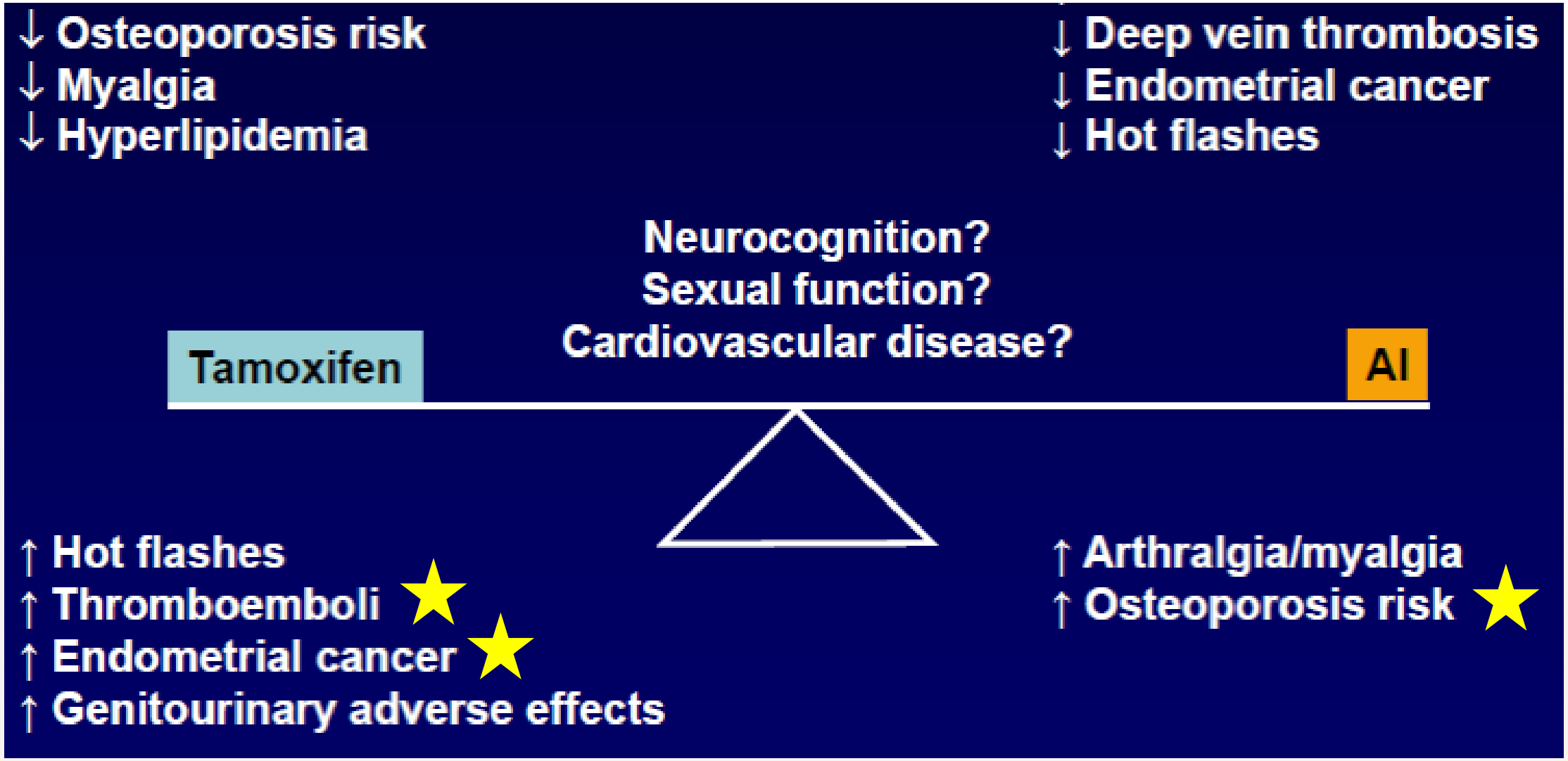
- Age ≥60 years
- Age < 60 years postmenopausal with

•underwent a bilateral oophorectomy.

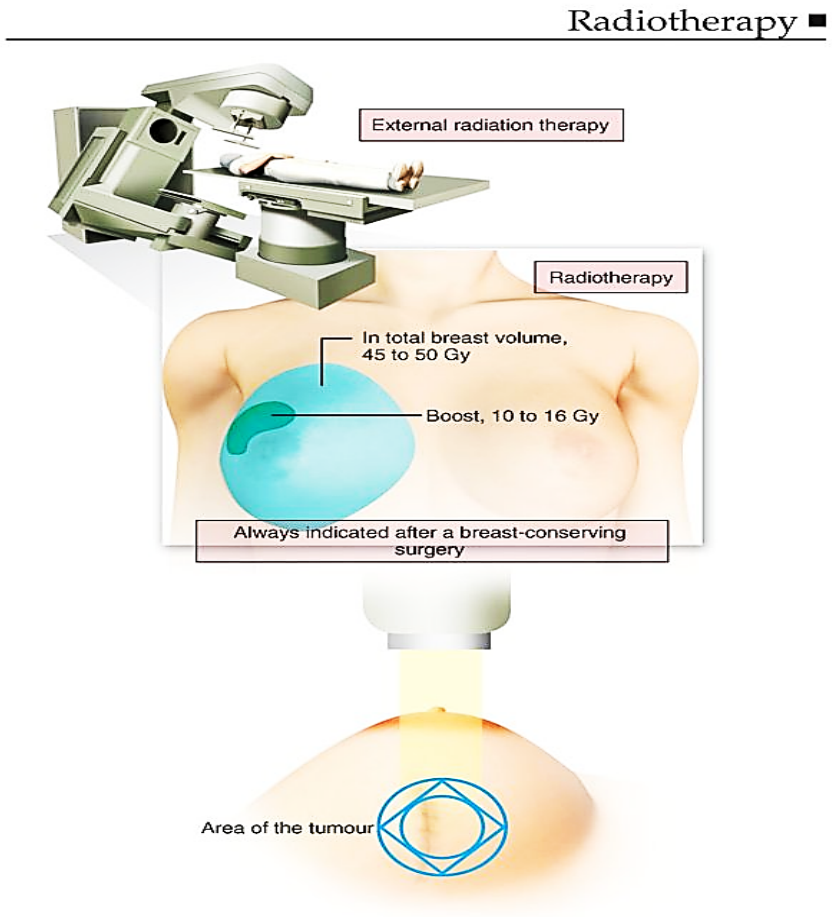
•not had any menstrual periods for ≥12 months in the absence of tamoxifen, chemotherapy or ovarian suppression

•FSH (increase) and plasma estradiol (decrease) level in menopausal range

Side effects of endocrine treatment



Breast Cancer : Radiotherapy

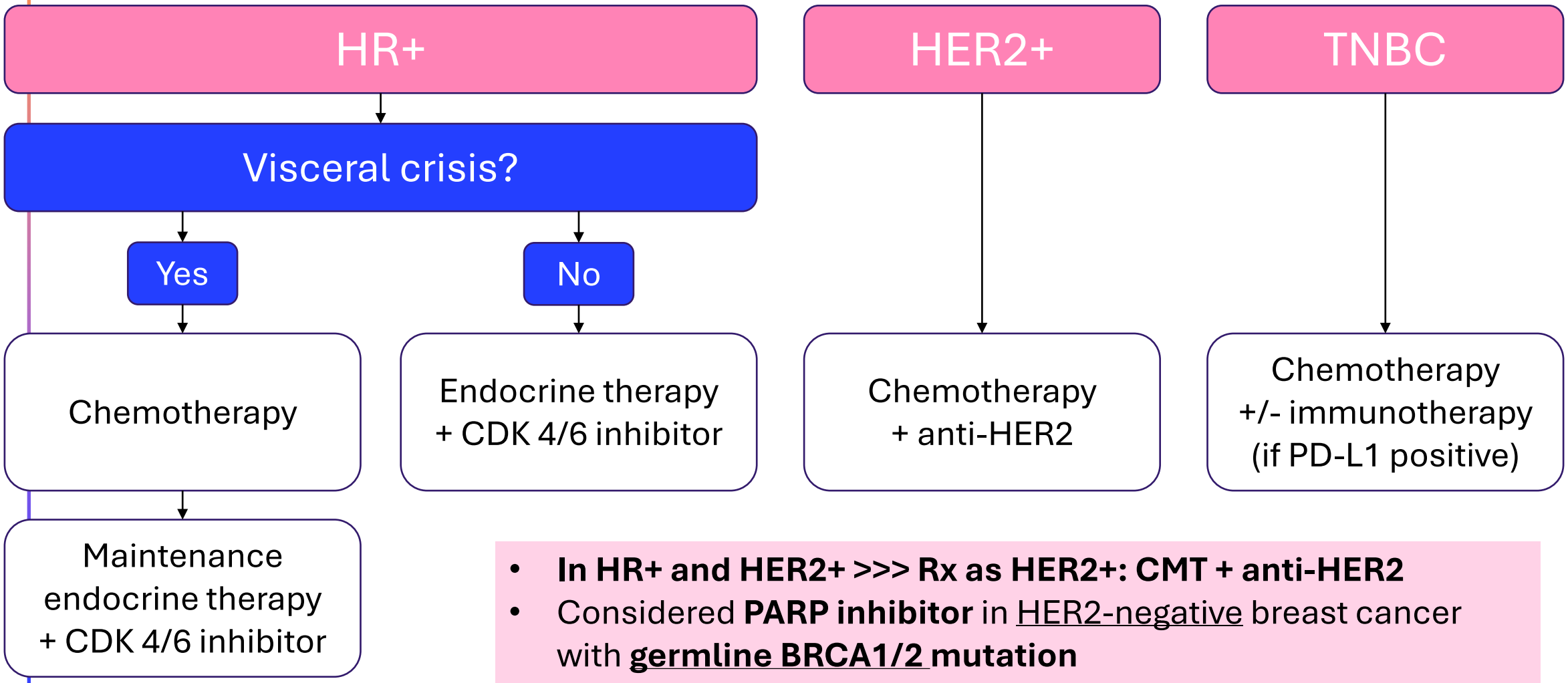


Indication

- **Breast conserving Surgery (All)**
- Tumor > 5 cms
- Node positive (absolute indication in LN +ve more than 4 nodes)
- Margin positive

METASTASIS
BREAST CANCER MANAGEMENT

Metastatic breast cancer



- **In HR+ and HER2+ >>> Rx as HER2+: CMT + anti-HER2**
- Considered **PARP inhibitor** in HER2-negative breast cancer with **germline BRCA1/2 mutation**

Definition of visceral crisis in HR+/HER2- mBC

- **Visceral crisis** is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.
- For example:
  - Lymphangitis carcinomatosis
  - Bone marrow metastasis with BM failure
  - Extensive liver metastasis with liver dysfunction

Endocrine therapy in HR+ mBC

❑ **Pre-menopause**

✓Convert to menopause by ovarian function suppression (OFS) then AI +/- CDK4/6 inhibitor

- Medical OFS: GnRH agonist
- Surgical OFS: bilateral oophorectomy

- In case that can’t do OFS >>> Tamoxifen

❑ **Post-menopause**

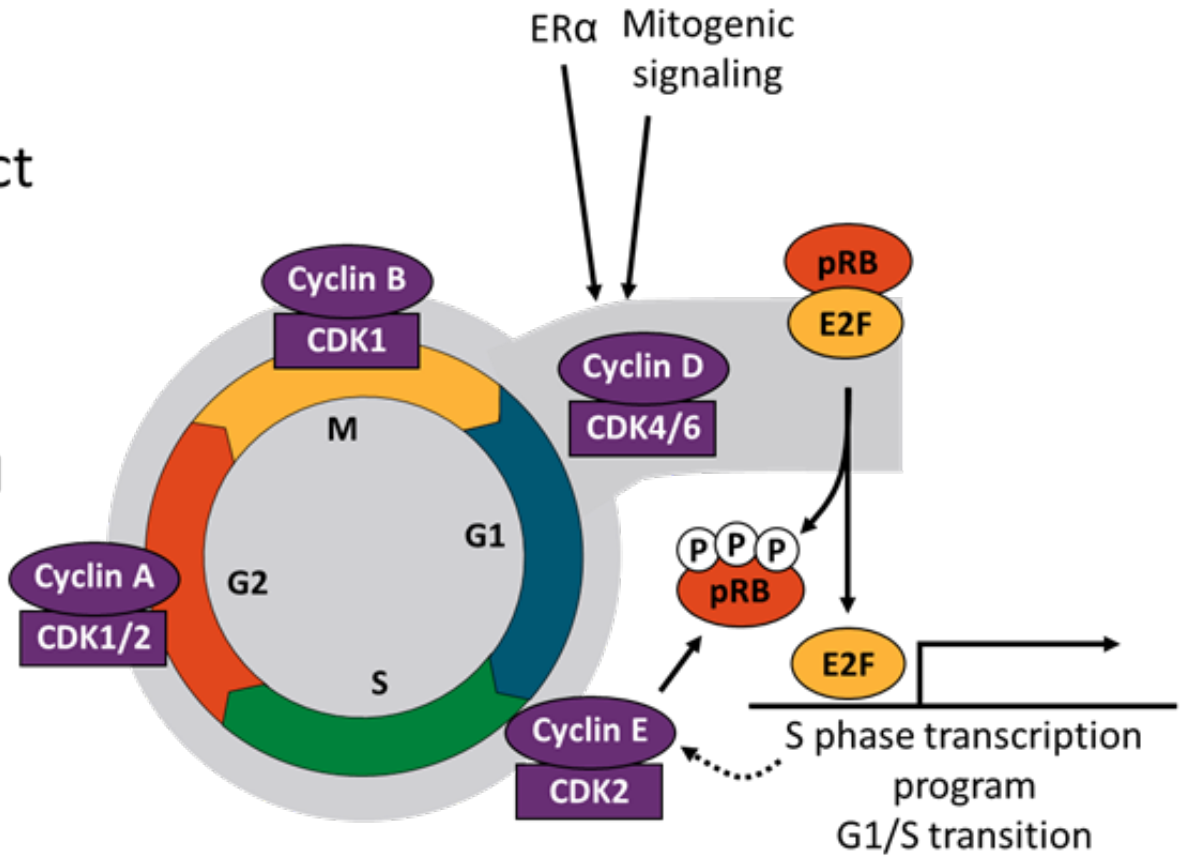
✓AI +/- CDK4/6 inhibitor

❑ **Duration**: until disease progression/unacceptable toxicity

CDK 4/6 inhibitor

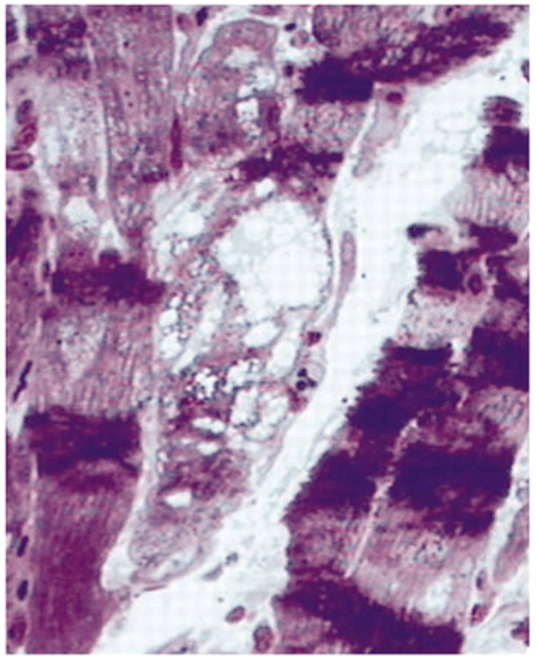
Palbociclib
Ribociclib
Abemaciclib

- Growth of HR+ MBC is dependent on cyclin D1, a direct transcriptional target of ER
- Cyclin D1 activates CDK4/6, resulting in G1-S phase transition and cell cycle entry[1]
- Some cell-line models of endocrine resistance show dependence on cyclin D1 and CDK4/6[2,3]



1. Asghar. Nat Rev Drug Discov. 2015;14:130. 2. Miller. Cancer Discov. 2011;1:338. 3. Thangavel. Endoc Relat Cancer. 2011;18:333.

The cardiac dysfunction observed with anti-cancer therapeutics



Chemotherapy

Type I
(eg doxorubicin)

Predominantly cellular destruction

Biopsy changes

Cumulative/ dose-related

Permanent damage

Anti-HER2 therapy

Type II
(eg trastuzumab)

Cellular dysfunction

No typical biopsy changes

Not cumulative/ dose-related

Predominantly reversible

TTZ induced CHF

- Asymp CHF 10%
- Symp CHF 2%

Reversible 86%

Monitor LVEF before and during Rx q 3 mos.

Ewer & Ewer 2008

Summary of breast cancer treatment

Early stage

- **Surgery** is mainstay
- Adjuvant therapy if indicated :
  CMT, anti-HER2, endocrine therapy, RT

Locally advanced stage

- Consider **neoadjuvant therapy**
  - **TNBC**: CMT + pembrolizumab
  - **HER2+ve**: CMT + trastuzumab +/- pertuzumab
  - **HR+ve**: CMT alone

Advanced stage

- **Systemic therapy** is mainstay
- May adjunct with local therapy if obvious (or uncontrolled) local symptom
- **TNBC**: Chemotherapy +/- immunotherapy (if PD-L1+)
- **HER2+ve**: Chemotherapy + anti-HER2
- **HR+ve** and **HER2-ve**: CDK 4/6 inhibitor + endocrine therapy
- **HER2-ve** with **germline BRCA mutation**: PARP inhibitor

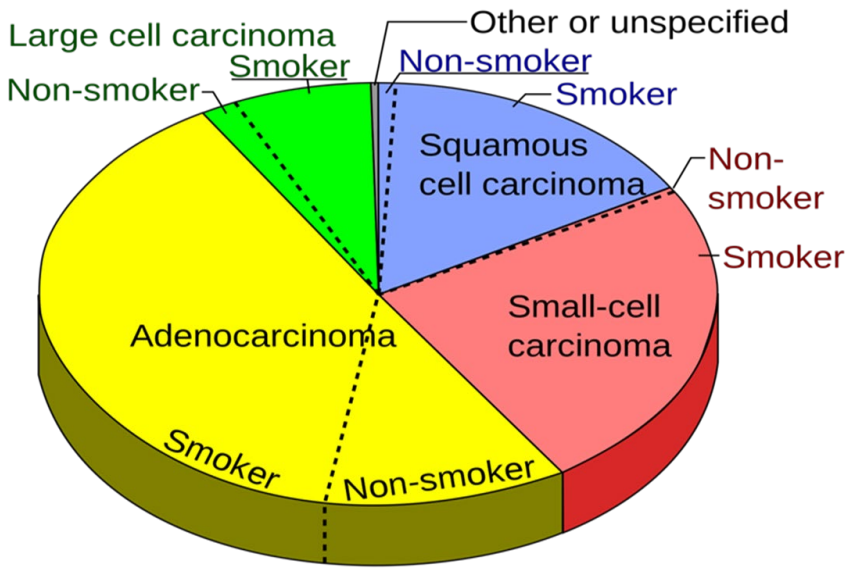
Lung Cancer

Lung cancer Subtypes

Lung cancer

Small cell (SCLC)

Non-small cell (NSCLC)



Squamous cell

Non-squamous cell

Adenocarcinoma

Others- LCNEC, Lymphoepithelioma,
Sarcomatous carcinoma,
Large cell carcinoma etc.

Kenfield SA, et al (2008). Comparison of aspects of smoking among the four histological types of lung cancer . Tob Control. 17 (3): 198–204.

Character	SCLC (10-15%)	NSCLC (85-90%)	
		Squamous (25-30%)	Non-squamous (50-55%)
• Smoking	+++	++	+/-
• Local symptoms	Central lesions SVC +	Central lesions SVC + Horner's	Peripheral lesions
• Paraneoplastic syndrome	Neuroendocrine: LEMS, SIADH, ACTH	HyperCa2+ (Squamous) HOA (Hypertrophic osteoarthropathy)	
• Natural history	Systemic disease at the onset Rapidly progression (< 3 mo)	Localized disease at the onset	
• Imaging	Central Rare: cavitation Common to have brain metastasis	Central, Cavitation	Peripheral, Pleural effusion, GG opacity, Multifocal disease
• Staging	Limited vs. Extensive stage	TNM stage	
• Response to treatment	Chemo-sensitive tumor	Relatively Chemo-resistant tumor	

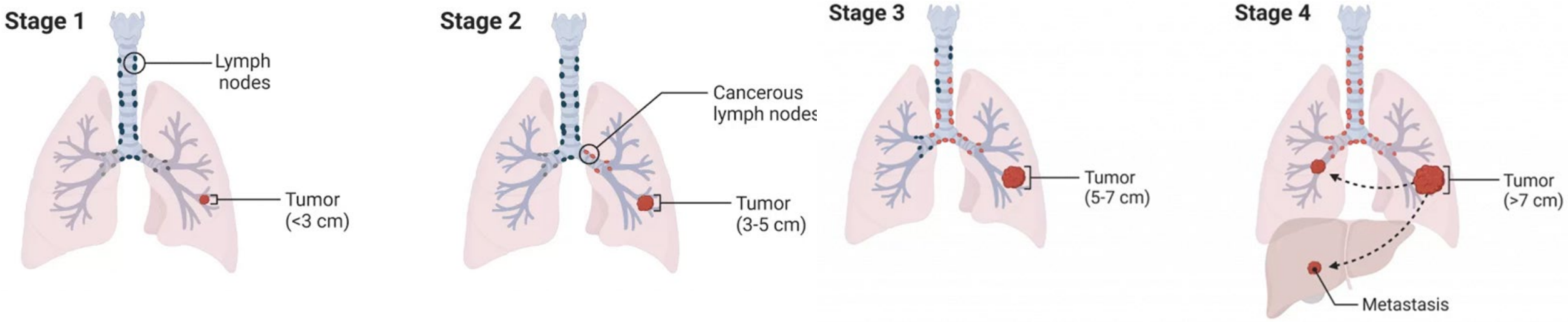
Histology & IHC

	SCLC	NSCLC	
		Squamous	AdenoCA
Histology	Small round cell neoplasm	Polygonal, Desmosome or intercellular bridge, Keratin	Glandular, Intracytoplasmic mucin
IHC	AE1/3+, TTF-1+ NET: Chromogranin, Synaptophysin, NSE (neuron specific enolase)	CK5/6; p63	CK7+, CK20- TTF-1+

Non-small cell lung cancer

NSCLC Staging

- Lung cancer staging is based on **pathological examination** and results of **imaging** (CT scan, MRI brain, Bone scan/PET scan)



Early stage (stage I, II)

Locally advanced stage (stage III)

Advanced stage (stage IV)

Aim: Curative

Aim: Palliative

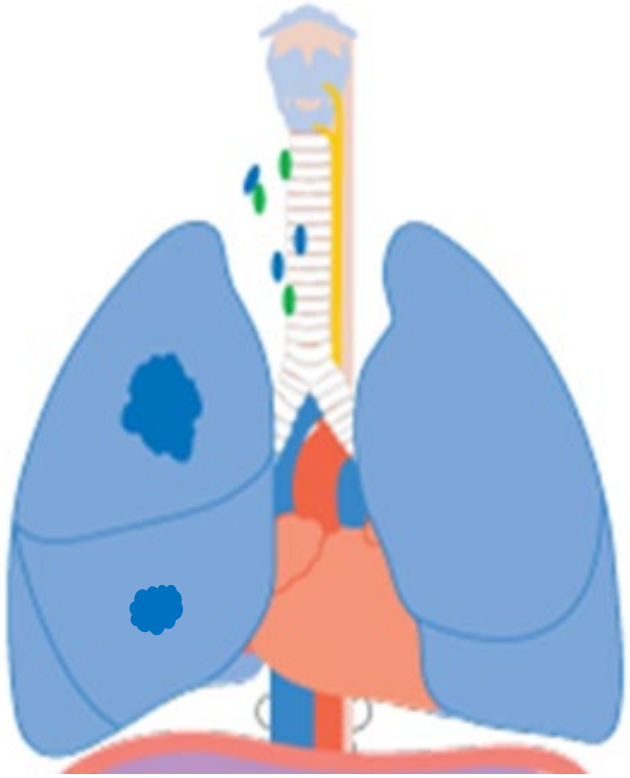
NSCLC Staging : 8th AJCC

Table 1. **Definitions for T, N, M**

T		Primary Tumor
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1		Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
	T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
	T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2		Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
	T2a	Tumor >3 cm but ≤4 cm in greatest dimension
	T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3		Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4		Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

TNM Staging : Definition of T4

- Size > 7 cm or
- Separate tumor nodule(s) in an ipsilateral lobe different from of the primary or
- Invading any of the following:
  - Diaphragm
  - Carina, mediastinum, heart, trachea, esophagus
  - Great vessels (e.g. SVC obstruction)
  - Recurrent laryngeal nerve (hoarseness of voice)
  - Vertebral body



NSCLC Staging : 8th AJCC

Table 1. **Definitions for T, N, M (continued)**

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

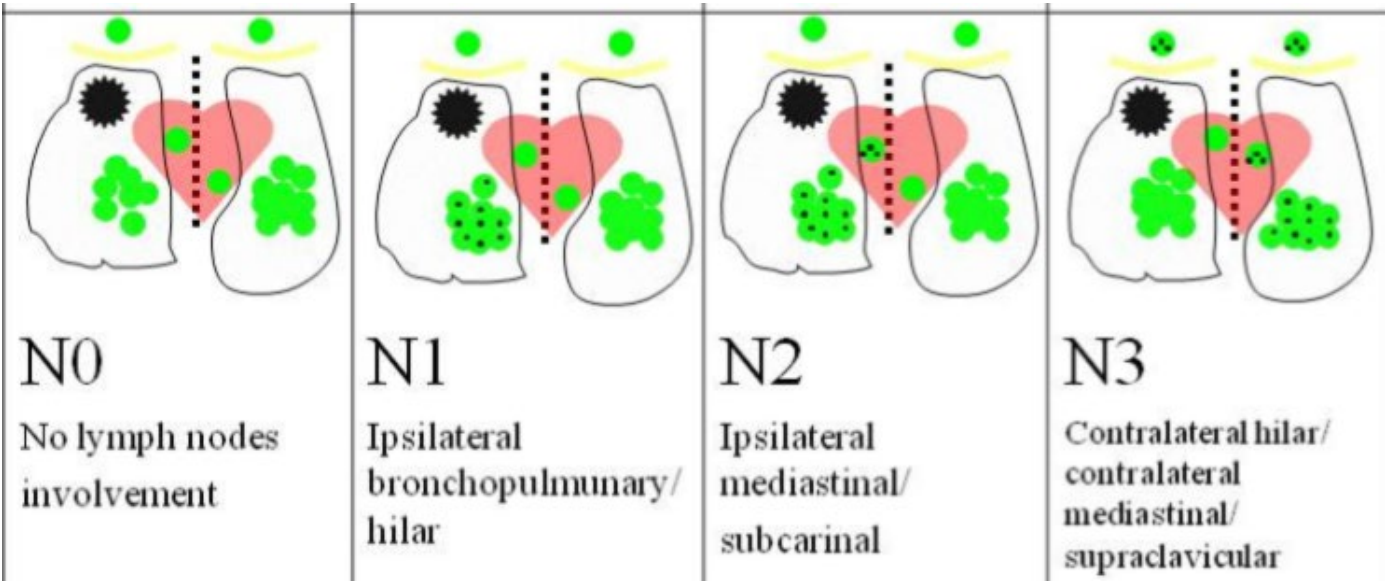
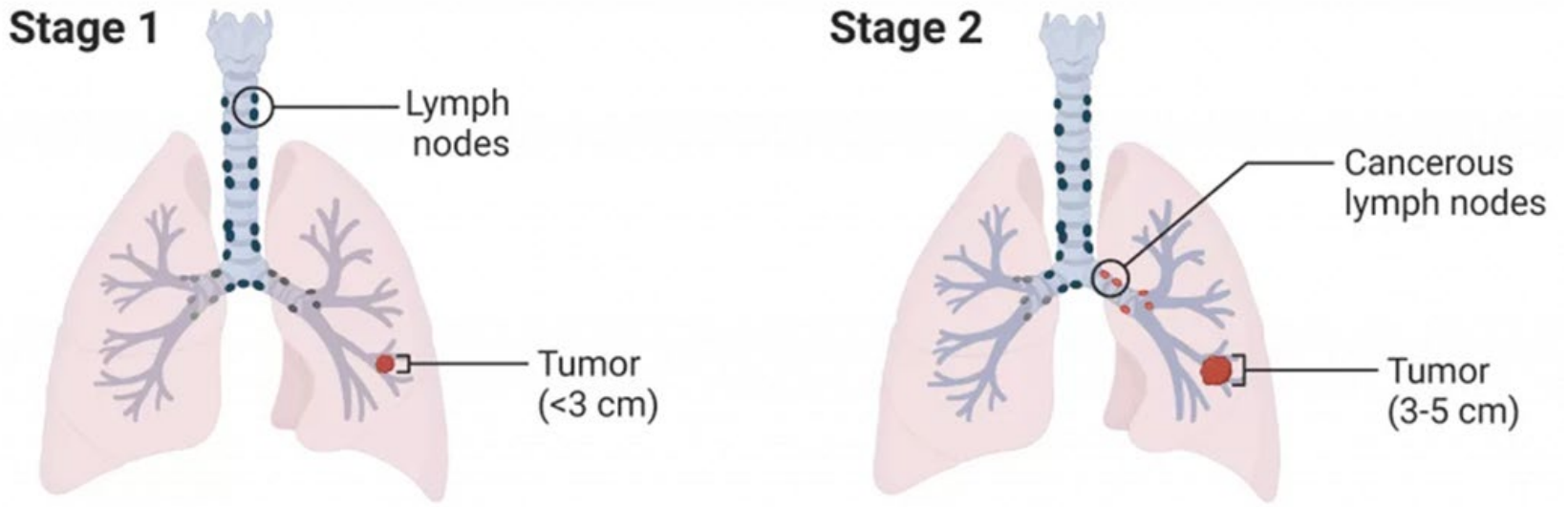


Table 2. **AJCC Prognostic Groups**

	T	N	M
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1mi	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0

	T	N	M
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

NSCLC treatment: Early stage

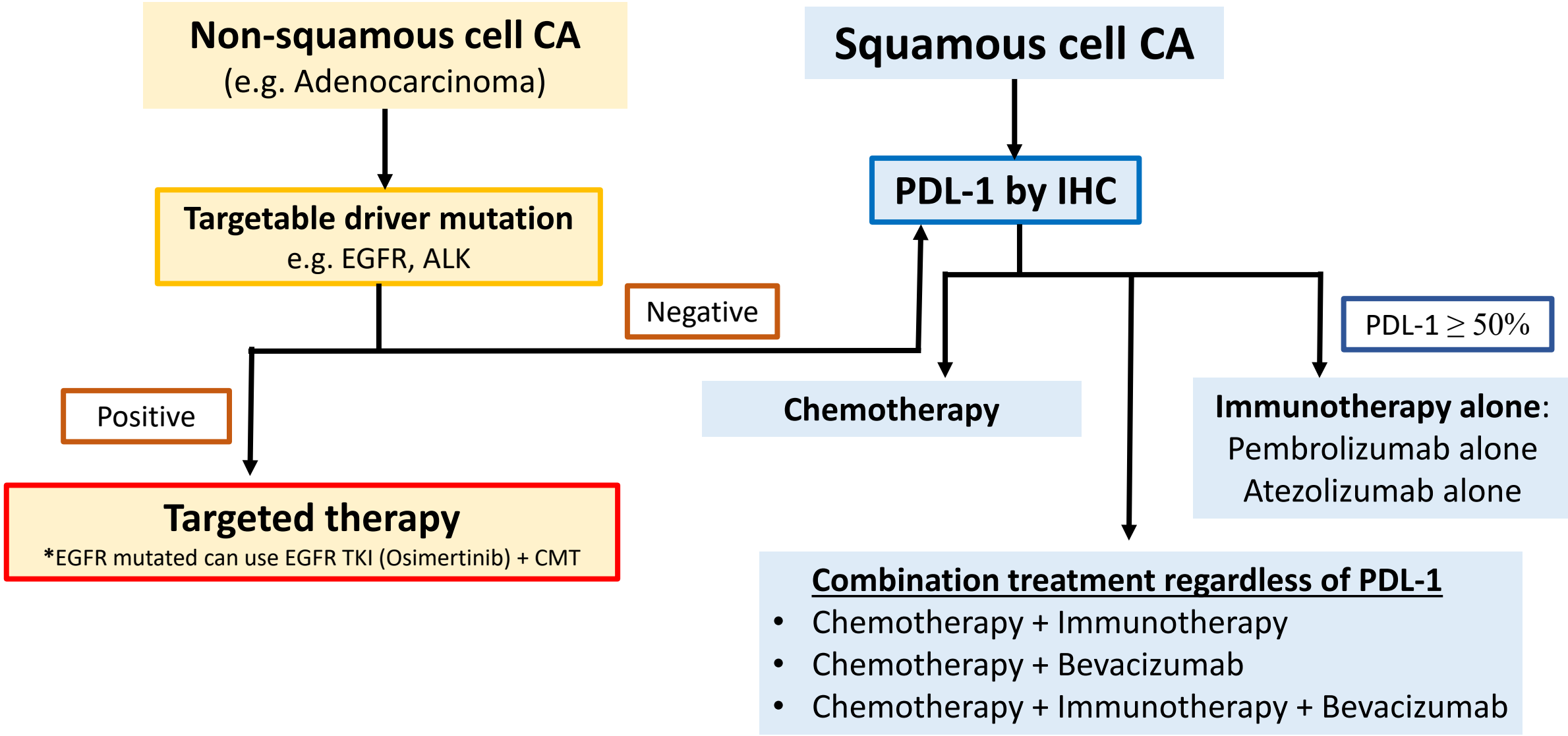


- Mainstay treatment is surgery (lobectomy with lymph node dissection)
- Adjuvant chemotherapy may consider in high-risk patients e.g.
  - Tumor size > 4 cm.
  - Lymph node involvement (N+)
- Adjuvant Osimertinib for 3 years is recommended in EGFR-mutated patients (Exon19del/L858R), particularly in stage II/IIIA
- Considering neoadjuvant/ perioperative systemic treatment in stage IIA-IIIA

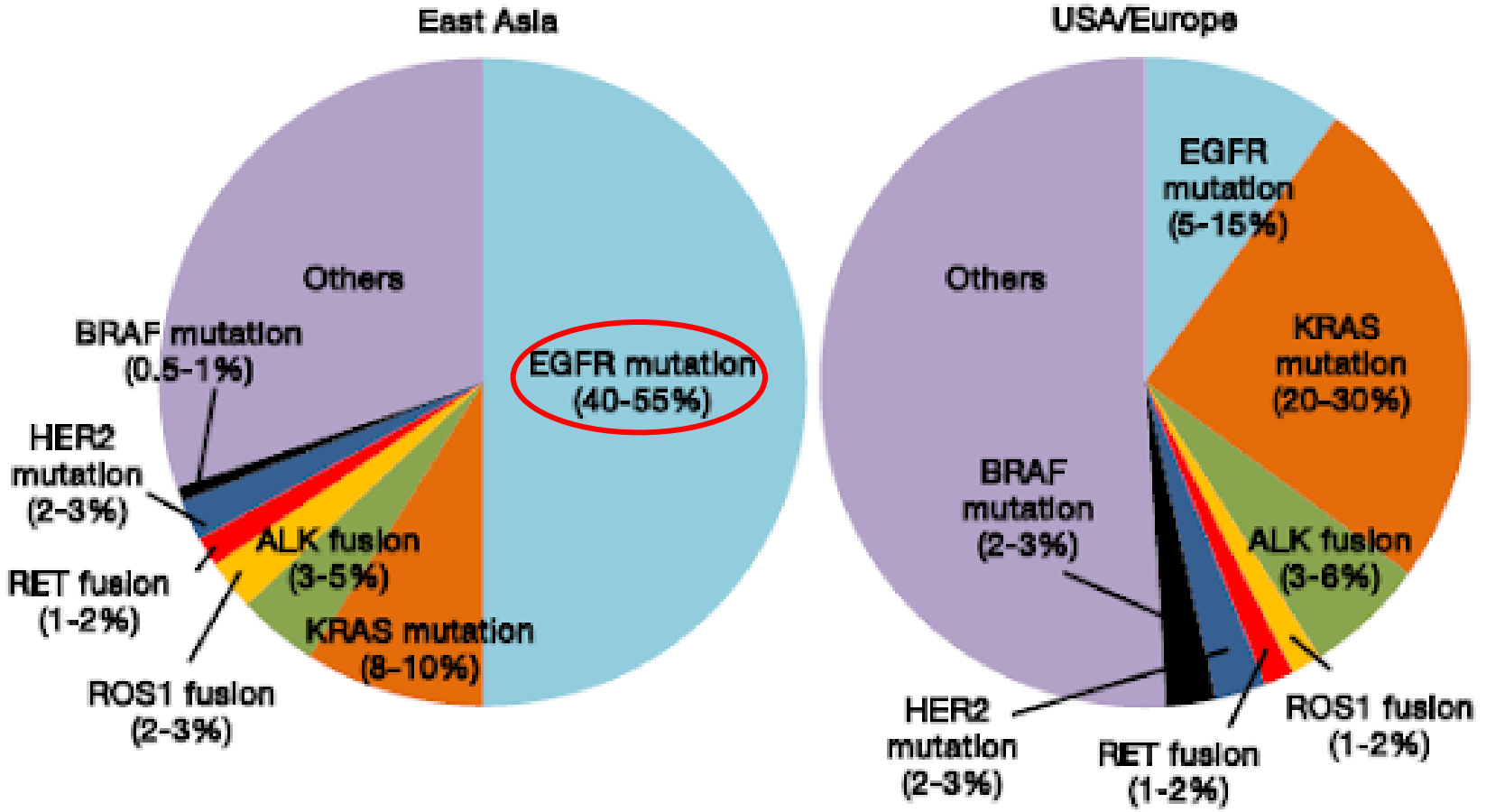
NSCLC treatment: Locally advanced stage

- ❖ Heterogeneous group
- ❖ Resectable vs *(Potentially resectable)* vs Unresectable
- ❖ **For unresectable cases e.g. cT4N2M0, cTxN3M0:**
  - ✓ **Mainstay treatment is concurrent chemoradiation (CCRT) then consider**
    - ➢ Durvalumab for 1 years in non-EGFR mutated patients
    - ➢ Osimertinib until disease progression in EGFR mutated patients

Simple algorithm in advanced NSCLC treatment

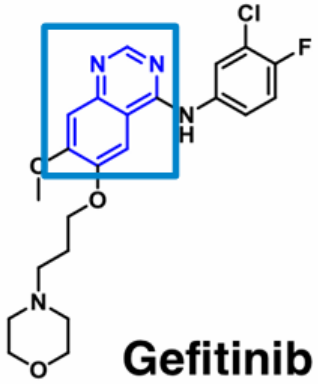


Targeted therapy in NSCLC

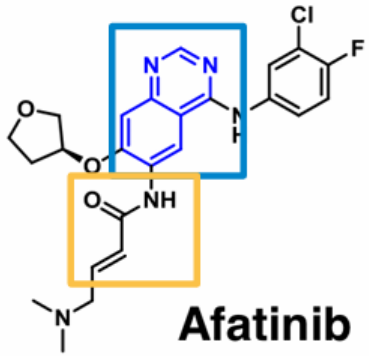


❖ The most common targetable driver mutation in East Asia is EGFR mutation (≈ 50%)

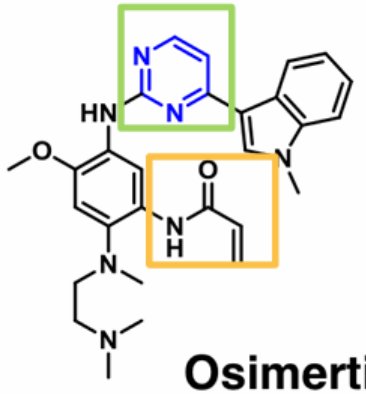
Generations of EGFR tyrosine kinase inhibitor (TKI)



Gefitinib



Afatinib



Osimertinib

	First Generation	Second Generation	Third Generation
Drugs	Gefitinib, Erlotinib	Afatinib, Dacomitinib	Osimertinib
MoA	Reversible ATP competitive	Irreversible, covalent (Cys797)	Irreversible, covalent (Cys797)
Structure	Quinazoline-based	Quinazoline-based	Pyramidine-based
Key features	-	• Pan-HER inhibition: Target HER2/ HER3 mediated resistance • Preclinical activity against T790M and exon20 ins	• T790M specific • WT sparing • CNS penetrant
EGFR Del19	+	+	+
EGFR L8585R	+	+	+
EGFR T790M	-	±	+
EGFR WT	+	+	-

Zhou W, et al. Nature. 2009 Dec 24;462(7276):1070-4.

Small cell lung cancer

The Veterans Administration (VA) Lung Study Group

❖**LD (limited stage disease)(1/3)**

- Lesion confined to one hemithorax
- Can be safely encompassed within a radiation field
- Regional LN metastasis:
  - ipsilateral hilar, SPC LN
  - ipsilateral/contralateral mediastinal LN
  - contralateral hilar and SPC LN -> controversial

❖**ED (extensive stage)(2/3)**

- Disease beyond the ipsilateral hemithorax
- Including malignant pleural or pericardial effusion (positive cytology)
- Distant metastasis (10% brain metastasis at diagnosis)

Kalemkerian GP.et al.Cancer Imaging 2011;11:253-258

Treatment for SCLC

❖ **Limited stage**

- Concurrent chemoradiation (CCRT) with cisplatin and etoposide
- Patients with complete or partial response → Prophylactic cranial irradiation (PCI)

❖ **Extensive stage**

- Palliative CMT (carboplatin + Etoposide) +/- immunotherapy
- Patients with complete or partial response and no brain metastasis consider
  1. PCI
  2. MRI brain surveillance

Colorectal Cancer

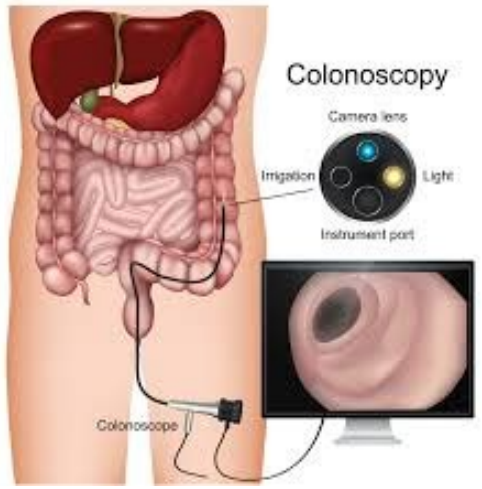
Colorectal cancer (CRC) screening

Who needs to screen colorectal cancer?

1. Average risk: age ≥ 45 years
2. Family Hx of CRC: age 40 years or 10 yr prior to earliest diagnosis of CRC
3. High risk hereditary syndrome:
   HNPCC (hereditary nonpolyposis syndrome)
   FAP (familial adenomatous polyposis)

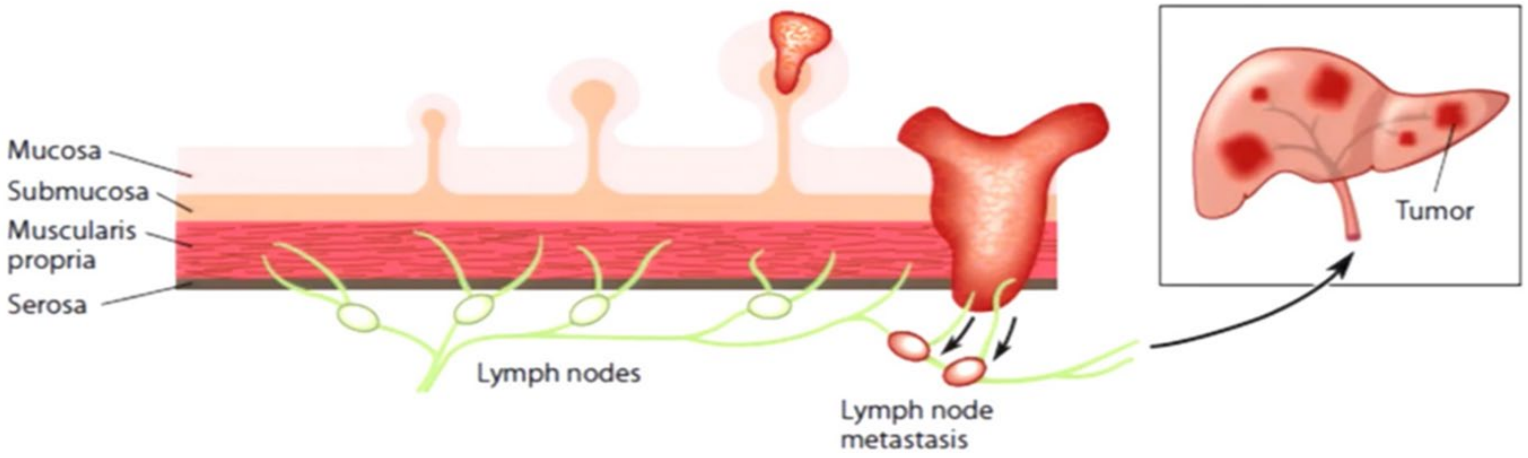
How to screen colorectal cancer?

1. Colonoscope q 5-10 yr
2. Stool occult blood q 1 yr



Colorectal cancer: Staging

- TNM staging according to AJCC 8th edition
  - Stage I = T1/T2N0M0
  - **Stage II = T3/T4N0M0**
  - **Stage III = anyTN+M0**
  - Stage IV = anyTNM1



	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Colorectal cancer: Staging

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colon Cancer 8th ed., 2017

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres** to adjacent organs or structures

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

M	**Distant Metastasis**
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Treatment in Localized Colon cancer

- **Stage I** >>> Surgery alone

- **Stage II** >>> Surgery then adjuvant chemotherapy in

➢ high risk group (+ one of poor prognostic risks)

: T4, LN sampling < 12, Poorly-diff, Perforation/Obstruction, PNI, LVI

- **Stage III** >>> Surgery then adjuvant chemotherapy

Adjuvant chemotherapy in Localized colon cancer

- **Goal:** Eradicate potentially present micro-metastases,

  thereby **increasing the cure rate** in those patients undergone curative resection
- **Start** after surgery **4-8 weeks** (not more than 12 weeks)
- **Regimen CMT**
  - Stage II high-risk: 5FU+LV or Capecitabine

  *Stage II with deficient MMR (mismatch repair protein)/MSI-high

  = no benefit from single agent of adjuvant 5FU/capecitabine
  - Stage III: 5FU+LV or Capecitabine + Oxaliplatin (CAPEOX, FOLFOX)
- **Duration:** standard = **6 months**

  3 months in low-risk stage III (T3N1M0) with CAPEOX

LV5FU2 (de Gramont)	- **Leucovorin** 200 mg/m2 IV drip in 2 hr D1, D2 - **5FU** 400 mg/m2 IV bolus D1, D2 - **5FU** 600 mg/m2 IV drip in 22 hr D1, D2	**Q 2 Weeks**
5FU (Mayo regimens)	- **Leucovorin** 20 mg/m2/d IV D1-D5 - **5FU** 425 mg/m2/d IV bolus D1-D5	**Q 4 Weeks**
5FU (Roswell park regimens)	- **Leucovorin** 500 mg/m2 IV drip in 2 hr D1, D8, D15, D22, D29, D36 rest 2 weeks - **5FU** 500 mg/m2 IV bolus D1, D8, D15, D22, D29, D36 rest 2 weeks	**Q 8 Weeks**
FOLFOX4	- **Oxaliplatin** 85 mg/m2 IV D1 - **Leucovorin** 200 mg/m2 IV drip in 2 hr D1, D2 - **5FU** 400 mg/m2 IV bolus D1, D2 - **5FU** 600 mg/m2 IV drip in 22 hr D1, D2	**Q 2 Weeks**
mFOLFOX6	- **Oxaliplatin** 85 mg/m2 IV D1 - **Leucovorin** 400 mg/m2 IV drip in 2 hr D1 - **5FU** 400 mg/m2 IV bolus D1 - **5FU** 1200 mg/m2 IV drip in 23 hr D1, D2	**Q 2 Weeks**
FLOX	- **Oxaliplatin** 85 mg/m2 IV D1, D15, D29 - **Leucovorin** 500 mg/m2 IV drip in 2 hr D1, D8, D15, D22, D29, D36 rest 2 weeks - **5FU** 500 mg/m2 IV bolus D1, D8, D15, D22, D29, D36 rest 2 weeks	**Q 8 Weeks**
Capecitabine	- **Capecitabine** 1000-1250 mg/m2 bid x 2 Weeks	**Q 3 Weeks**
CAPEOX	- **Oxaliplatin** 130 mg/m2 IV D1 - **Capecitabine** 1000 mg/m2 bid x 2 Weeks	**Q 3 Weeks**

Treatment in Localized Rectal cancer

- **Stage I**: Surgery alone

- **Stage II and III (locally advanced)**:

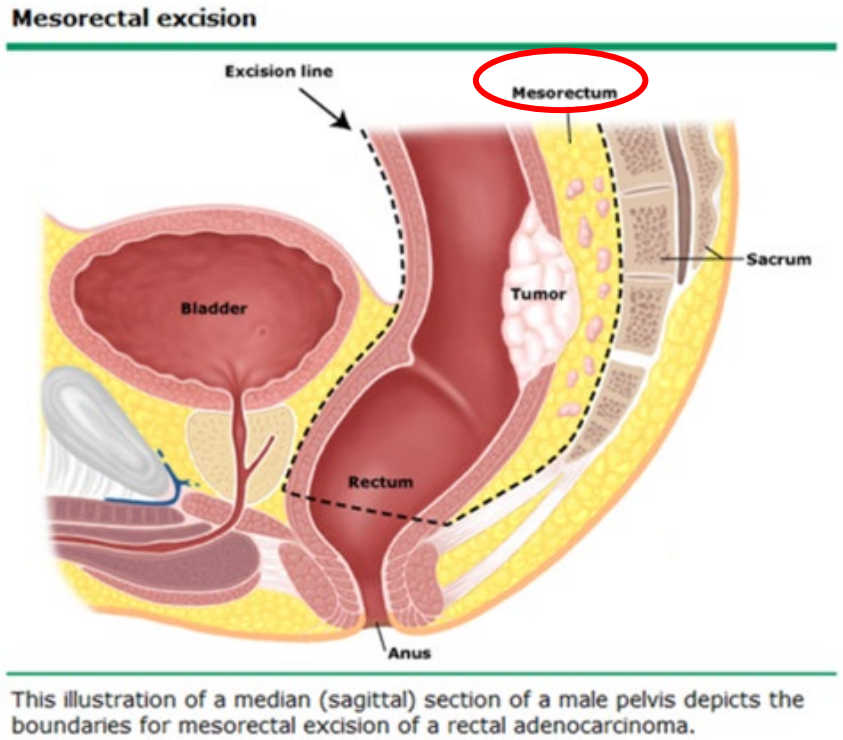
  Preoperative Radiation (RT) or Concurrent chemoradiation (RT)

  +/- chemotherapy then surgery

Rectal cancer

- Definition
  - Below peritoneal reflection line or 3-12 cm from AV

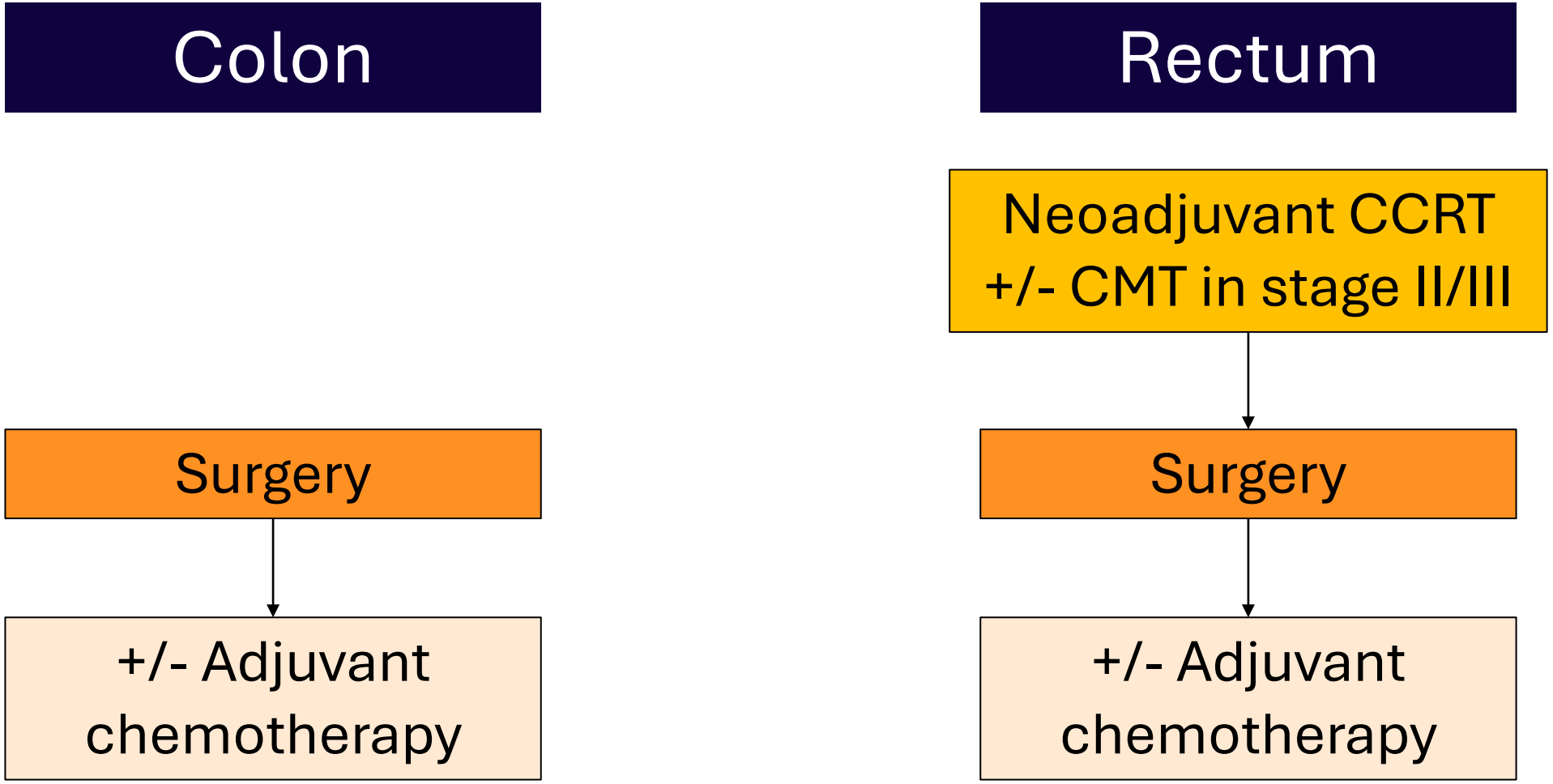
- **No peritoneal coverage**
  - High risk of local recurrence
  - 25-50% locoregional failure for T3-4 or node positive
  - Role of local control → XRT



This illustration of a median (sagittal) section of a male pelvis depicts the boundaries for mesorectal excision of a rectal adenocarcinoma.

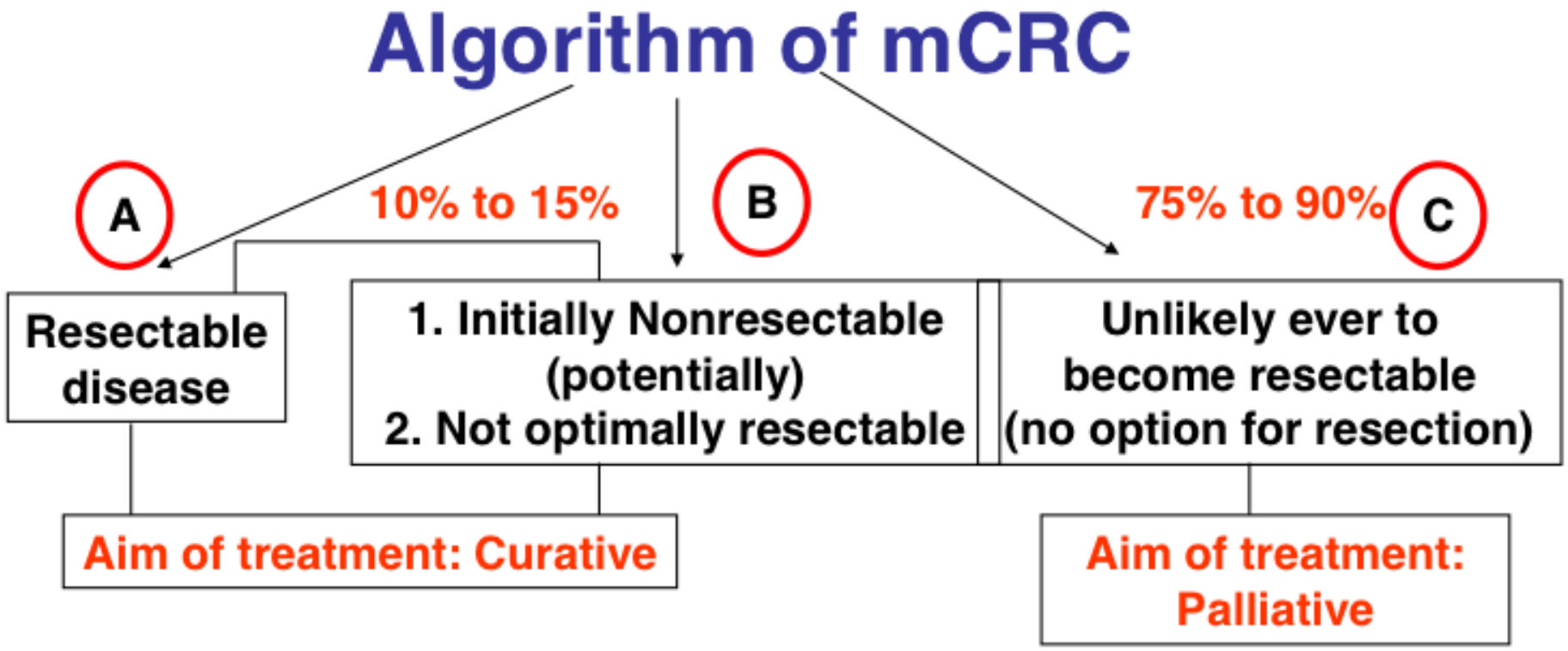
- **Lymphatic drainage and blood supply contained in the mesorectum**
- Surgery need expertise
  - Complex anatomy and intrapelvic region

Localized colon vs rectal cancer treatment



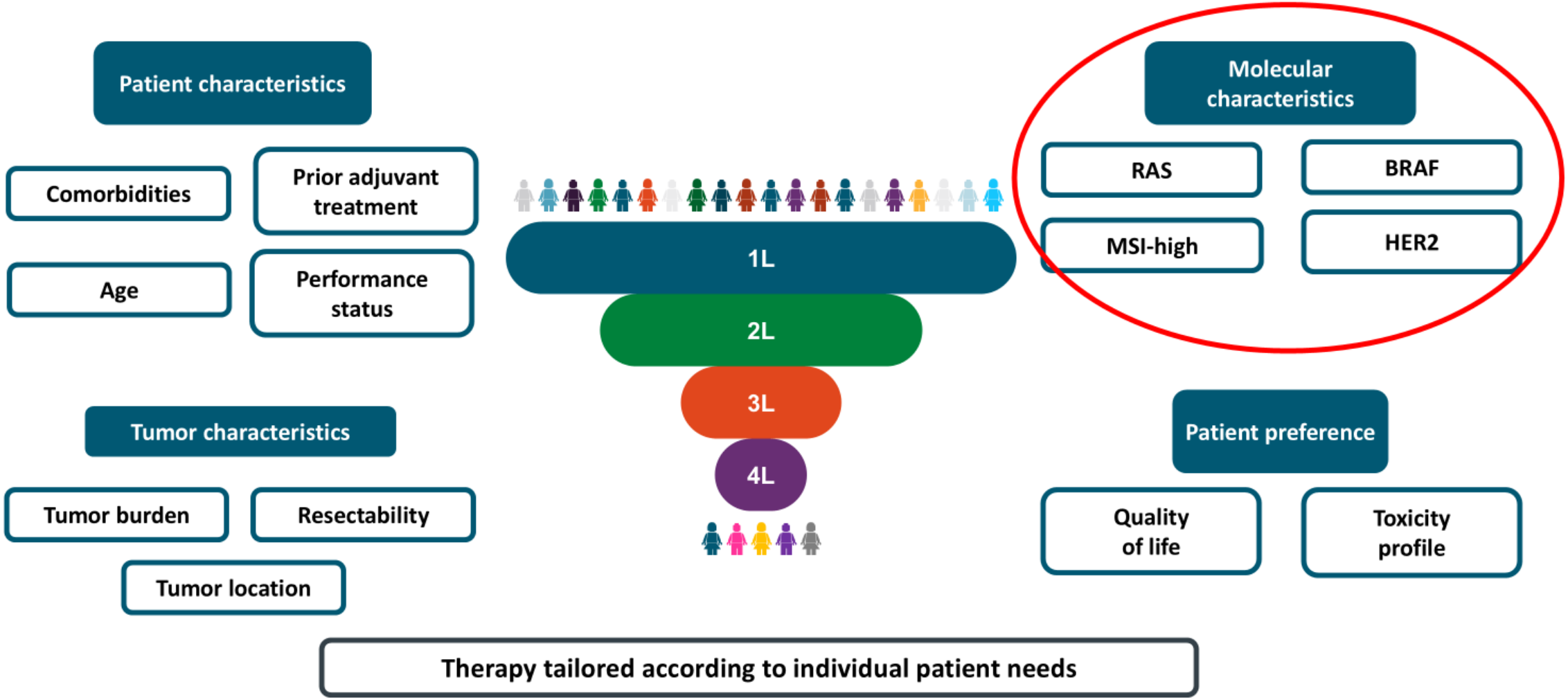
Treatment in metastasis Colorectal Cancer (mCRC)

Metastatic Colorectal Cancer



- Consider colon resection or colostomy if risk for obstruction/ significant bleeding
- mCRC with oligo-metastasis(lung/liver) is candidate for curative treatment

What Influences Treatment Choices in mCRC?



Modified from Van Cutsem. Ann Oncol. 2016;27:1386.

Systemic therapy in metastatic CRC

❖ **Chemotherapy**

- Combination
  - FOLFOX, XELOX
  - FOLFIRI, XELIRI
  - FOLFOXIRI/FOLFORINOX
- Single agent
  - 5-FU/LV, capecitabine

❖ **Targeted therapy**

- Anti-VEGF
  - Bevacizumab
- Anti-EGFR (RAS/BRAF wild type)
  - Cetuximab
  - Panitumumab

❖ **Immunotherapy** (MSI-H/dMMR)

Role of targeted therapy in mCRC

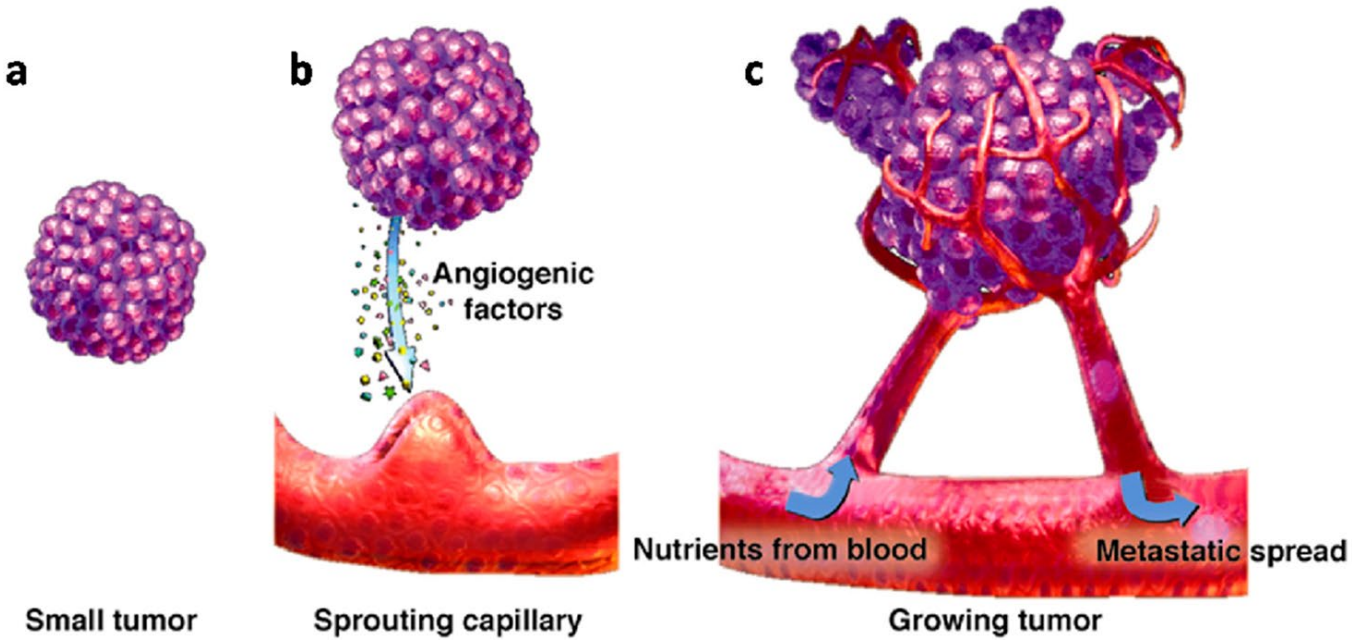
- **First line setting: combined with CMT**
  - Colorectal cancer with potentially resectable liver metastasis:
    increase response rate and chance of curative surgery
  - Colorectal cancer with high tumor burden:
    increase disease control rate and control symptoms

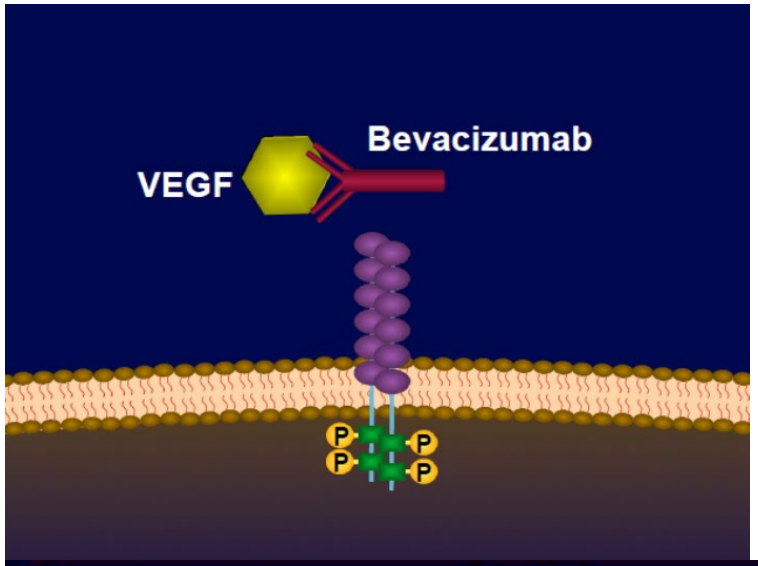
- **Second or later line setting**
  - Colorectal cancer patient who fail standard first-line chemotherapy

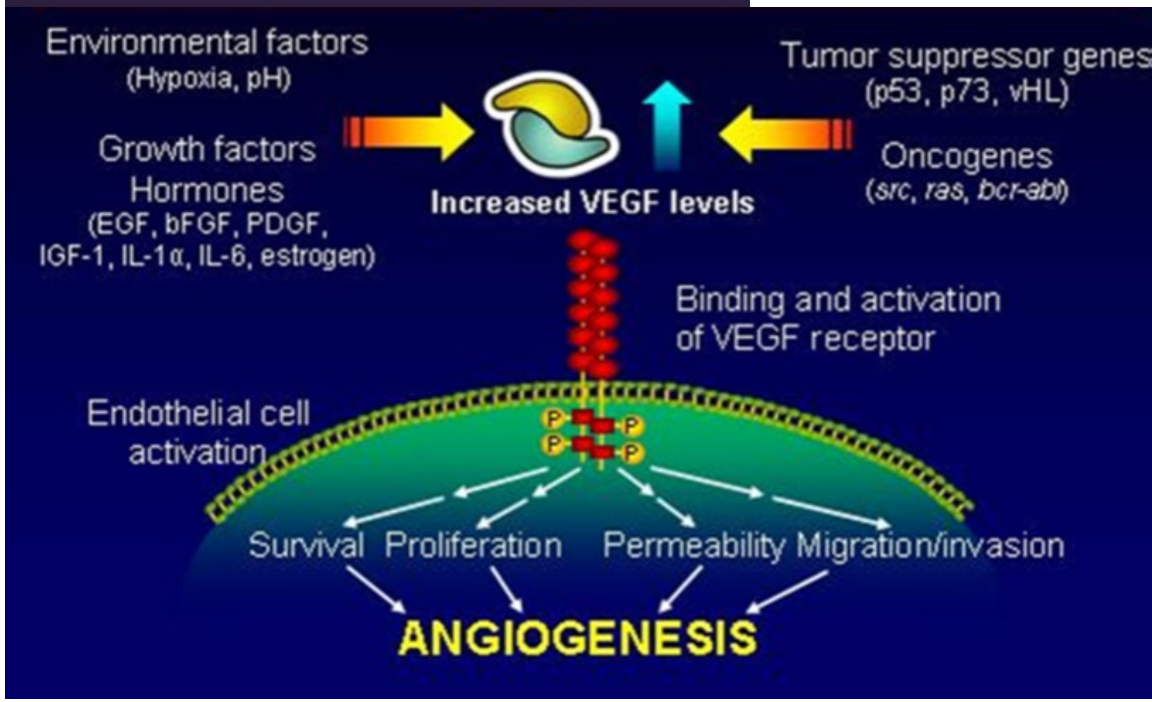
Bevacizumab

= monoclonal antibody to VEGF (Anti-VEGF)
inhibit angiogenesis

- Can use in any RAS/BRAF status







❖ **Side effect**: hypertension, proteinuria, bleeding/thrombosis

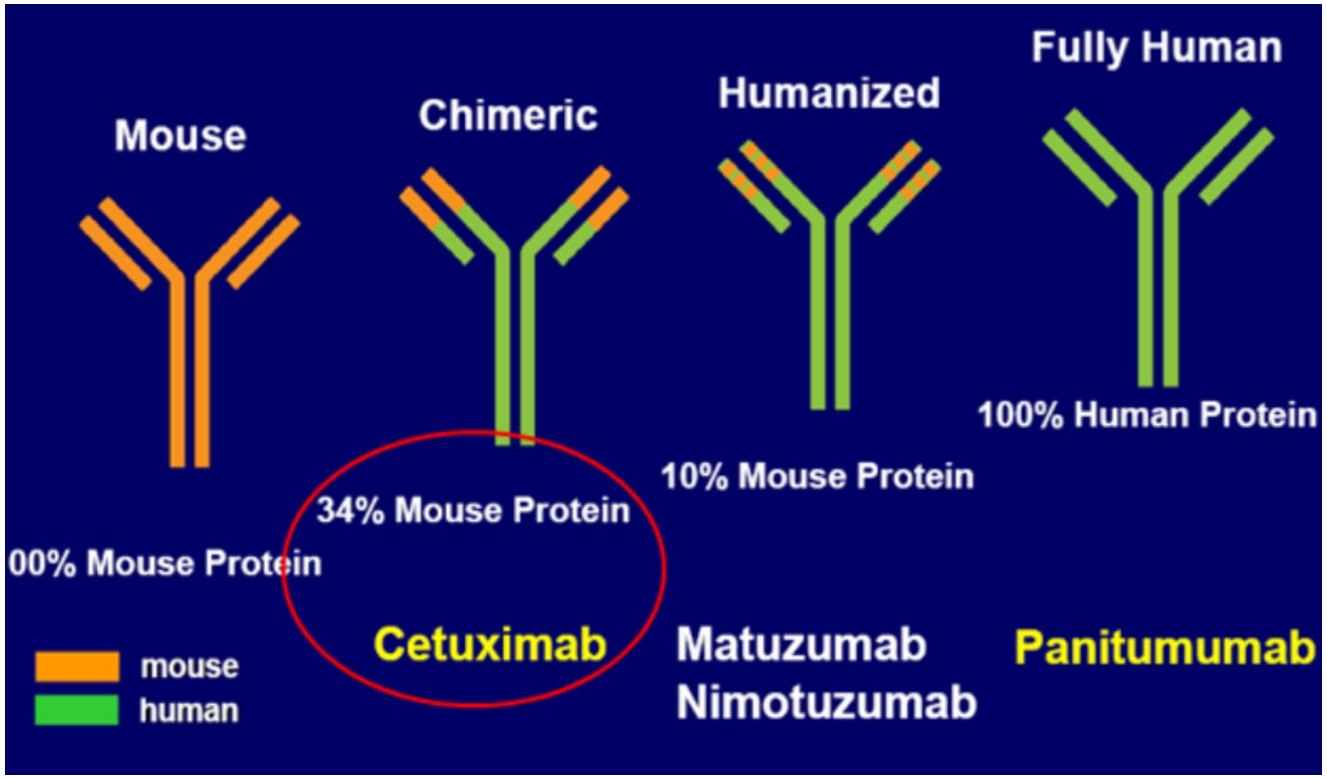
>>> monitor blood pressure and proteinuria

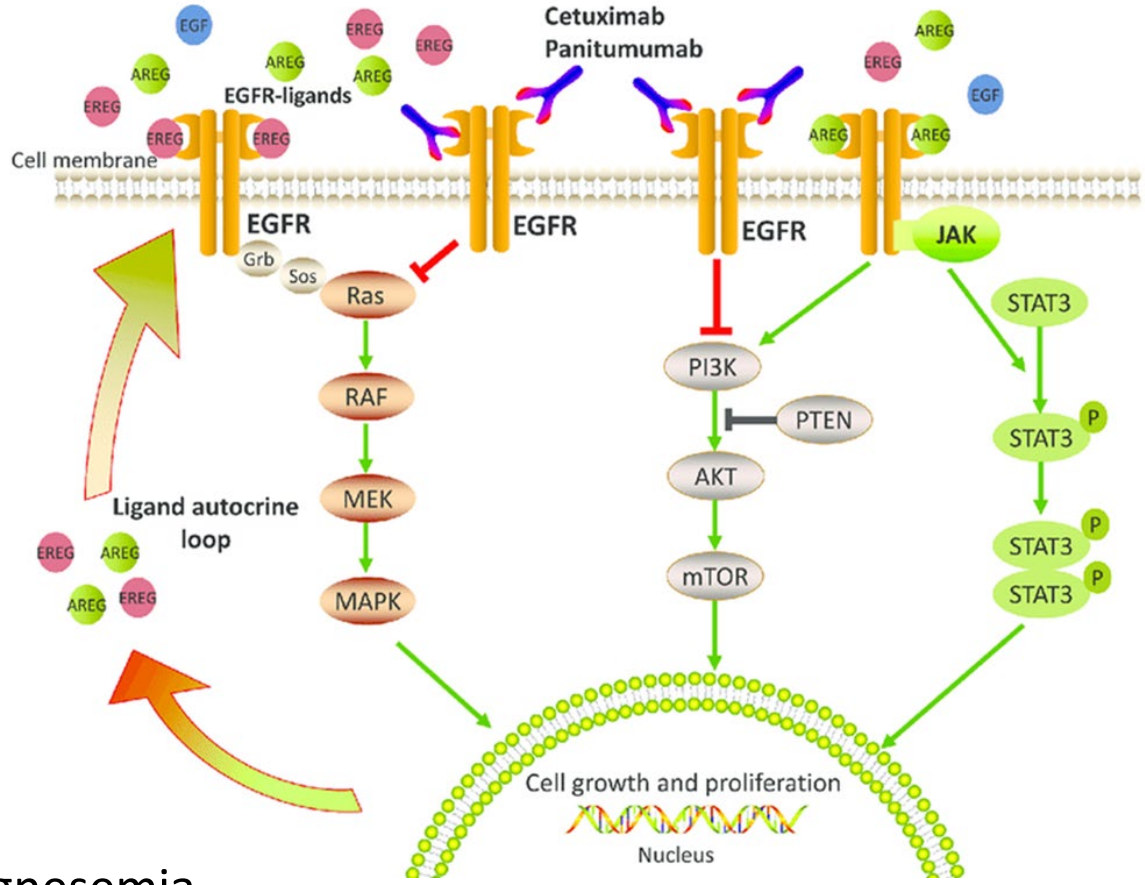
Anti-EGFR (Epidermal growth factor receptor)

= monoclonal antibody to EGFR

inhibit tumor growth and proliferation

benefit in extended RAS/BRAF wild type





❖ Side effect: rash, dry skin, mucositis, diarrhea, hypomagnesemia

Role of immunotherapy in mCRC

- Immunotherapy >>> Immune checkpoint inhibitor
  - Anti-PD1: Pembrolizumab, Nivolumab
  - Anti-CTLA4: Ipilimumab

- Need to test predictive biomarker:
  - MSI (Microsatellite instability)
  - MMR (Mismatch repair protein)

- Benefit in MSI-high/deficient MMR metastasis colorectal cancer

Summary metastatic CRC treatment

❖ **Resectable e.g. limited liver metastasis**

- Surgery then post-operative CMT
- Perioperative CMT then surgery

❖ **Potential resectable**

- RAS/BRAF wild-type (no mutation): Doublet CMT + Anti-EGFR
- RAS/BRAF mutated: Doublet/Triplet CMT + Anti-VEGF

❖ **Unresectable**: palliative CMT +/- targeted therapy

- Considering immunotherapy in MSI-high/deficient MMR tumor

❖ **Don’t forget to correct local problem e.g. colonic obstruction before starting systemic treatment**

Hepatocellular carcinoma (HCC)

Screening: HCC

- **Methods**: USG liver **and** serum AFP **q 6 months**

- **High risk population**
  - Any Cirrhosis from any cause (start screening at time of diagnosis)
  - Chronic HCV infection + advanced Fibrosis (F3)
  - Chronic HBV infection + additional risk factor
    - Family history of HCC
    - Asian males ≥ 40 years
    - Asian females ≥ 50 years
    - African/North Americans Blacks

Diagnosis: HCC

- **Normally, pathological examination not needed !**
- Non-invasive diagnosis of HCC can be made by stringent criteria on multiphase contrast imaging (**multiphasic CT or multiphasic MRI**)

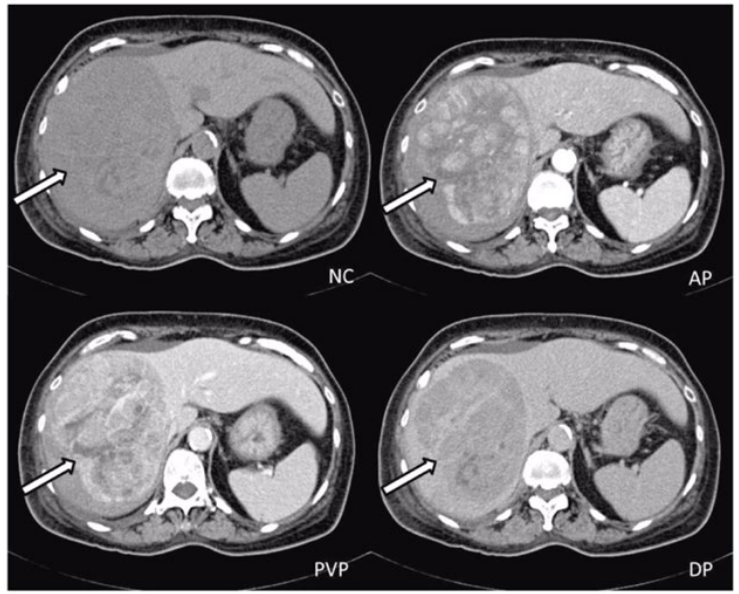
"Arterial enhancement + Venous/Delayed washout"

in **high risk patients (Cirrhosis/Chronic HBV infection)**

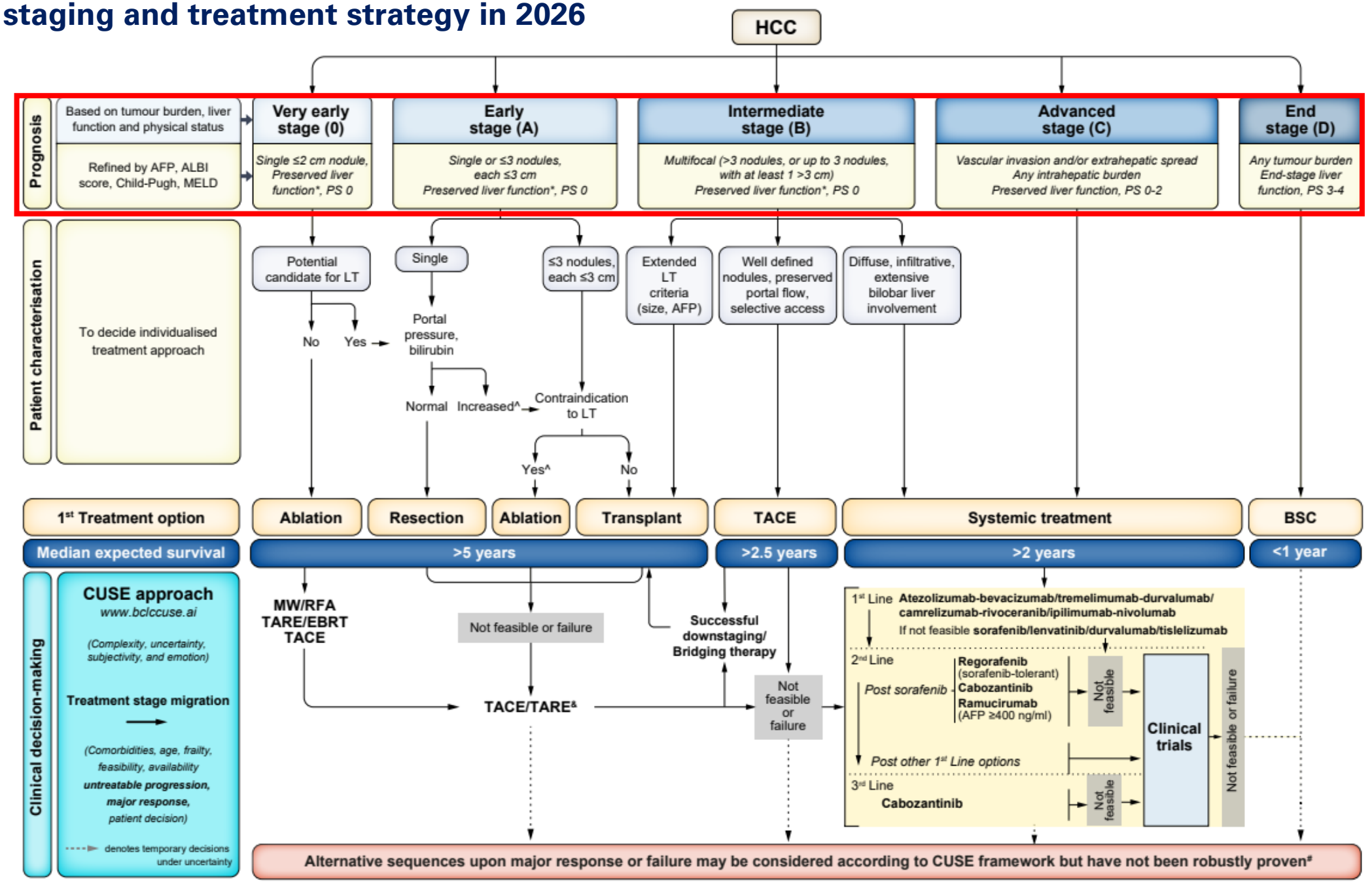
High risk patient ✚ **Typical imaging**

↓

Dx: Typical HCC



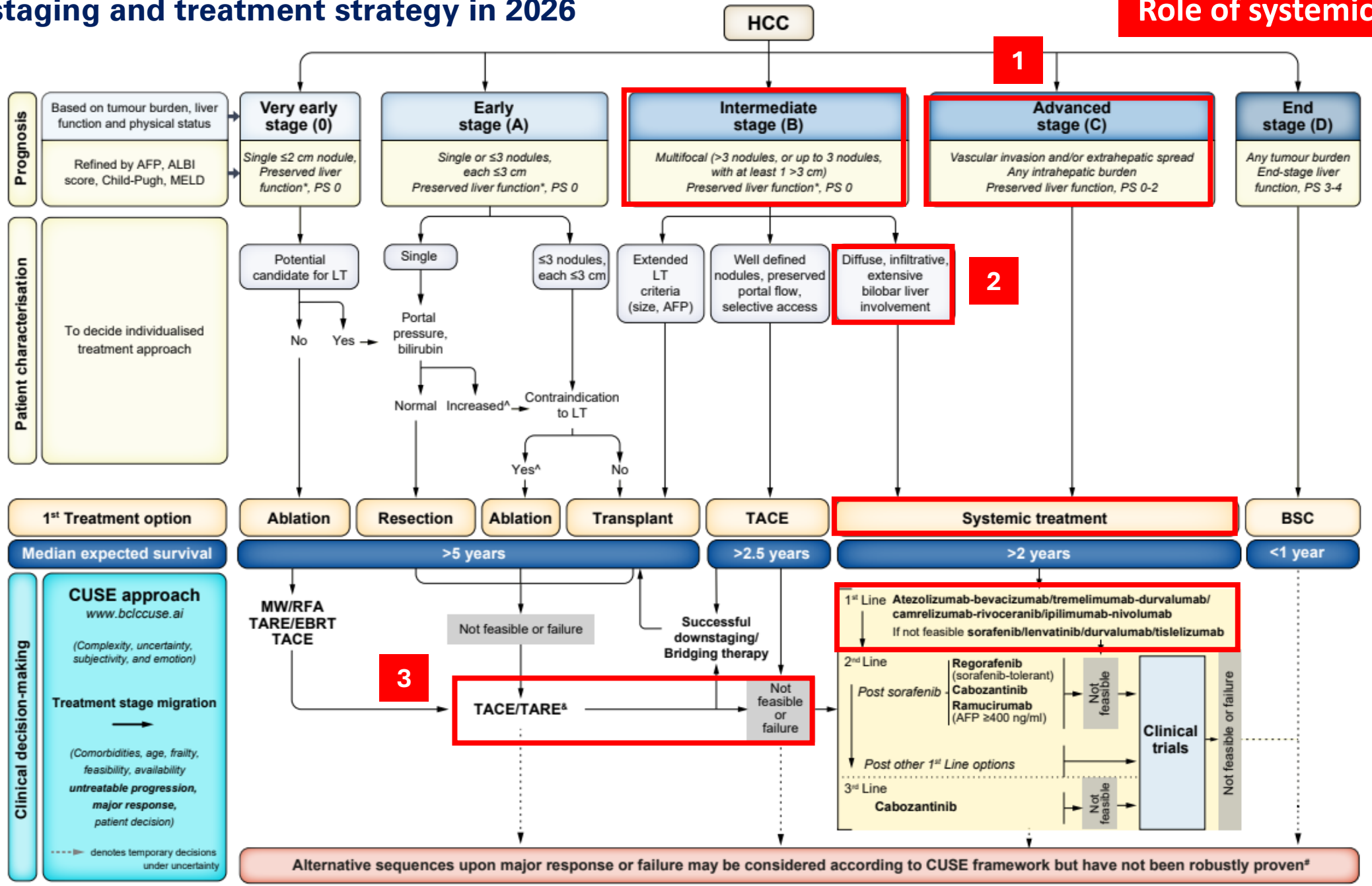
BCLC staging and treatment strategy in 2026



Reig, Maria et al. Journal of Hepatology, 2026

BCLC staging and treatment strategy in 2026

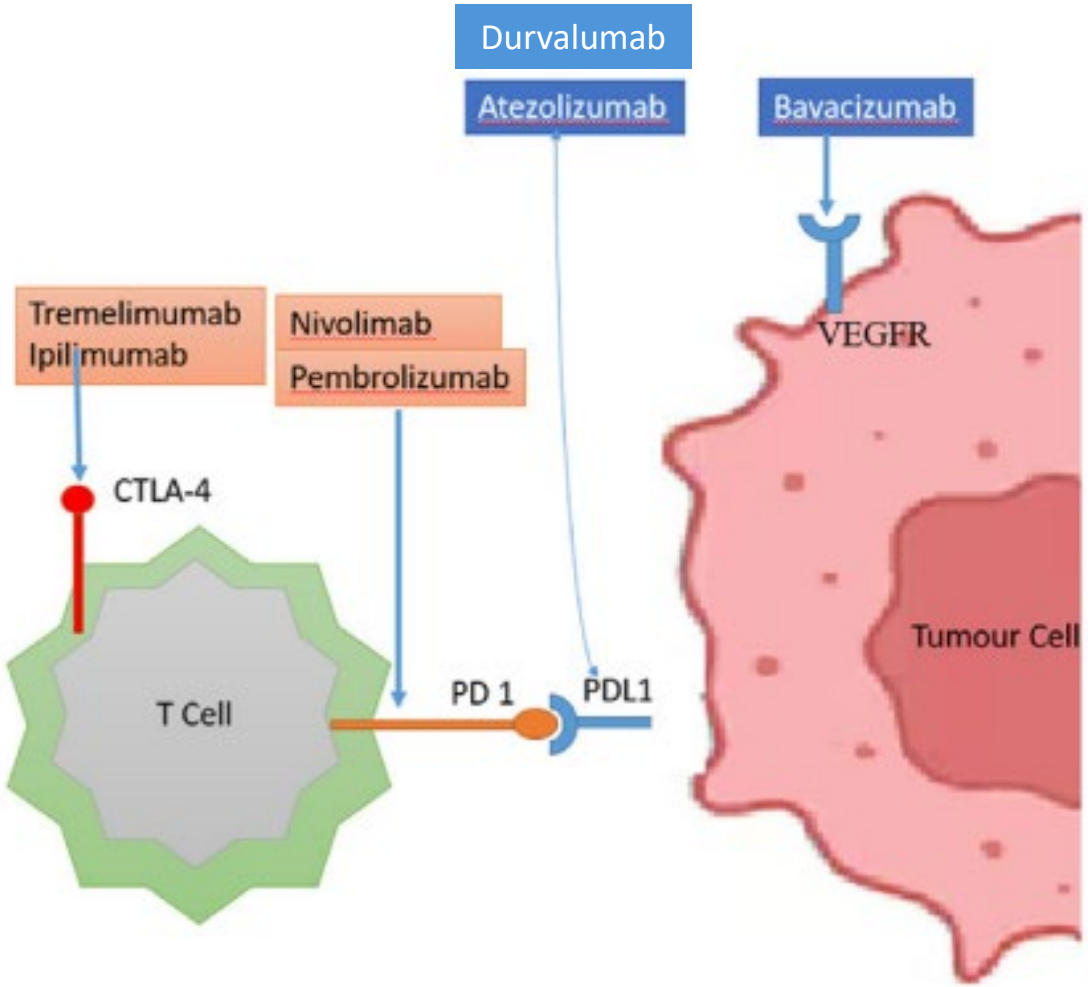
Role of systemic treatment



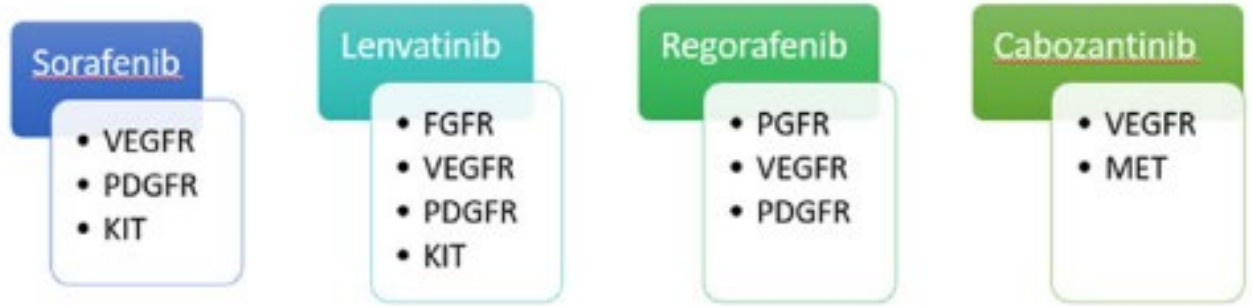
Reig, Maria et al. Journal of Hepatology, 2026

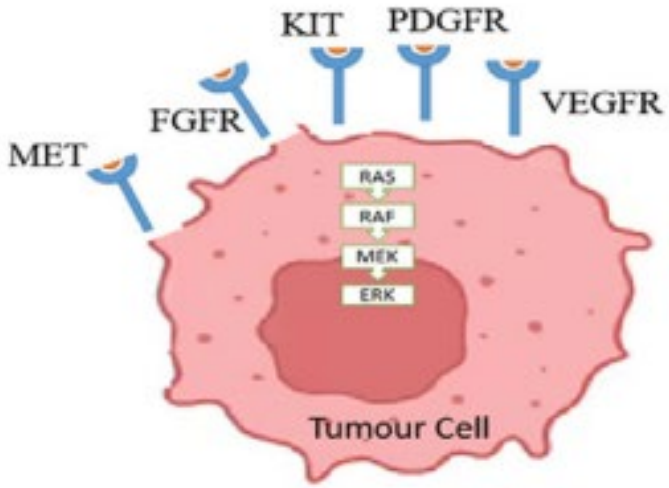
Treatment target in advanced HCC

Immune checkpoint inhibitors +/- antiangiogenesis

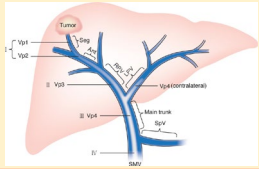


Multitargeted tyrosine kinase inhibitors (TKI)





Karan Kumar et al. Journal of Clinical and Experimental Hepatology, Volume 15, Issue 5, 2025.

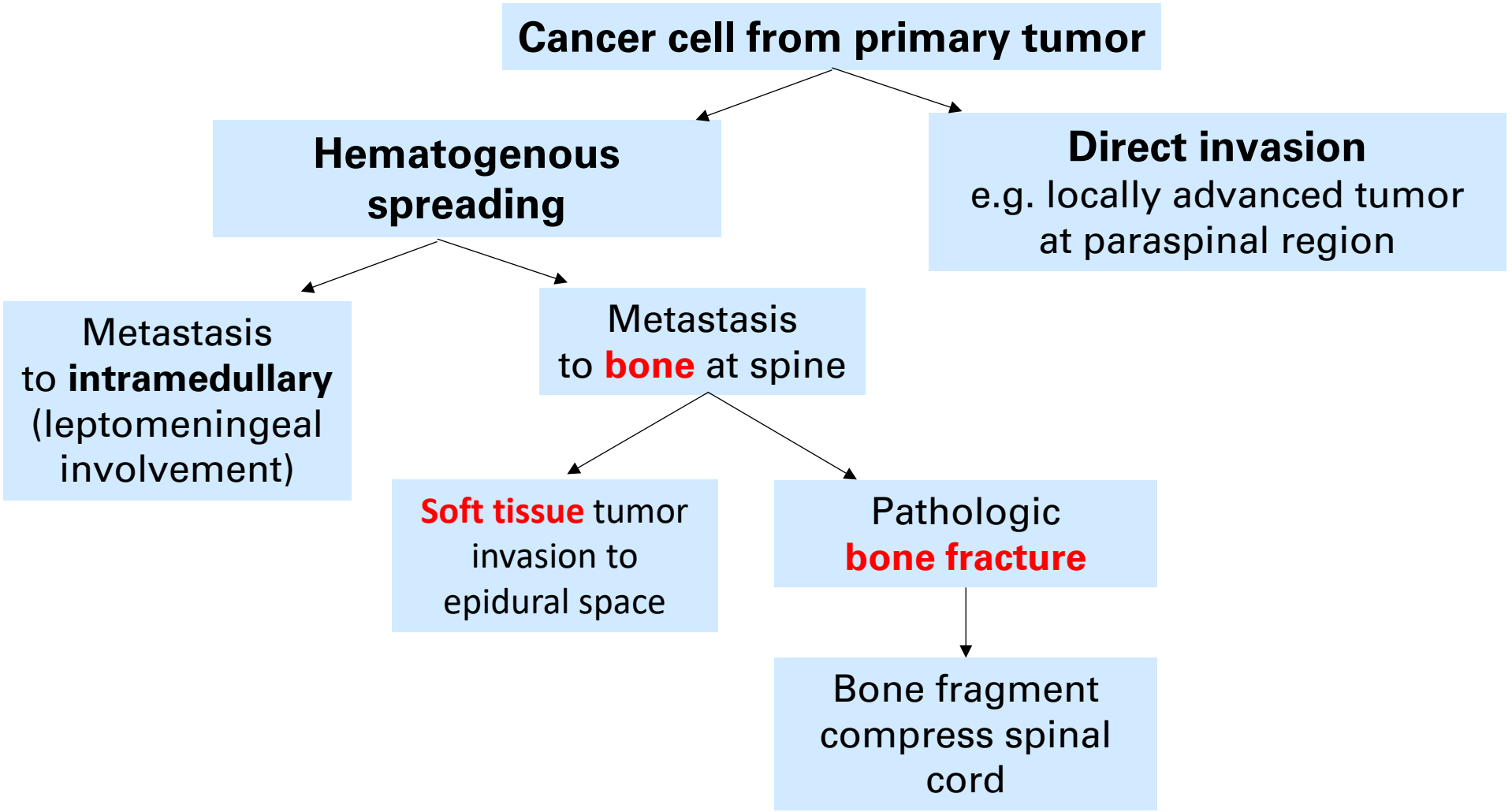
	REFLECT	IMbrave150	Rationale 301	Himalaya		Checkmate 9DW
Study design	RCT, NI, Phase III (open labeled)	RCT, Phase III (open labeled)	RCT, Phase III (open labeled)	RCT, Phase III (open labeled) NI in ARM: Durvalumab		RCT, Phase III (open labeled)
Main Exclusions	≥50% liver occupied Main PV/Bile duct invasion	Recent bleeding/ Untreated varices (EV/GV)	Main portal vein thrombosis (vp4) or IVC	Main portal vein thrombosis (vp4) Active coinfection with HBV and HCV		
BCLC A/B/C (%)	0/20/80	2/15/82	0/20/80	0/20/80		8/18/73
HBV/HCV (%)	50/20	50/20	60/14	31/28	30/27	34/27
Intervention	**Lenvatinib**	**Atezolizumab + Bevacizumab**	**Tislelizumab**	**Tremelimumab+ Durvalumab**	**Durvalumab**	**Nivolumab + Ipilimumab**
Control	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Lenvatinib (85%) Sorafenib (15%)
PEP	OS	OS+PFS	OS	OS		OS
Tumor assessment	mRecist, investigator	Recist, BICR	Recist, BICR	Recist, investigator		
OS (month)	13.6 vs 12.3** (HR = 0.92)	19.2 vs 13.2* (HR = 0.66)	15.9 vs 14.1** (HR = 0.85)	16.4 vs 13.8* (HR = 0.78)	16.6 vs 13.8** (HR = 0.86)	23.7 vs 20.6* (HR = 0.79)
TTP/PFS (month)	8.9 vs 3.7* (HR = 0.66)	6.8 vs 4.3* (HR = 0.65)	2.1 vs 3.4 (HR = 1.1)	3.8 vs 4.1 (HR = 0.9)	3.7 vs 4.1 (HR 1.02)	9.1 vs 9.2 (HR 0.87)
ORR (CR+PR) (%)	24.1 vs 9.2*	30 (CR 8) vs 11*	14.3 (CR 3) vs 5.4*	20 (CR 3) vs 5	17 (CR 1.5) vs 5	36 (CR 7) vs 13

*Statistical significance, **Non-inferiority

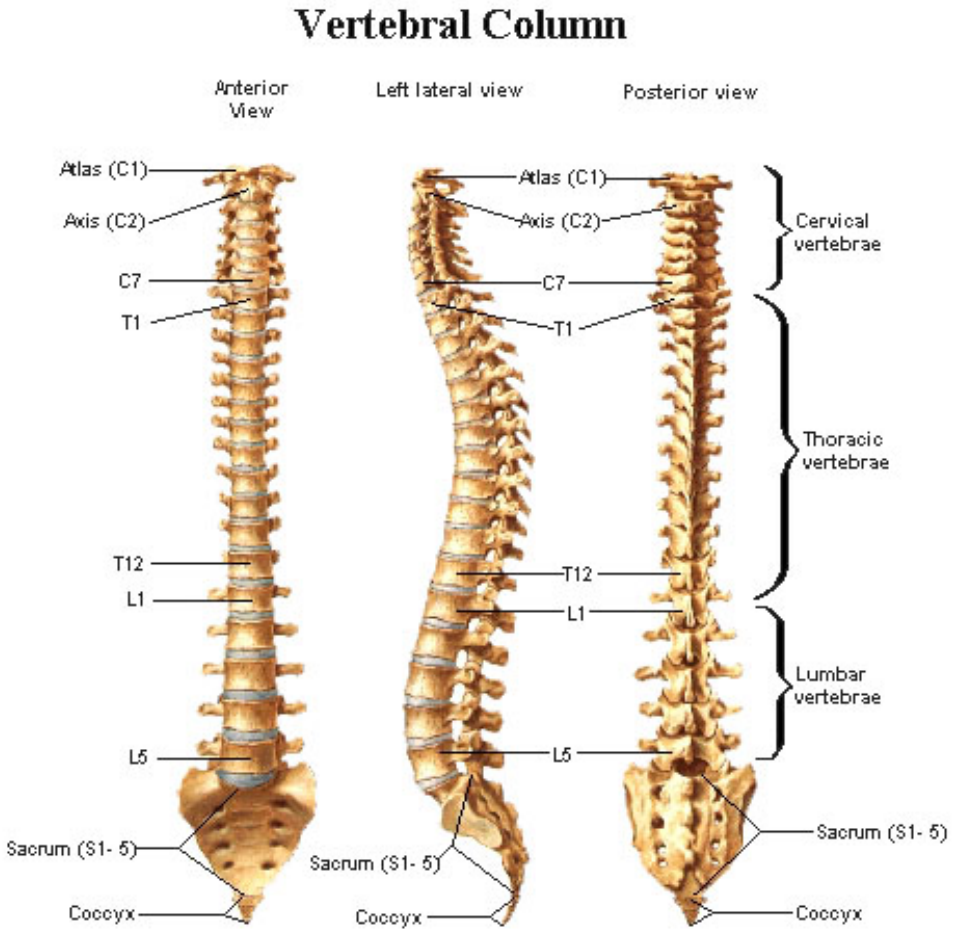
Oncologic Emergency

Malignant cord compression

MSCC : MECHANISMS



MSCC: LOCATIONS



Cervical	10%
Thoracic	70%
Lumbar	20%
Multiple	20%

Metastatic tumor mostly involves **vertebral column** especially **pedicle** > any other part of bony skeleton

MSCC : CLINICAL PRESENTATIONS

- **Back pain: first symptom**
  - Bone pain: intractable pain, night pain, awakening pain
  - Radicular pain, referred pain
  - Aggravate pain by cough, sneezing, recumbent position, Valsalva maneuver
  - Usually present for **weeks or months before** neurological symptom

****All new onset back pain should prompt an immediate assessment ****

MSCC : CLINICAL PRESENTATIONS

- **Neurological Symptoms**
  1) Quadriplegia (cervical), Paraplegia (thoracic)
  2) Sensory loss
     - Temperature, light touch, pain, pinprick sensation
     - Band-like paresthesia: ominous sign of epidural spinal-cord compression
  3) Autonomic dysfunction (upper lumbar)
     - Urinary retention, Constipation

Table 5. Clinical features of spinal cord and cauda equina compression

Clinical features	Spinal cord	Cauda equina
Motor strength	Symmetrical, spastic paralysis	Asymmetrical, flaccid paralysis
Reflexes	Increased or absent knee and ankle reflex, extensor plantar reflex	Decreased knee and ankle reflex, flexor plantar reflex or absent
Sensory loss	Symmetrical, anatomical level	Asymmetrical, saddle area
Sphincters	Distended bladder, late present	Distended bladder, spared often

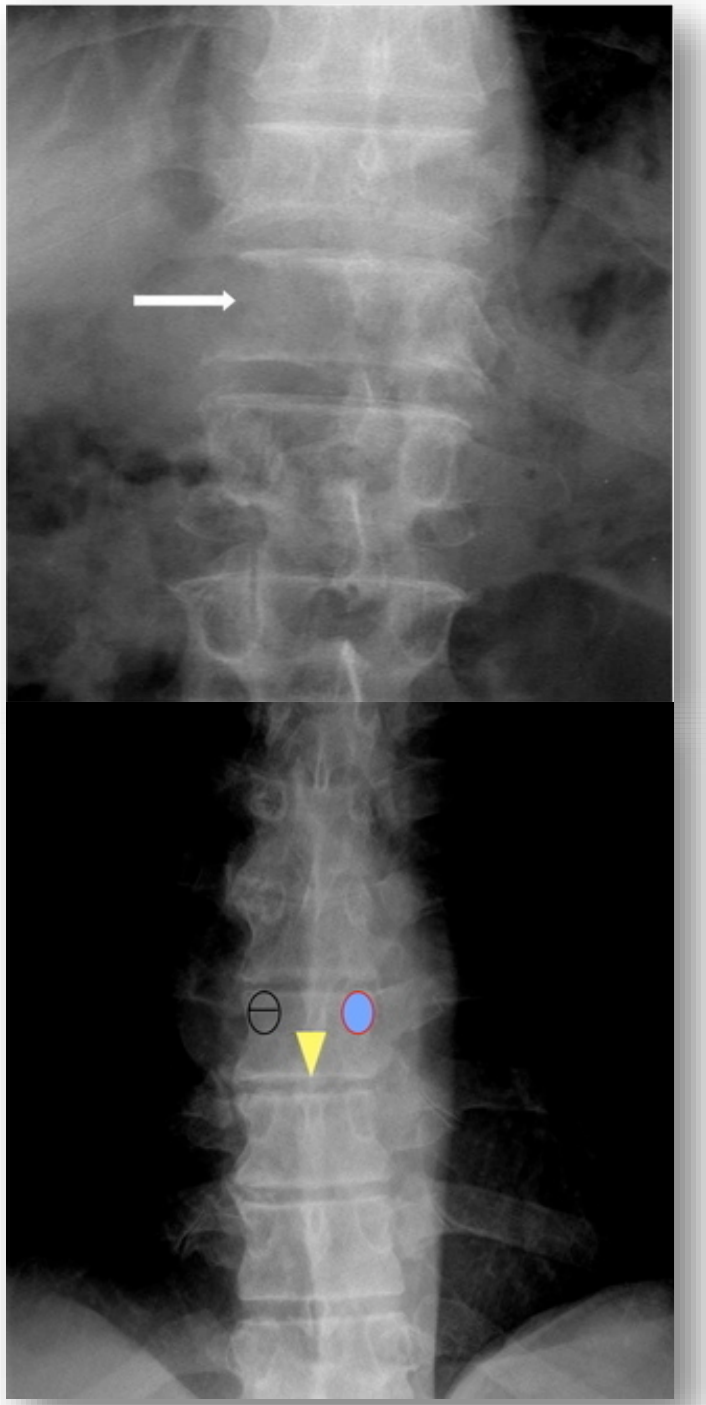
MSCC : Investigation

❑Plain film x-ray of spine

- Can perform immediately
- Low specificity: high false-negative rate (17%)
- Low sensitivity: Vertebral metastases

  are only visible when 50% of bone is lost
- Findings:

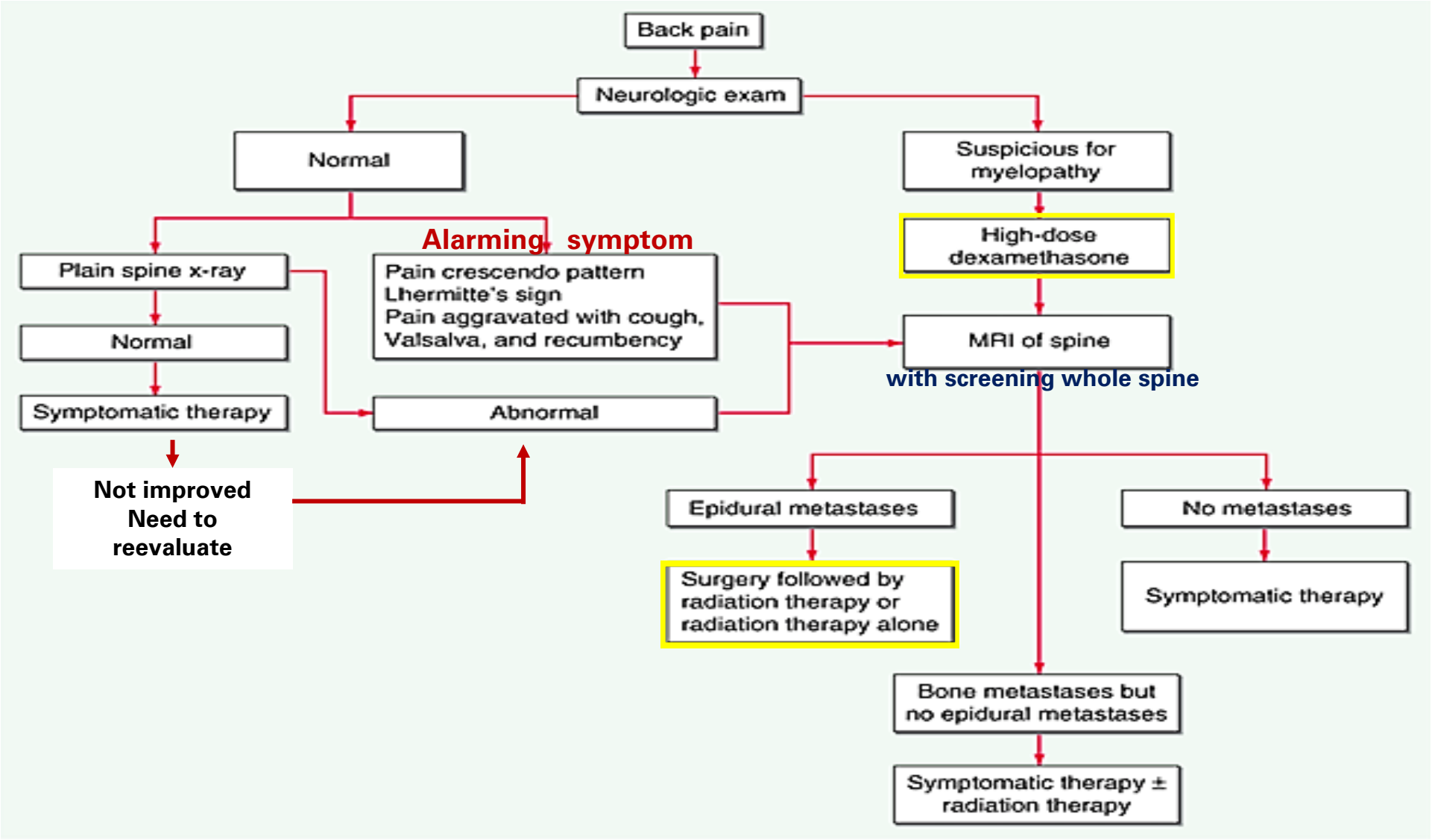
  - Erosion of the pedicles **("winking owl" sign)**
  - Collapse of vertebral body
  - Osteolytic or osteoblastic lesion



MSCC : Investigation

- **MRI spine**
  - Gold standard, Overall accuracy 95%
  - Recommend whole-spine MRI for known malignancy
    - Multiple levels ~20-30%
  - Within 1 week: suspected spinal metastases
  - Within 24 hours: suspected MSCC with neurological S&S
- **Myelography**
  - Diagnostic procedure of choice in the pre-MRI era
  - Reserved for who have poor MR images or contraindicated for MRI
- **Bone scan**
  - Most useful screening for bone metastases
  - Inadequate to evaluate spinal cord compression

Management of MSCC



MSCC : Surgery

Pros

- Correct spinal instability and bone fragment
- Immediate decompression
- Tissue diagnosis (unknown primary site and no other accessible tumor for biopsy)
- Radioresistant tumor or tumor progression during/previous radiation

Cons

- Post operative morbidity (20%) and mortality (5%)
- Long duration for rehabilitation and recovery (not suitable for short life expectancy)
- Take time for start palliative chemotherapy

MSCC : MANAGEMENTS

Disease factors

- Cause of cord compression (soft tissue or bone fragment)
- Number of lesion of cord compression
- Tumor type: radioresistant tumor (e.g. Melanoma, RCC)
- Extent of disease (other site of metastasis and tumor burden)
- Previous field of radiation
- Known primary site of cancer or unknown (other accessible site of tumor for biopsy)

Patient factors

- Motor function at presentation
- Duration of neurological deficit
- Co-morbidity
- Life expectancy (depend on tumor type and extent of disease also)

MSCC: key massage

- **MSCC is true oncologic emergency**
- **Key for diagnosis**: Early diagnosis
  - Back pain & no neurological deficit suspected spinal metastasis : should MRI spine within 1 week
  - Back pain with neurological deficit suspected MSCC : should MRI spine within 1 day
  - Should MRI at suspected lesion and screening whole spine

- **Goal of treatment**: Restoration/preservation of neurologic function (maintain good quality of life)
  - Initiate dexamethasone immediately when MSCC is suspected (not need to wait for MRI result)
  - Multidisciplinary team approach (Ortho, RT, Onco)
  - Selected patient who might have benefit from surgery

SVC syndrome

SVCS : Etiology

	Malignant causes (90%)	Benign causes (10%)
Extraluminal causes	• Mediastinal tumor: NHL, Germ cell tumor, Thymoma, Thymic carcinoma • Mediastinal LN metastasis: SCLC, NSCLC, etc.	• Substernal goiters • Aortic aneurysm • TB • Sarcoidosis • Etc.
Intraluminal causes	• Tumor invasion with clot formation	• Catheter induced thrombosis • Other thrombosis cause

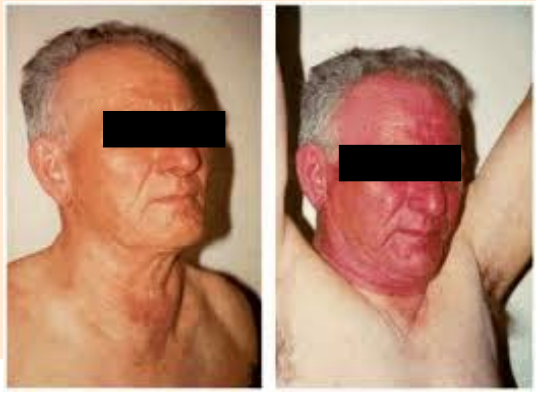
SVCS : Clinical Presentations

Symptoms

- Dyspnea,orthopnea,cough:
  lying down may aggravate the symptoms
- Face and neck swelling
  esp. periorbital
- Upper airway obstruction due to laryngeal edema
- Increase intracranial pressure: headache, vomiting, confusion, coma

Signs

- Facial and upper extremities edema
- Facial plethora
- Distention of neck vein and anterior chest wall vein
  (collateral vss >>> not acute)
- Cyanosis
- Stridor
- Pemberton sign



SVCS : Clinical Presentations

- **Usually develop within 2-3 weeks**

- **Severity depend on**
  - Degree of SVC narrowing
  - Speed of narrowing (collateral vessels)

- **Emergency conditions:**

  "True emergency"
  - Laryngeal edema: Stridor
  - Cerebral edema: confusion, obtundation
  - Cardiovascular collapse: syncope

Symptoms	Patients Affected (%)	Physical Findings	Patients Affected (%)
Dyspnea	63	Venous distention of neck	66
Facial swelling and head fullness	50	Venous distention of chest wall	54
Cough	24	Facial edema	46
Arm swelling	18	Cyanosis	20
Chest pain	15	Plethora of face	19
Dysphagia	9	Edema of arms	14

DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 9th ed. 2011.

SVCS : Diagnosis

- **Clinical diagnosis**

- **CXR PA and lateral**
  - Most have abnormal chest film
  - Most common abnormalities are widening mediastinal

- **CT chest with contrast**
  - Most useful
  - Confirm diagnosis
  - Identify etiology >>> external compression, thrombosis

SVCS : Management

❑ **Supportive treatment**

- Head elevation
- Avoid intravenous injection, procedure, measure blood pressure at upper extremities
- Oxygen support in case of hypoxemia
- No role of diuretics
- Role of steroid?

SVCS : Management

❑ **Specific treatment depend on**

- Emergency condition or not?
  - In case of true emergency condition: consider vascular stent
  - No emergency condition: need tissue diagnosis as soon as possible
- Chemosensitive tumor or not?

  Chemosensitive >>> CMT

  Chemo-nonsensitive >>> Radiation
- Staging of cancer

  E.g. SCLC limited stage >>> CCRT

  extensive stage >>> CMT (carboplatin+etoposide)
- Thrombolytic treatment if have evidence of thrombus

Management : SVCS

	Advantages	Disadvantages
Radiation	• Non-invasive • Treat underlying cancer	• May compromise tissue diagnosis if not yet obtained • May initially worsening symptom due to inflammation • Symptom relief 2-3 weeks
Chemotherapy	• Non-invasive • Treat underlying cancer (chemosensitive tumor: SCLC, lymphoma, Germ cell tumor)	• May compromise tissue diagnosis if not yet obtained • Patient may be too sick to tolerate chemotherapy • Systemic toxicity • Symptom relief 1-2 weeks
Vascular stent	• Rapid relief of symptoms within 24-72 hours: consider in emergency condition only • Does not compromise tissue diagnosis • Recurrent disease who have previously received systemic therapy or RT	• Invasive procedure • Does not treat underlying cancer • Bleeding complications • Increased risk for thrombosis due to foreign body

SVCS : key massage

- SVCS is clinical diagnosis

- True emergency condition:
  - Cardiovascular collapse (syncope)
  - Laryngeal edema (stridor)
  - Cerebral edema (alteration of conscious)

- If no true emergency condition
  >>> need tissue diagnosis before start treatment

- Specific treatment depend on stage and type of cancer
  >>> chemo-sensitive tumor or not

Hypercalcemia

Hypercalcemia of malignancy : Etiology

1. **Bone metastasis (Osteolytic lesion)**
    - Hypercalcemia, Hyperphosphatemia, high ALP
    - Bone pain, Osteolytic lesion from imaging
    - E.g. NSCLC, breast cancer, RCC, Multiple myeloma

2. **1,25-dihydroxyVitamin D related**
    - Hypercalcemia, Hyperphosphatemia
    - Associated hematologic malignancy e.g. lymphoma

Hypercalcemia of malignancy : Etiology

3. PTHrP related (PTH related peptide)

- Hypercalcemia, hypophosphatemia
- Associated with squamous cell carcinoma
  e.g. head and neck cancer

4. PTH related (Tumor secreting parathyroid hormone)

- High serum PTH level, Hypercalcemia, hypophosphatemia
- Ectopic secretion PTH from tumor (rare)
  e.g. small cell lung cancer, parathyroid carcinoma
- Beware syndrome associated with parathyroid hyperplasia or adenoma e.g. MEN1,2A syndrome

Hypercalcemia : Clinical Presentations

- Maybe misdiagnosis because of non-specific symptoms

- Suggest work up serum calcium in
  - Any tumor with osteolytic bone metastasis
  - Unexplained fatigue, N/V, abdominal pain, constipation, alteration of conscious, rising creatinine

- If diagnosis hypercalcemia >>>

  Don’t forget to do EKG (short QT interval < 300 ms)

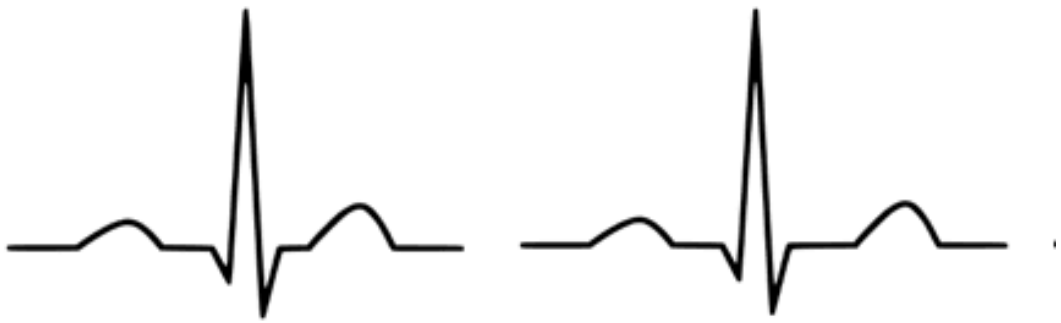
Hypercalcemia : Investigation

❑ All case

- Serum Calcium
  - ➢Corrected calcium = measured calcium + 0.8 x (4-albumin)
- Albumin
- BUN/Cr
- Electrolyte
- Phosphate
- ALP
- EKG 12 leads (severity)

❑ Selected case

- Serum iPTH
- Serum PTHrP
- 1, 25$(OH)_2$ D



Hypercalcemia : Diagnosis

- Symptomatic vs asymptomatic

- Severity grading
  - mild 11.0-12.0 mg/dl
  - Moderate 12.0-13.5 mg/dl
  - severe >13.5 mg/dl

- Known history of malignancy, staging, prognosis

- Etiology of hypercalcemia

Management of Hypercalcemia

	Mode of action	Onset	Duration	Indication	Advantage	Disadvantage
Saline 200-500 ml/h or 2-4 L/d or UO 200 ml/h	Enhances filtration and excretion of Ca	Hours	During infusion	Symptomatic or severe hyperCa	**Rehydration**	**Volume overload** **↓ Ca 1-3 mg/dl**
Furosemide 10-20 mg IV	Inhibit Ca resorption in distal tubule	Hours	During Rx	**Following adequate rehydration**	Rapid action	Dehydration, hypokalemia
Calcitonin 4-8 IU/kg SC or IM q 6-12 h D1-3	Inhibit bone resorption, augment Ca excretion	4 h	6-12 h	Symptomatic or severe hyperCa	**Rapid action** Minimal toxicity	**Tachyphylaxis** (limit use < 72 h) Vomiting, cramps, flushing
Dialysis Little or no Ca in dialysate	Diffuse passively along gradient	Hours	During Rx	Life-threatening, refractory to other Rx, renal failure	High potency	Invasive procedure

Management of Hypercalcemia

	Mode of action	Onset	Duration	Indication	Advantage	Disadvantage
Glucocorticoids Hydrocortisone 200 mg/d IV x3d Prednisone 60 mg/d x10 d	Inhibit vitamin D conversion to calcitriol	Days	2-4 wk	Hematologic malignancy, granulomatous disease, vit D intoxication	Anti-tumor effect	Adverse effect from Steroid
Bisphosphonates • Pamidronate 60-90 mg IV over 2-4 hr • Zoledronate 4 mg IV over 30 min	Inhibit osteoclast action & bone resorption	1-2 d	2-3 wk 3-4 wk	Hypercal of malignancy	High potency	Nephrotoxicity (dose adjust in renal impairment), osteonecrosis of jaw, flu-like symptom, hypoCa, hypoPO_4 Rebound ↑ Ca in hyperPTH Max effect at 72 h
Denosumab 60-120 mg SC (can repeat dose next 1 week)	Rank-ligand inhibitor Inhibit maturation of osteoclast	3 d	Weeks to month	Hypercal of malignancy, refractory to bisphos-phonate	Can use in renal impairment	Hypocalcemia, osteonecrosis of jaw

Hypercalcemia : key massage

❑ Beware misdiagnosis because of non-specific symptom

❑ Consider disease and patient factors to decide treatment or not?

❑ **Key for treatment**

- Adequate NSS IV hydration: need to monitor urine output
- **Consider bisphosphonate simultaneously with calcitonin in severe hypercalcemia if no contraindication**
- Don’t forget specific treatment of primary cancer

Febrile neutropenia

Definition of FNP

- **Fever:**
  - Single temperature equivalent to ≥ 38.3 °C orally
  - Equivalent to ≥ 38.0 °C orally over 1 hr period

- **Neutropenia**
  - ANC ≤ 500 /µl
  - ANC ≤ 1000/µl and a predicted decline to ≤ 500/µl over 48 hr

Initial evaluation : FNP

- **History**
  - Organ specific symptom
  - Previous CMT regimen
  - Date of last dose CMT
  - Prior neutropenia or febrile neutropenia
  - Received GCSF prophylaxis or not
  - Prior infections
  - Previous antibiotics
  - Comorbidity
  - Nutritional status
  - HIV status

- **Physical examination**
  - Vital signs (SIRs)
  - IV site, skin lesion
  - Sinus
  - Oral cavity
  - Lung
  - Abdomen
  - Perivaginal & perirectal

Initial evaluation : FNP

- **Laboratory/radiology assessment (routine)**
  - CBC with slide,BUN/Cr,Elyte,LFT
  - Hemo c/s x 2 sets (peripheral or catheter)
  - CXR
  - UA
  - Urine C/S (symptomatic, catheter, abnormal urinalysis)
  - Site specific
    - Diarrhea (*C. difficile*, enteropathogenic pathogens)
    - Skin lesions
    - Vascular access cutaneous site with inflammation (fungal/mycobacterium)
  - Viral culture
    - Vesicular/ulcerated lesions skin or mucosa
    - Throat or nasopharynx for RSV,FLU

Febrile neutropenia : Management

- **“Medical emergency”**
- Early recognize neutropenic fever
- **Initiate empiric antibacterial therapy immediately** after blood cultures have been obtained and before any other investigations have been completed
- Mortality rates up to 70% if initiation of antibiotics was delayed
- Optimal timing for empiric antibacterial therapy in neutropenic fever is not known
- Stabilize vital signs: IV hydration

Causative organisms

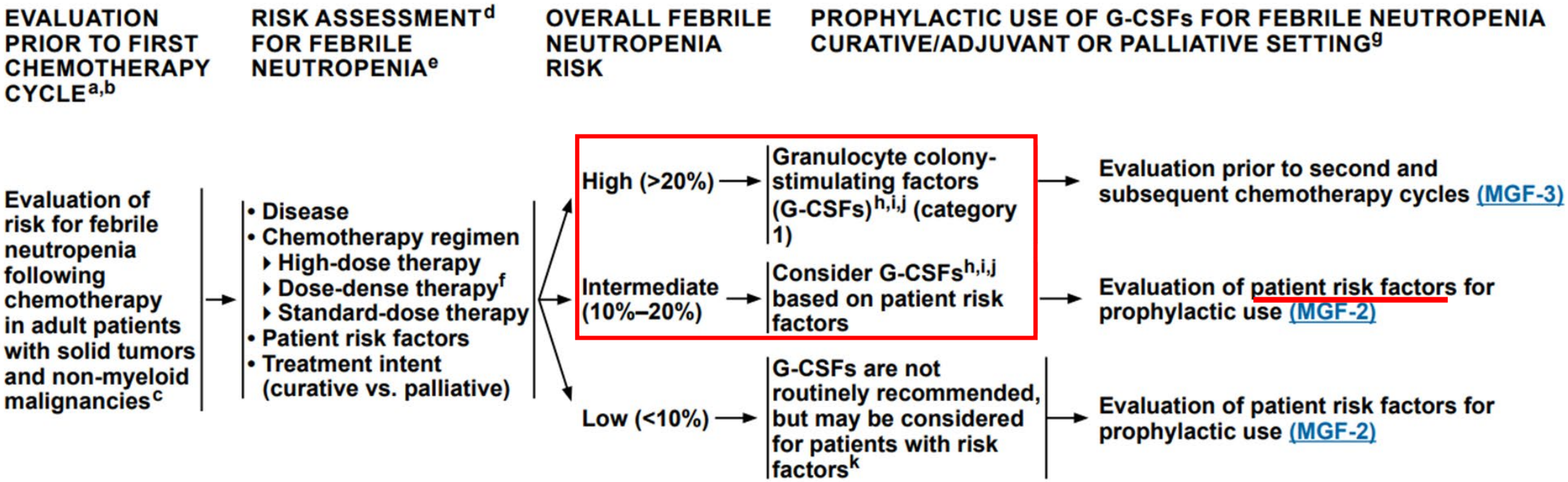
- **Gram negative bacteria** esp. Pseudomonas spp.
- **Gram positive bacteria**
  - S. aureus, S. epidermidis and Streptococcus species
  - Chemotherapy induced mucositis
  - Central venous catheterization
  - Cellulitis/ skin infection
  - Anti-gram-negative-bacterial prophylactic antibiotics
- **Candida albican, Non-candida albican**
  - Bone marrow transplantation
- **Fungus: Aspergillus, Fusarium, Trichosporon**
  - Prolonged neutropenia

Role of GCSF???

Indication of GCSF

1. Primary prophylaxis for febrile neutropenia (FNP)

- CMT regimen with high risk for FNP > 20%
- CMT regimen with intermediate risk for FNP 10- 20% + high risk patient



NCCN V3.2026

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NCCN Guidelines Version 3.2026
Hematopoietic Growth Factors

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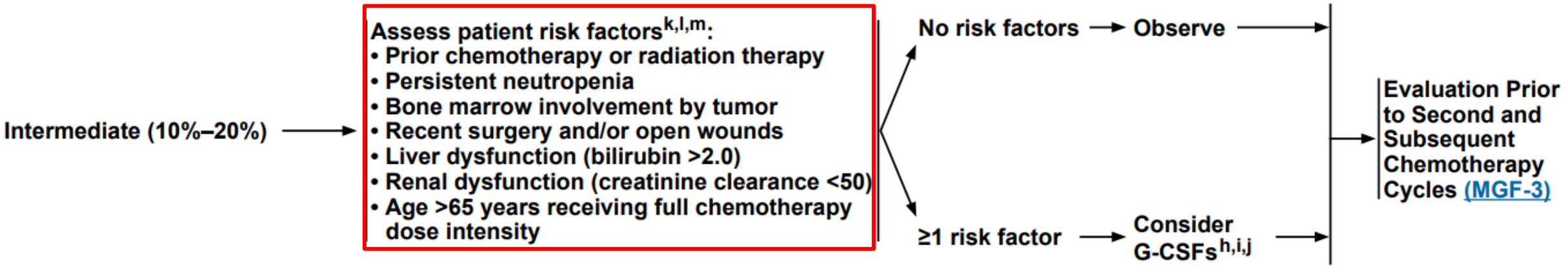


Indication of GCSF

2. Secondary prophylaxis for febrile neutropenia

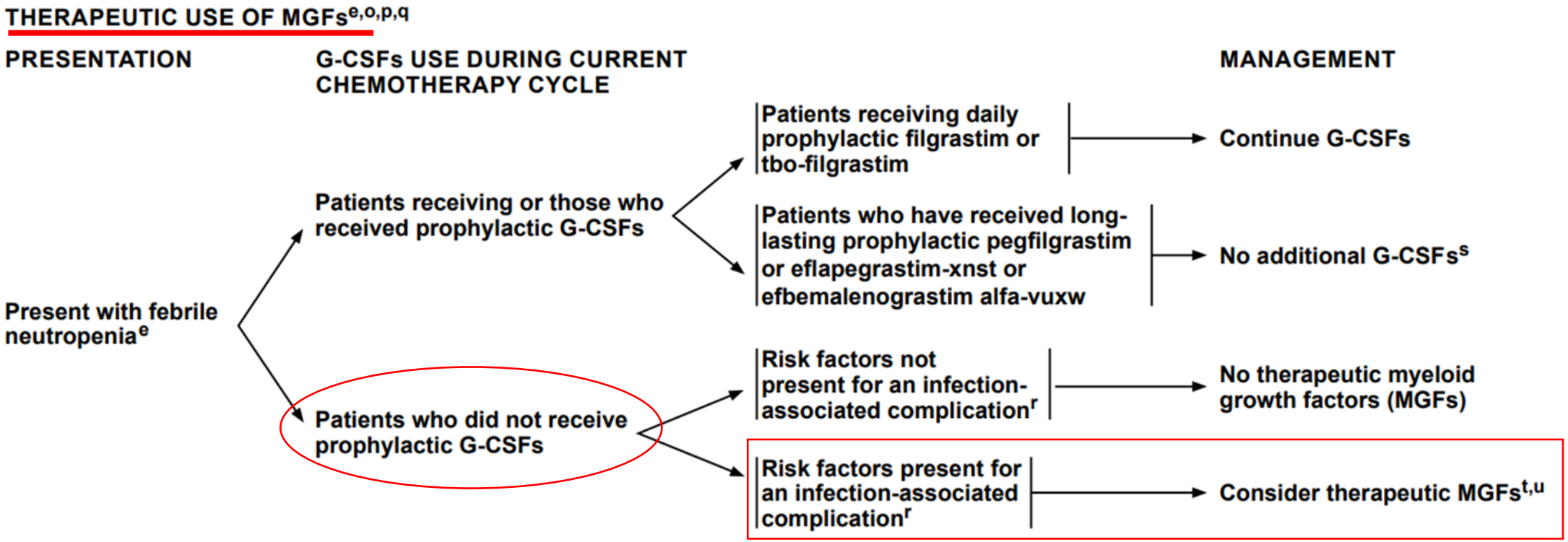
- Patients who have previous history of FNP or dose delay/limiting neutropenia event

Evaluation	FN or dose limiting neutropenia event	Prior use of GCSF	Secondary prophylaxis
▸ **Evaluate patient** prior to second and subsequent CMT cycles	**Yes**	**Yes**	▸ Consider CMT dose reduction or change in treatment regimen
		No	▸ Consider G-CSF
	No	-	▸ Repeat assessment after each subsequent cycle

Indication of GCSF

3. Therapeutic treatment in febrile neutropenia

: consider in patients who have risk factor for infection associated complication



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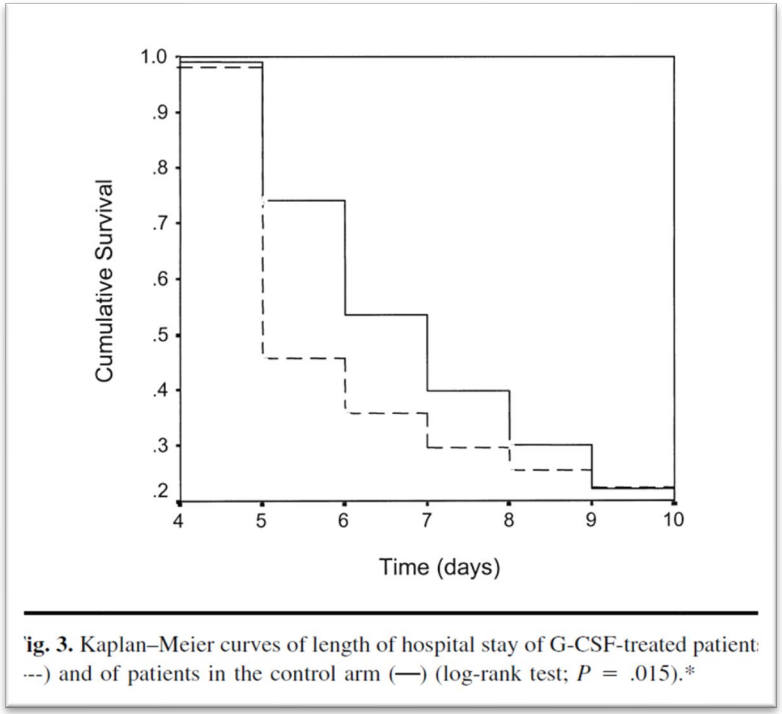
Risk factors for infection associated complication in FNP

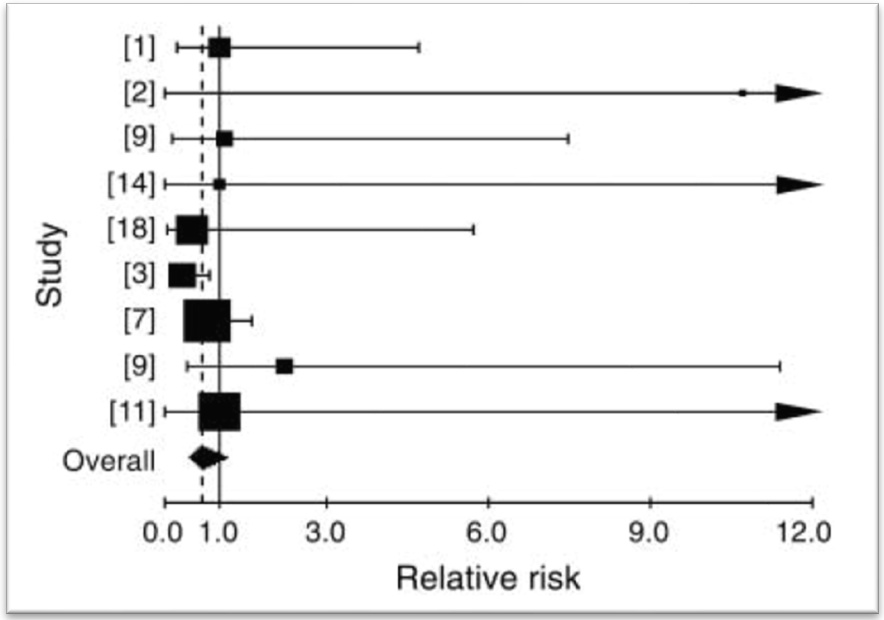
- Sepsis syndrome
- Age > 65 years
- ANC < 100 /mcL
- Neutropenia expected to be > 10 days in duration
- Pneumonia or other clinically documented infections
- Invasive fungal infection
- Hospitalization at the time of fever
- Prior episode of febrile neutropenia

Therapeutic Use of GCSFs

- RCTs: shorter duration of neutropenia,
  duration of fever, length of hospital stay
  - Grade IV neutropenia
    (median 2 vs 3 days; P = .0004)
  - Antibiotic therapy
    (median 5 vs 6 days; P = .013)
  - Hospital stay
    (median 5 vs 7 days; P = .015)
  - Median cost of hospital stay reduced by 17%
    (P = .01)
  - Median overall cost per patient admission reduced by 11% (P = .07)
- Meta-analyses: no survival benefit
  (RR 0.71; 95%CI 0.44-1.15)



ig. 3. Kaplan–Meier curves of length of hospital stay of G-CSF-treated patient
---) and of patients in the control arm (—) (log-rank test; $P = .015$).*



J Natl Cancer Inst. 2001 Jan;93(1):31-8. Support Care Cancer. 2002 Apr;10(3):181-8.

Febrile neutropenia: key massage

- ❑ Medical emergency

- ❑ Key for diagnosis: early recognize + patient education

- ❑ Key for treatment
- Initiate proper empiric antibiotic immediately
- Role of therapeutic GCFs in selected case (risk factor for infection associated complication)
- GCSF not reduce mortality rate from febrile neutropenia

GOOD LUCK :D