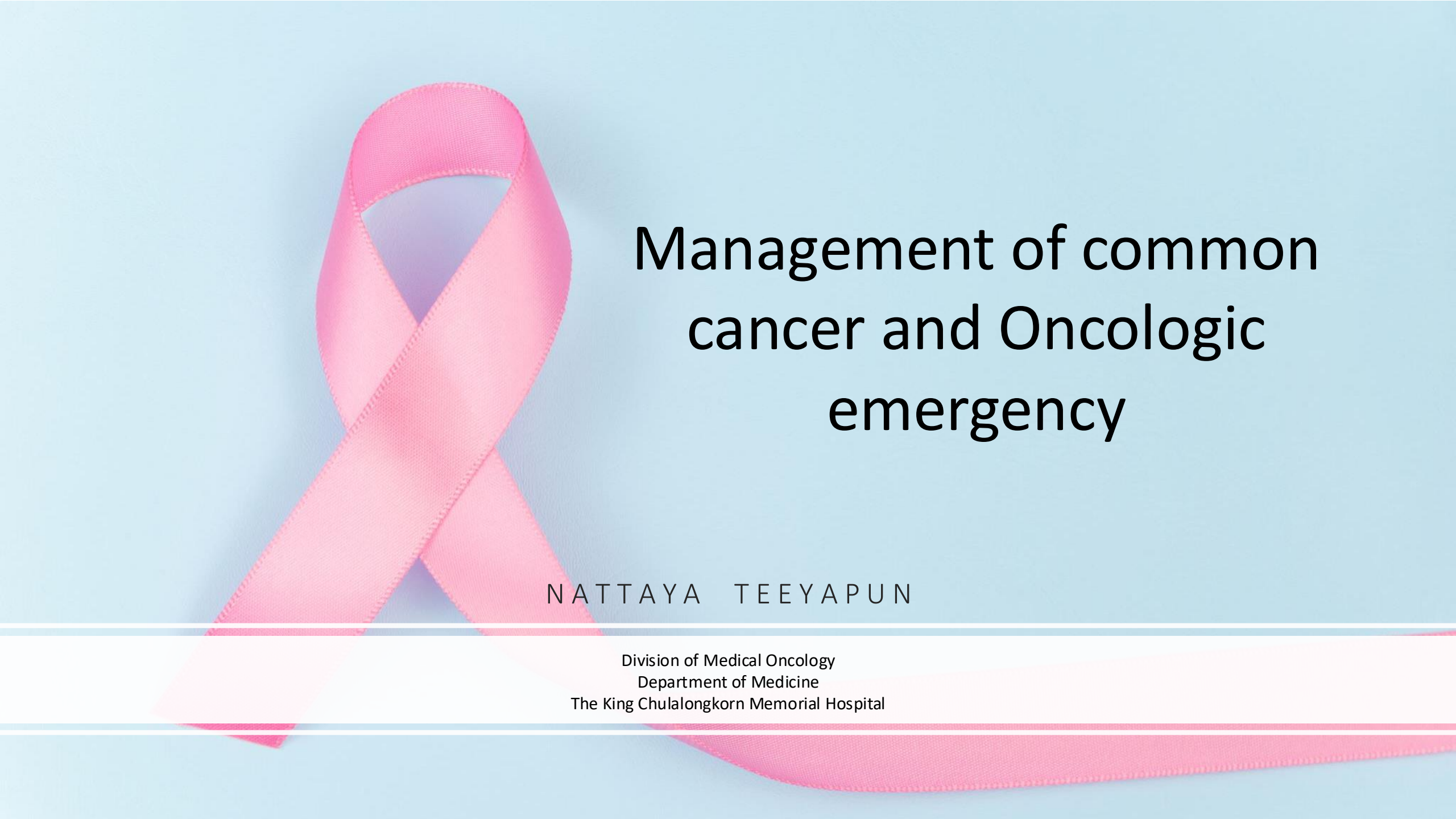

Management of common cancer and Oncologic emergency

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Long case examination

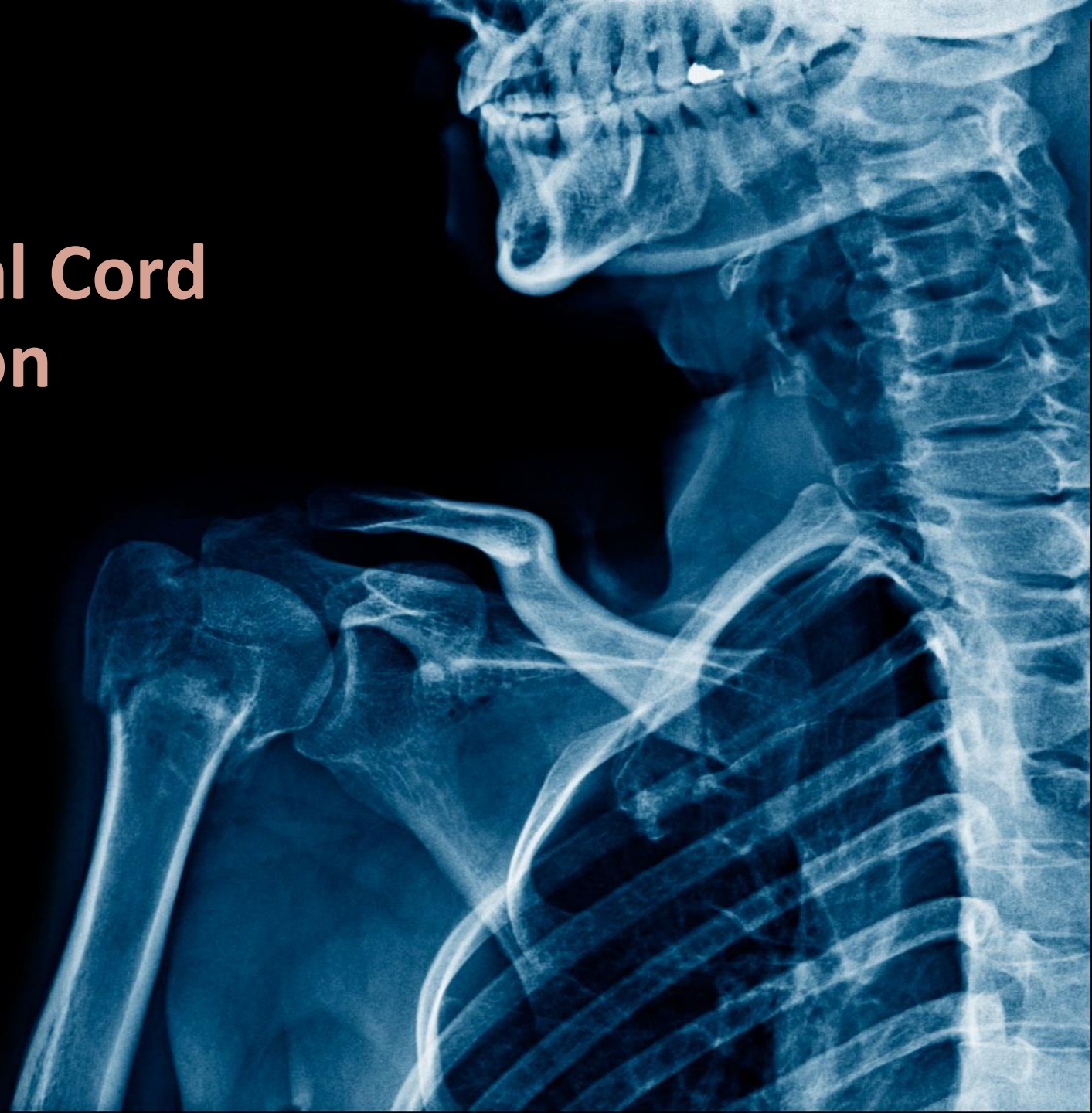
- Dyspnea
  - Malignant Pleural effusion
    - SVC sndrome
      - Ant mediastinal lesion
  - Malignant Pericardial effusion
  - Pulmonary embolism
- Neurologic symptom
  - Cord compression
    - Bone metastasis
  - Multiple cranial neuropathy
  - Mid brain syndrome
    - Primary CNS tumor
  - Headache
    - CNS metastasis
  - Alteration of conciousness
    - Hypercalcemia
  - Seizure
- Abdominal distension
  - Malignant ascites
- Gut obstruction
  - GI cancer / carcinomatosis peritoneii
- Hepatomegaly
  - Primary liver cancer
  - Liver met

Oncologic Emergency

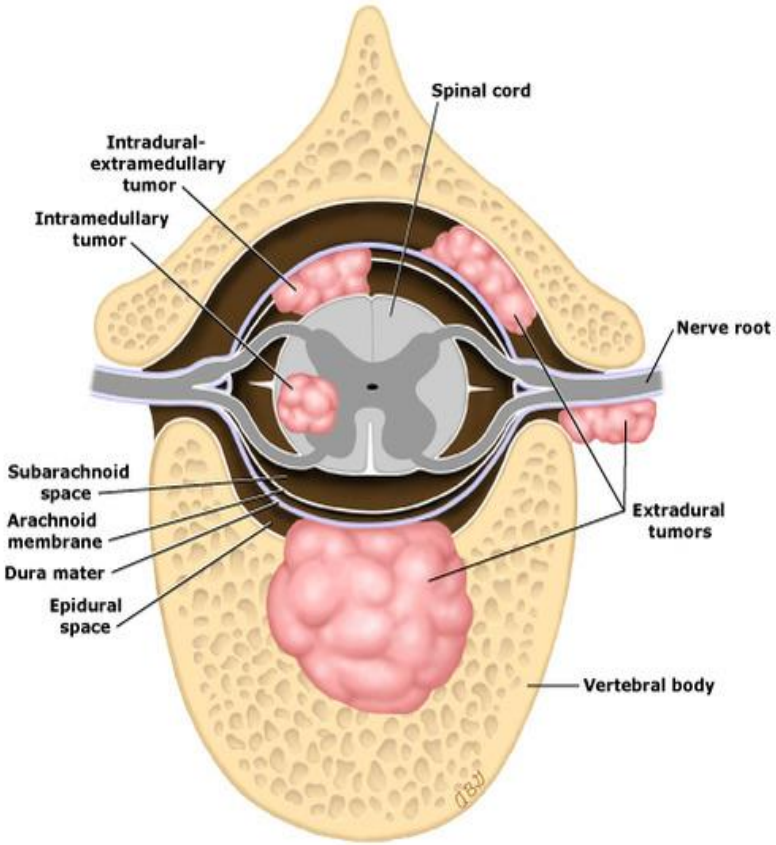
TOPICS

Structural-Obstructive Oncologic Emergencies	**Malignant Spinal Cord Compression (MSCC)** **CNS Metastases (Brain and leptomeningeal)** **Superior Vena Cava Syndrome (SVCS)**
Metabolic Emergencies	**Hypercalcemia of Malignancy**

Malignant Spinal Cord Compression (MSCC)



MSCC : MECHANISMS



Cancer cell from primary tumor

Hematogenous spreading

Metastasis to **intramedullary** (leptomeningeal involvement)

Metastasis to **bone** at spine

Soft tissue tumor invasion to epidural space

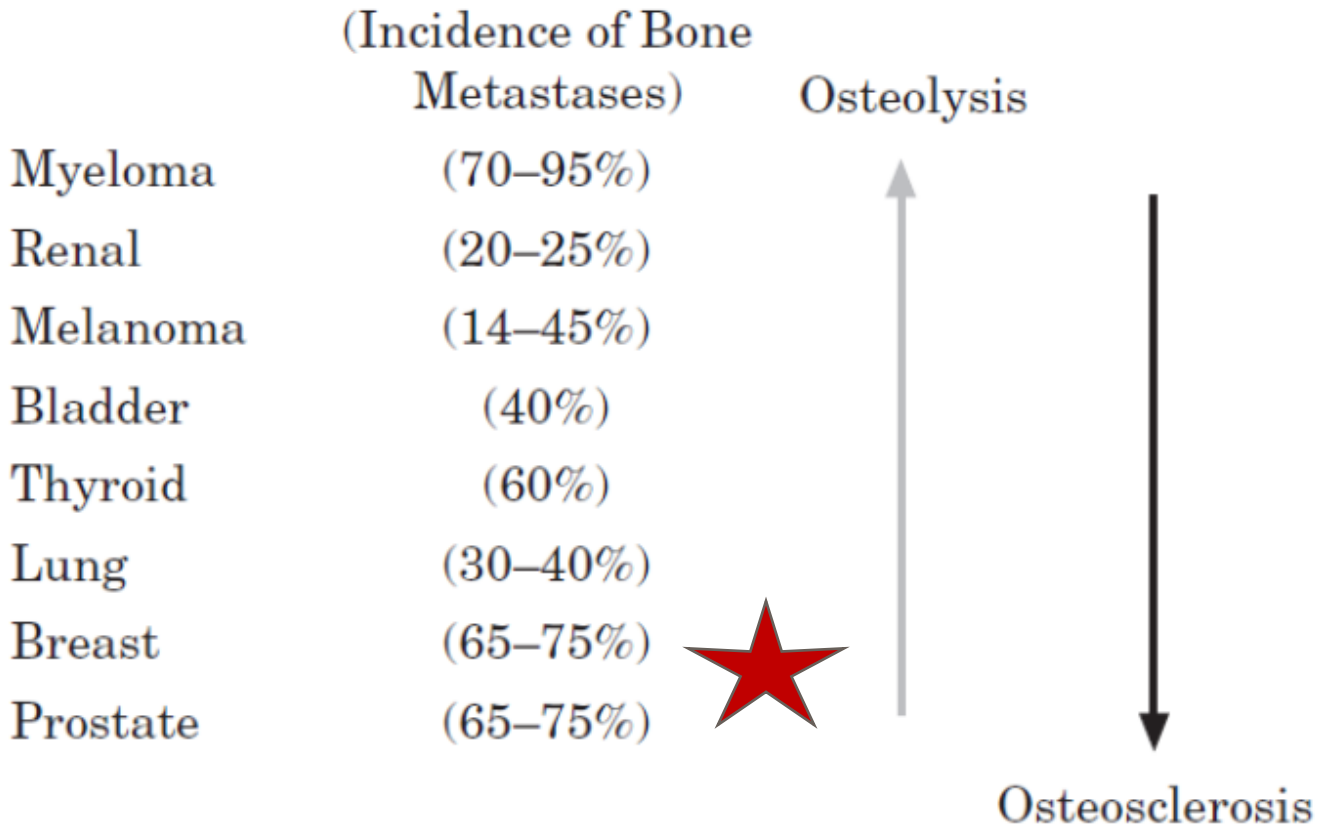
Pathologic **bone fracture**

Bone fragment compress spinal cord

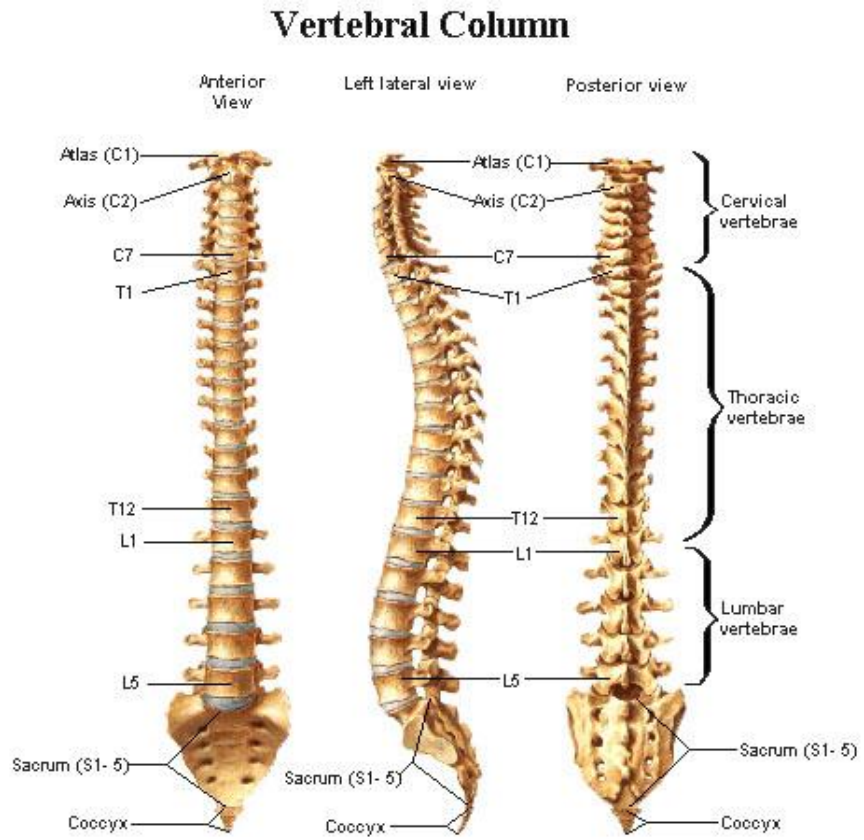
Direct invasion
e.g. locally advanced tumor at paraspinal region

MSCC : Etiologies

- Breast cancer 25%
- Lung cancer 20%
- Prostate cancer 15%
- Thyroid
- RCC
- Lymphoma
- Multiple myeloma
- Malignant melanoma



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, wakening pain
  - Radicular pain, referred pain
  - Cough, sneezing, recumbent position, valsava maneuver aggravate pain
  - Usually present for **weeks or months before** neurologic findings

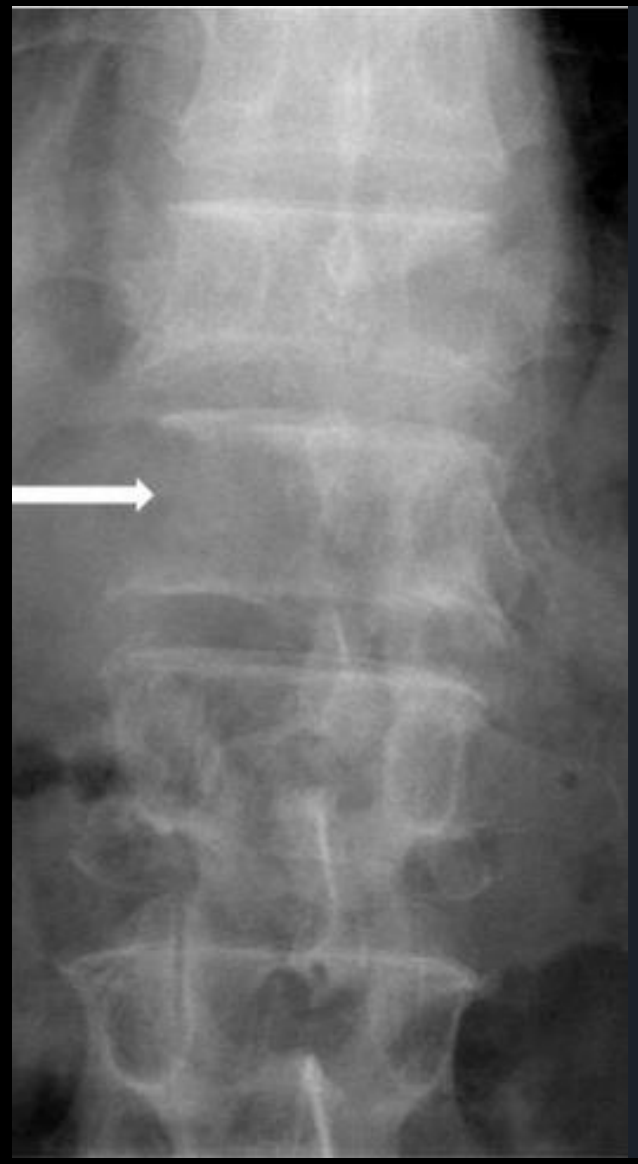
*** All reports of new onset back pain should prompt an immediate assessment ***

MSCC : CLINICAL PRESENTATIONS

- **Neurologic 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

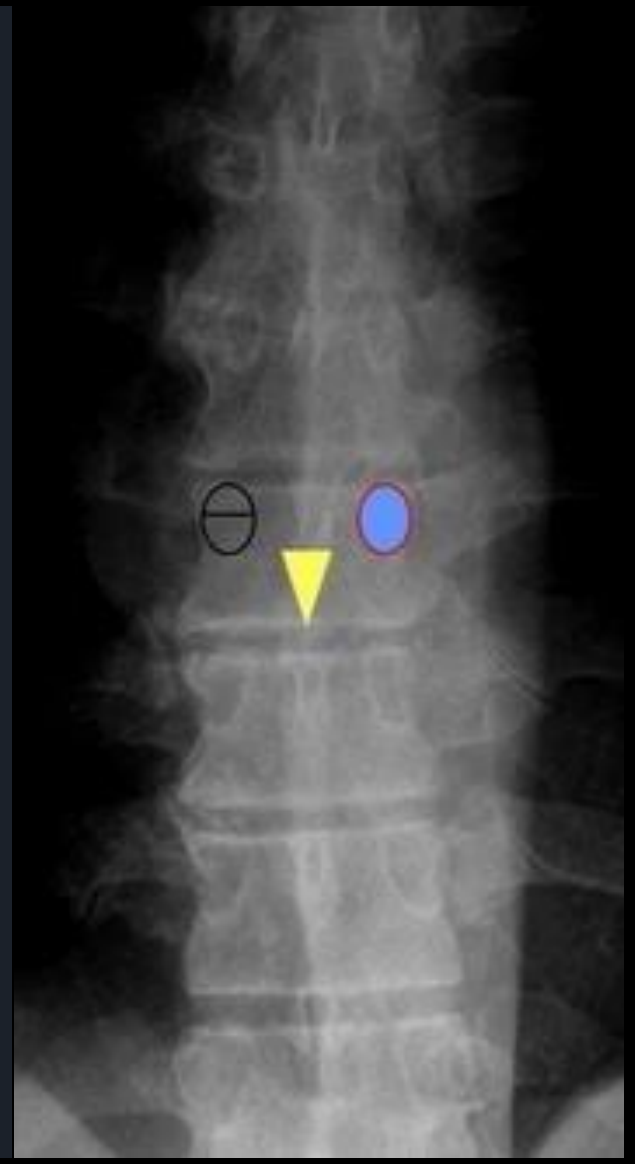
are only visible when 50% of bone is lost

- Findings:

- Erosion of the pedicles **("winking owl" sign)**

- Collapse of vertebral body

- Osteolytic or osteoblastic lesion



MSCC : Investigation

MRI spine

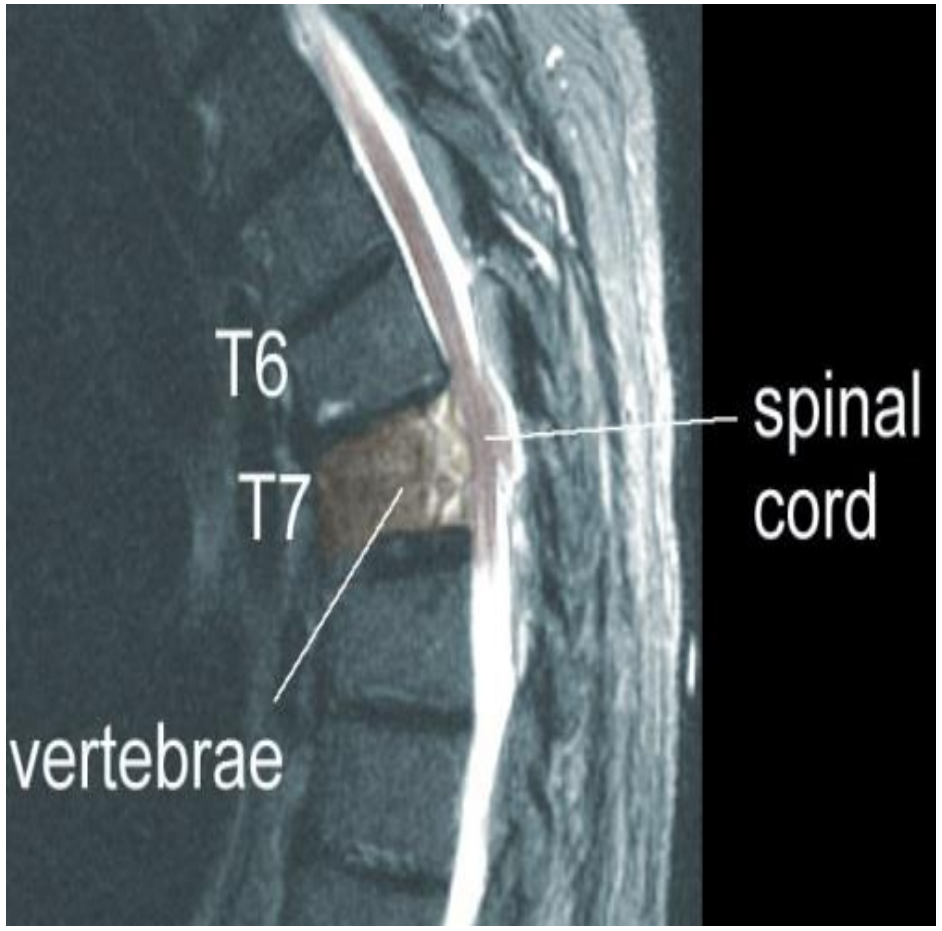
- Gold standard, Overall accuracy 95%
- Recommend whole-spine MRI for known malignancy
  - Multiple levels ~20-30%
- *Within 1 week: suspected spinal metastases*
- *Within 24 hours: suspected MSCC with neurological S&S*

Myelography

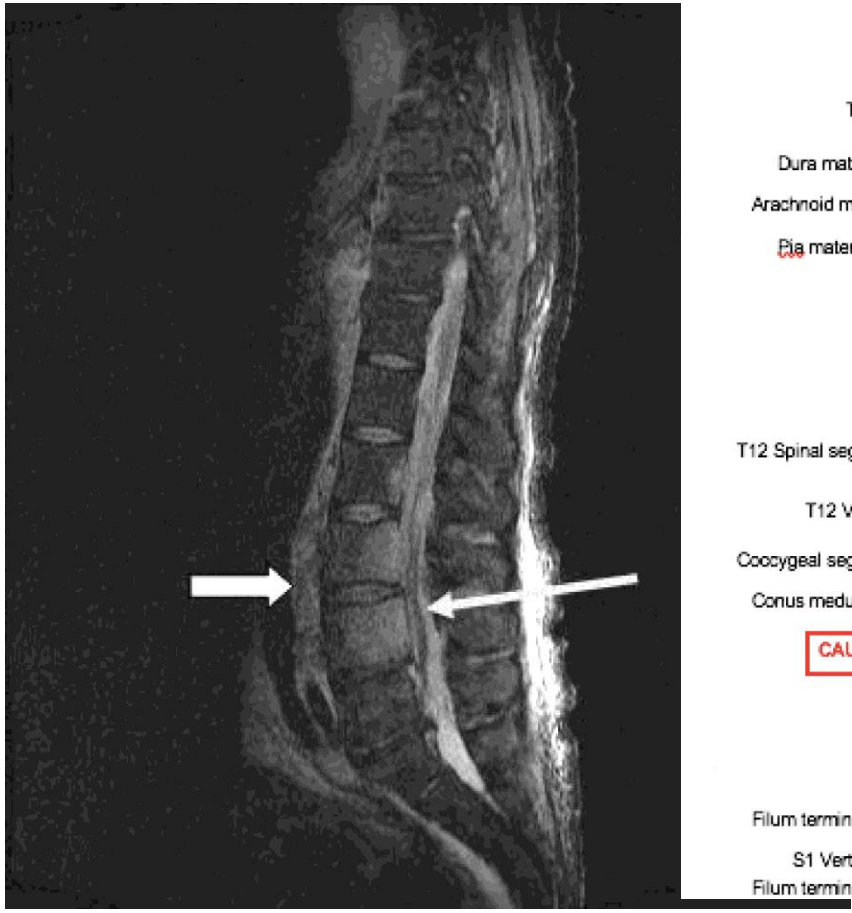
- Diagnostic procedure of choice in the pre-MRI era
- Reserved for who have poor MR images or contraindicated for MRI

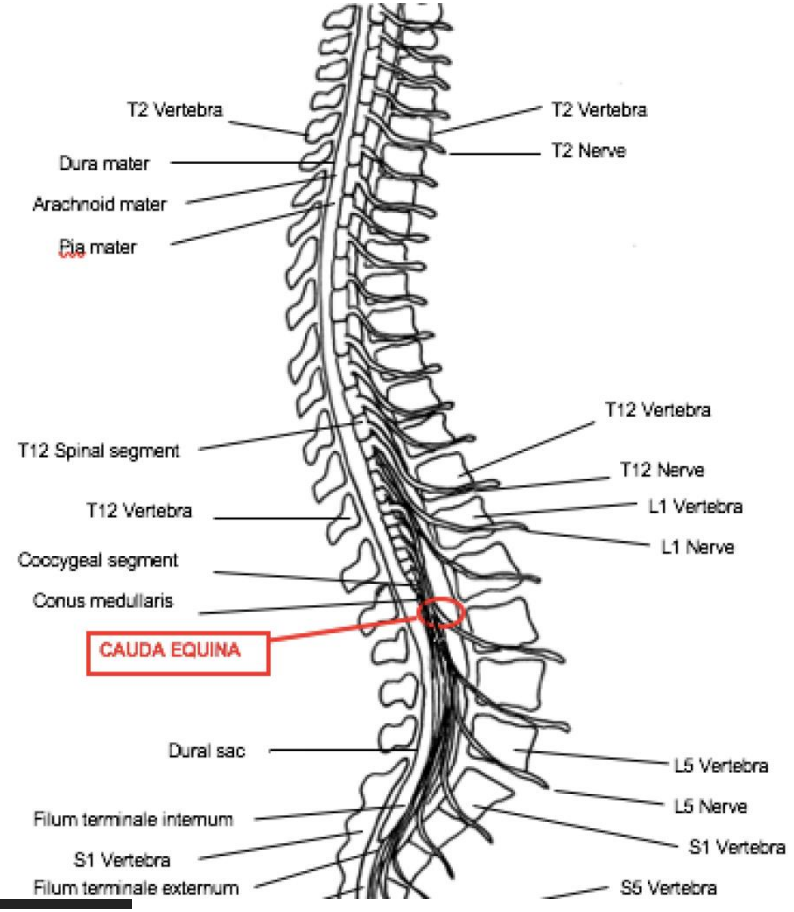
Bone scan

- Most useful screening for bone metastases
- Inadequate to evaluate spinal cord compression



Spinal cord compression





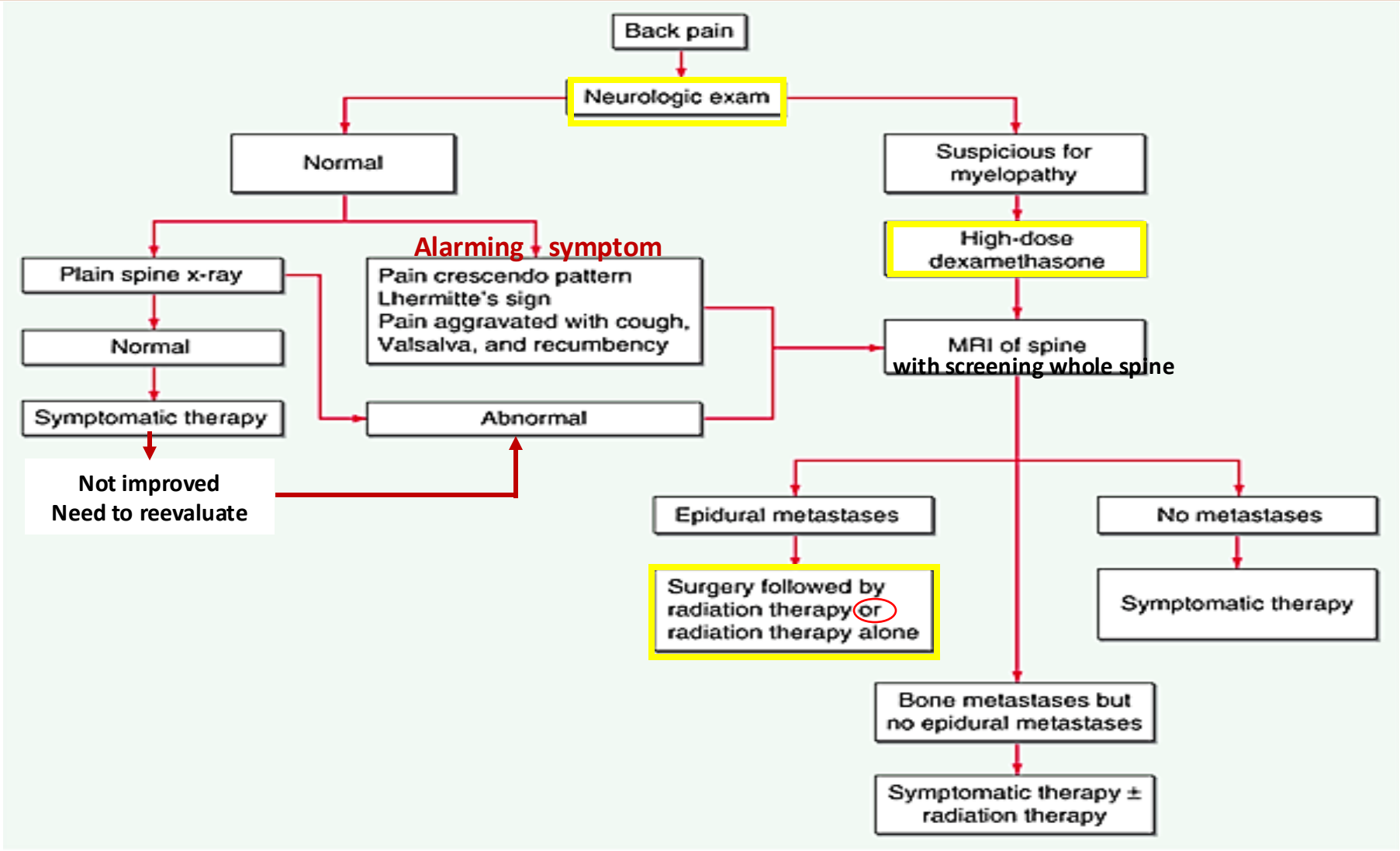
Cauda Equina Syndrome

MRI finding: Low signal intensity in T1 image and high signal intensity in T2 image

MSCC : MANAGEMENTS

- **True oncologic emergency**
- **Goal:**
  - Restoration/preservation of neurologic function
  - Relief of pain/ local tumor control/stabilization of spines
- **Prognosis:**
  - **Survival** depend on *tumor type and extent of disease*
  - Median OS with MSCC ranges from 3-16 months
    - Most die from systemic tumor progression
  - Functional outcome depend on *duration and severity of neurologic damage* at the time of treatment
    - Patients who are ambulatory before diagnosis: 75-100% remain ambulatory after therapy
    - Patients who develop paraplegia: only 15-30% are likely to regain useful function

Summary : Management



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

MSCC : MANAGEMENTS

- **Corticosteroids**
  - All patients with MSCC
  - Initiated immediately when MSCC is suspected
  - Reduce vasogenic cord edema and relief pain
  - What is the optimal dose?
    - Dexamethasone 10 mg IV bolus then 4 mg every 6 hours

Study	N	Maneuver	Dexa dose	Results
Sorensen et al. Small RCT	57	High dose dexamethasone vs. Nothing	96 mg IV bolus, 96 mg/d oral for 3 days the taper for 10 days	High-dose dexa significantly improves ambulation (81%v 63%), but higher adverse effects
Vecht et al. Small RCT	37	High dose vs. Low dose dexamethasone bolus	100 mg IV vs. 10 mg IV bolus, followed by 16 mg/d oral	There were no difference between high and low dose dexa on pain, ambulation
Heimdal et al. Case control	28	High dose vs. Low dose dexamethasone maintenance	96 mg/d vs. 16 mg/d	High dose dexa significantly increase serious adverse effects (14% v 0%)

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 RT

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: 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

CNS Metastasis

- **Brain (parenchyma) metastasis**
- **Leptomeningeal metastasis**

CNS metastasis : Clinical Features

- **Headache**
  - Severe, resistant to common analgesic
  - Maximum intensity upon awakening in the morning
  - Associated with increased intracranial pressure
- **Weakness**
- **Seizure**
- **Somnolence→ coma**

PE

- Papilledema :
  - Absence of venous pulsation is early sign
- Focal neurological deficit
- Meningeal irritation signs
- Assessment severity: consciousness, pupils, breathing pattern

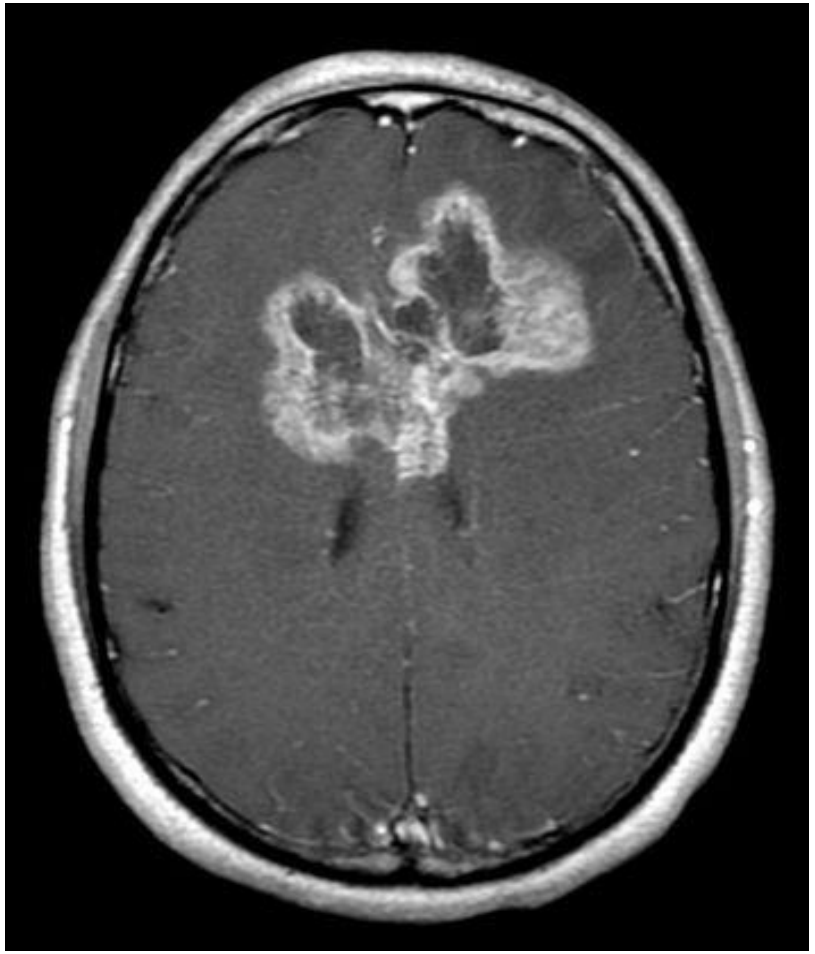
CNS metastasis : Diagnosis

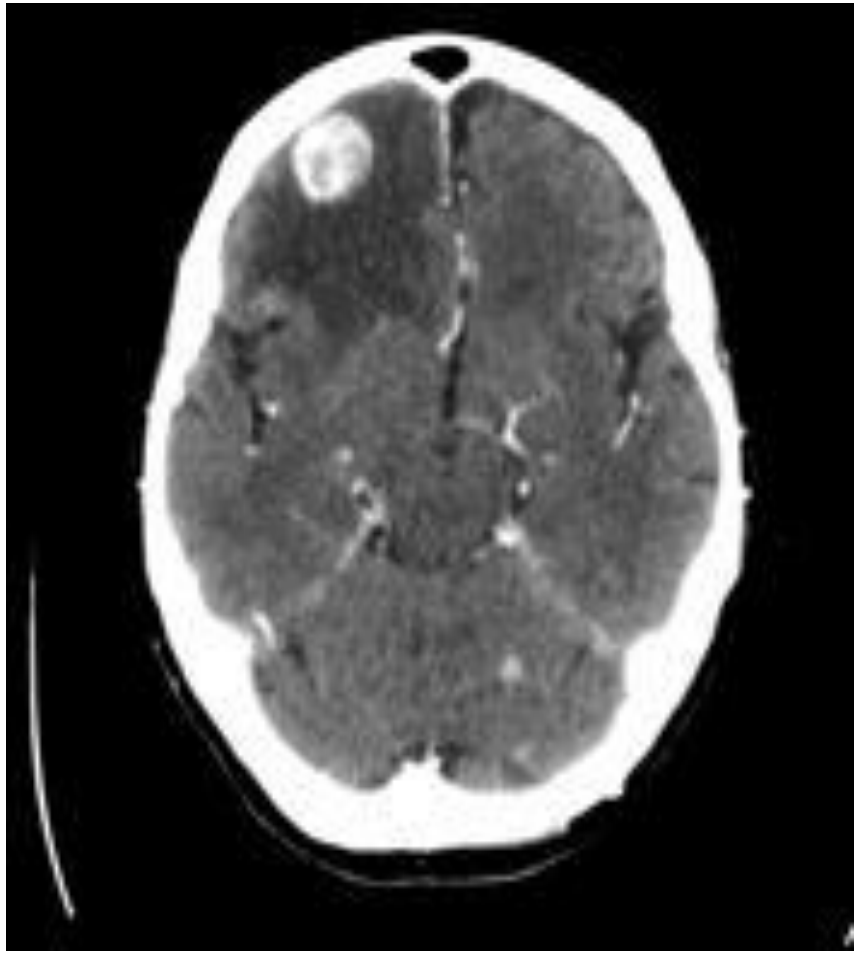
- **MRI brain**:
  - Imaging of choice
  - Higher sensitivity
  - More specificity
  - Better to evaluate posterior cranial fossa and leptomeninges
- **CT brain with contrast**
- **CSF analysis (cytology)**
  - Suspected leptomeningeal metastasis
  - Beware contraindication for lumbar puncture
  - High protein, Low sugar
- **CSF flow study**
  - Have evidence of leptomeningeal metastasis already
  - Evaluate CSF flow blockage before intrathecal CMT

Brain (parenchyma) metastasis

- Location : cerebrum > cerebellum > brain stem
- Median survival : 1-2 mo (untreated)
- Prognosis
  - Performance status
  - Extracranial metastasis
  - Primary tumor
- Common CA : lung CA (Adenocarcinoma, Small cell carcinoma), breast CA, melanoma, RCC
- Mechanisms : hematogenous spreading

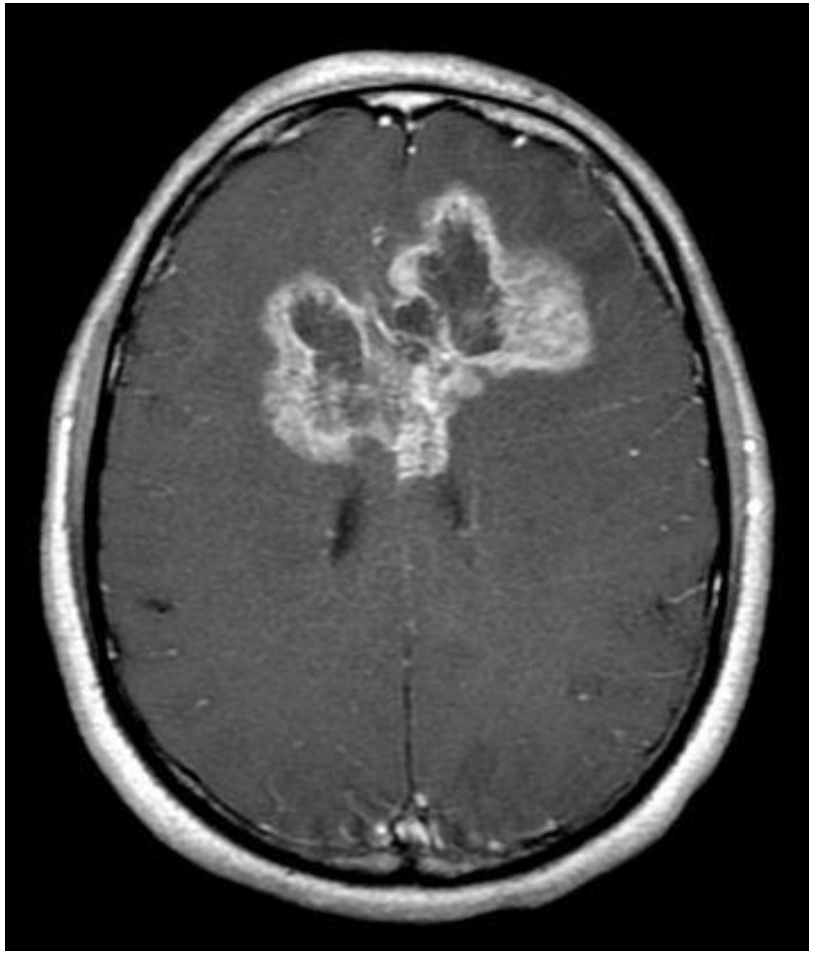
Brain tumor : Diagnosis



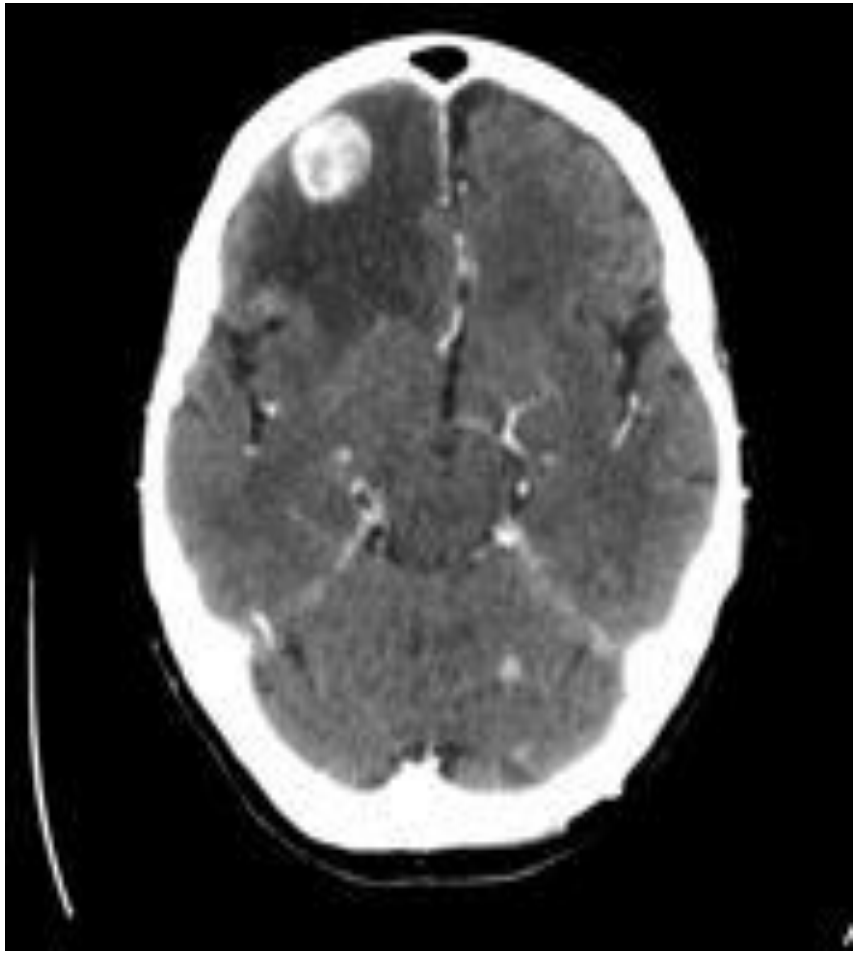


Brain tumor : Diagnosis

Primary brain tumor



Brain metastasis



Brain tumor : Diagnosis

❑ **Primary brain tumor vs brain metastasis?**

- Number of lesion
- Location:

  white matter vs gray white junction vs periventricular
- Cross midline via corpus collosum
- Perilesional edema
- Circumscribe and border:

  infiltrative, ill-defined vs well-circumscribe
- Necrosis or bleeding
- Known primary site of cancer

Brain metastasis : Management

- **Evaluate emergency condition**

  >>> consult neurosx for craniotomy release pressure
  - Brain Herniation
  - Hydrocephalic attack from obstructive hydrocephalus
- **Head elevation**
- **Isotonic saline for intravenous hydration**
- Corticosteroid
  - Dexamethasone 10 mg IV stat then 5 mg IV q 6 hr
  - Effective agent for increased ICP from vasogenic edema
- Anti-epileptic drug if have evidence of seizure

Brain metastasis : Management

Options of treatment
Craniotomy with tumor removal then PORT
(SRS or WBRT)
WBRT
SBRT
SBRT + WBRT
Systemic treatment e.g. EGFR TKI, ALK inhibitor
Individualize depends on disease, patient and
treatment factors

Leptomeningeal carcinomatosis diagnosis

LM : Diagnosis

- **CSF cytology : malignant cell in CSF**
  - Gold standard
  - False negative10-15%
  - To minimise false-negative CSF cytology
    large sampling volumes (>10 ml)
    prompt processing
    repeating CSF cytology is recommended
  - Don't forget to measure opened and closed pressure and send other profile:
    cell count, cell diff, protein-elevated, glucose-low,
    tumor marker in GCT (BHCG,AFP)

*****Beware contraindication for LP e.g. bulky intracranial mass*****

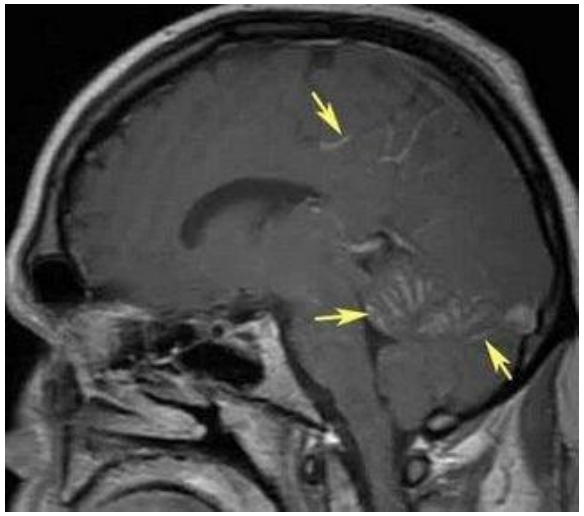
LM : Diagnosis

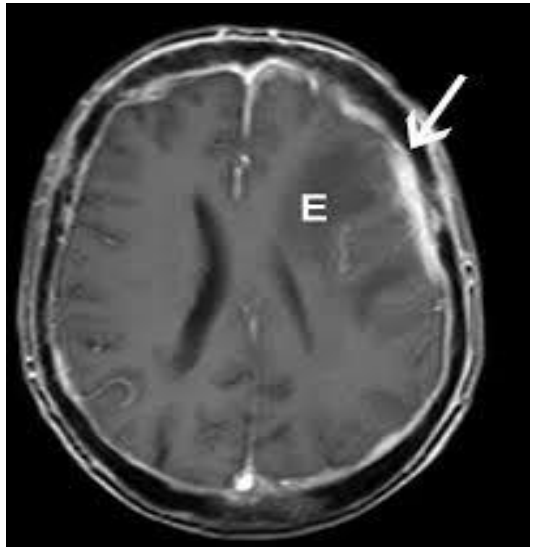
- **MRI brain and spine with Gd enhancement**
  - MRI can show the meningeal uptake of contrast medium in 40–60% of patients

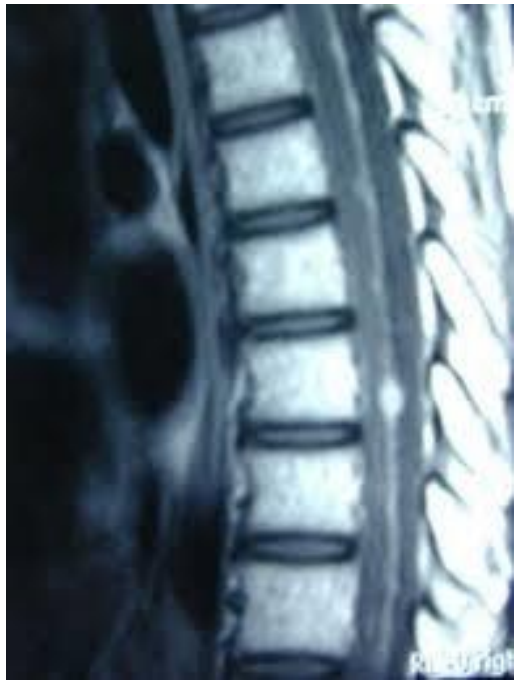
- CT brain with contrast : sensitivity only 30%

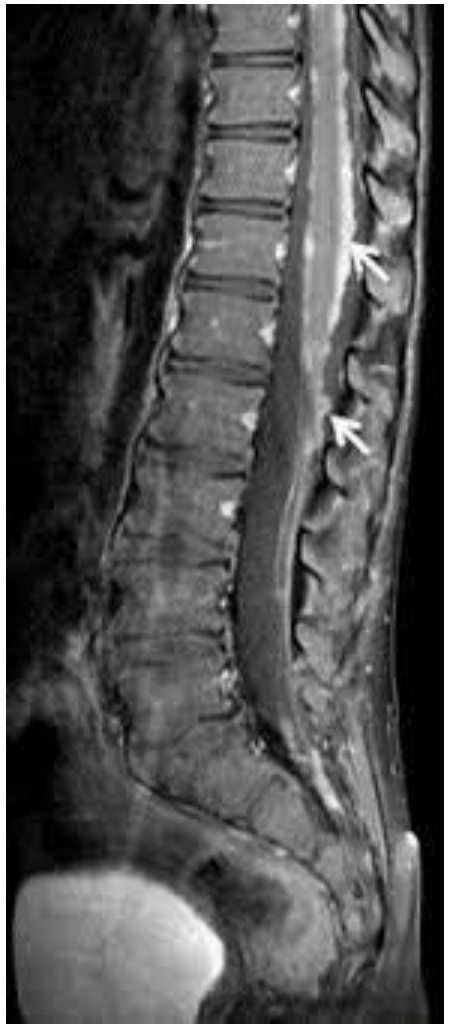
- Radioisotope CSF-flow studies :
  - not useful for diagnosis
  - can be used to establish the patency of CSF pathways before giving intrathecal chemotherapy

Imaging : MRI Brain/Spine









Leptomeningeal carcinomatosis treatment

LM : Treatment

❑ **Identify risk of patient: good vs poor risk**

- Performance status
- Neurological deficit
- Extension of CNS disease
- Systemic disease of primary cancer
- Effective systemic treatment option for primary cancer

LM : Symptomatic treatment

- **Lumbar puncture for release CSF**
  - Aim: reduce intracranial pressure to reduce symptom

  >>> release CSF to normal pressure

- **Surgery**
  - VP shunt for release intracranial pressure
  - Ventricular reservoir placement e.g. Ommaya reservoir

LM : Specific treatment

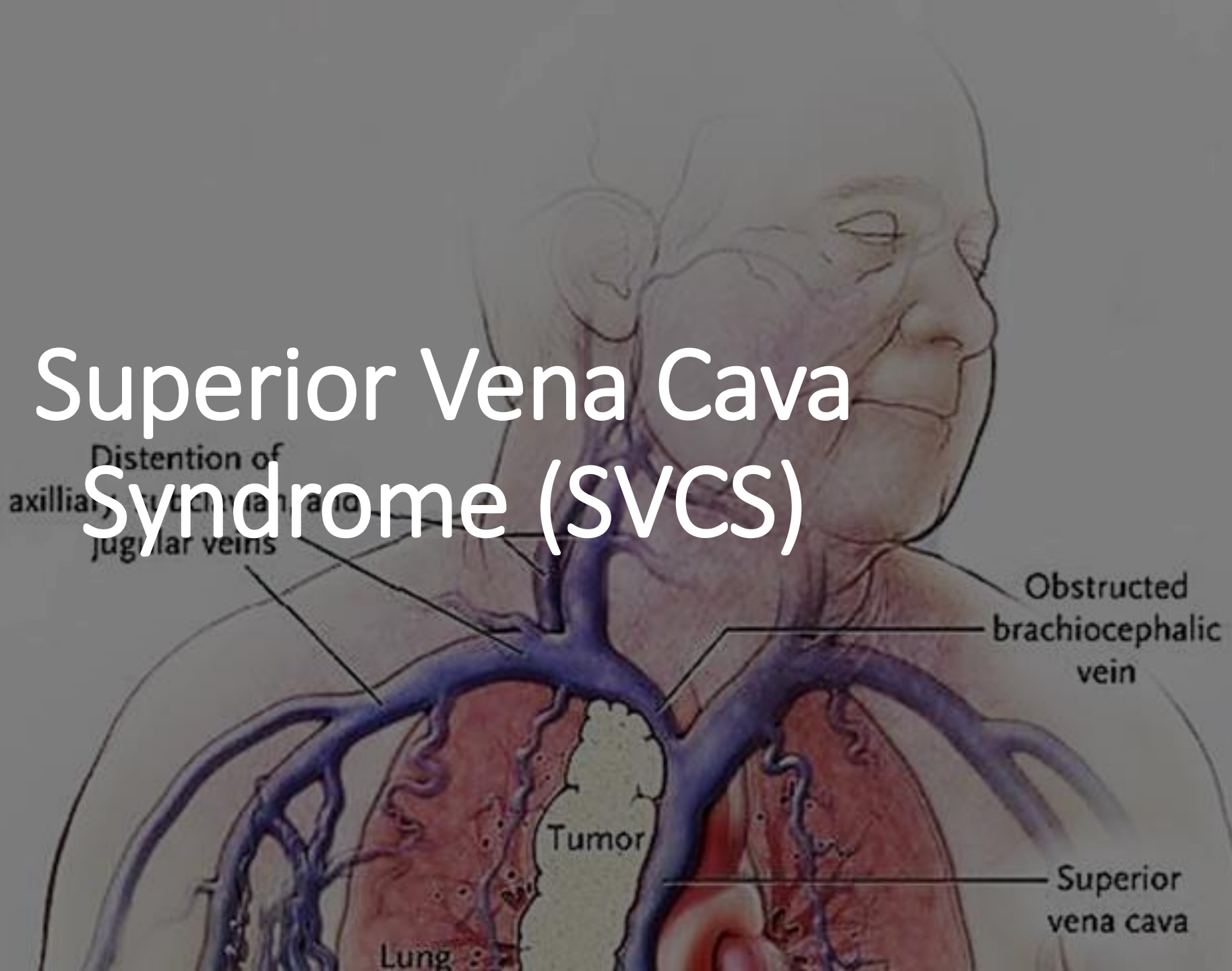
- **Radiation**
  - **bulky lesion**, CSF blockage from CSF flow scan

- **Intrathecal chemotherapy**
  - intrathecal methotrexate in breast cancer
  - can't concurrent with RT >>> increase risk leukoencephalopathy

- **Systemic treatment** e.g. EGFR TKI, ALK inhibitor

** Primary aim of treatment is to stabilize or improve neurological status**

Superior Vena Cava Syndrome (SVCS)



SVCS : Etiology

	Malignant causes (90%)	Benign causes (10%)
Extraluminal causes	• Mediastinal tumor: NHL12% ,GCT 3% Thymoma+ Thymic carcinoma 2%, • Mediastinal LN metastasis: SCLC 25 %,NSCLC 50%,etc.	• Substernal goiters • Aortic aneurysm • TB • Sarcoidosis • Etc.
Intraluminal causes	• Tumor invasion with clot formation	• Catheter induced thrombosis • Other thrombosis cause

Radiologic and pathologic correlation of anterior mediastinal lesions

Table 1 Prevascular mediastinal lesions

Lesion type	Clinical and laboratory findings	Imaging findings	Histopathology features
Thymic epithelial neoplasms			
Thymoma	(I) 40–60 years. (II) Equal gender predilection (3). (III) Association with autoimmune and paraneoplastic syndromes. (IV) Myasthenia gravis (MG) in 30–50%; 10–15% with MG have thymoma (4)	(I) CT: often unilateral smooth, encapsulated soft tissue density lesion, however may be cystic; calcification, necrosis, and irregular margins more common in non-encapsulated, invasive thymomas. (II) MRI: useful to discern or exclude soft tissue in cystic thymomas or high attenuation thymic cysts, respectively. (III) Nuclear medicine: may lack or demonstrate FDG-avidity on PET/CT	Dual population of cells: thymic epithelial cells (keratin positive by immunohistochemistry, IHC) and immature thymic lymphocytes (TdT positive by IHC)
Thymic carcinoma	(I) 6th decade. (II) Slight male predilection. (III) Up to 50% have distant metastases at diagnosis (3)	(I) CT: more likely to demonstrate invasive features, lymphadenopathy, pleural/pericardial effusions, and distant metastases. (II) MRI: both T1 and T2 hyperintense relative to muscle, however calcification, hemorrhage, cystic change or necrosis may cause signal heterogeneity	Histological features are similar to carcinomas of other organs. Most thymic carcinoma cells are positive for CD5 and CD117 by IHC
Thymic neuroendocrine tumor	(I) 3:1 male to female predilection (5). (II) Half functionally active, most often associated with endocrinopathies such as Cushing syndrome due to ectopic ACTH; association with multiple neuroendocrine neoplasia (MEN) type 1 (5,6). (III) 50–75% may have regional or distant metastases (3)	(I) CT: commonly large and infiltrative (7); calcification in up to 30% (3); avid enhancement of non-necrotic areas. (II) MRI: similar T1 and T2 signal characteristics in comparison to thymoma, iso- to hyperintense on T1 and hyperintense on T2 (7). (III) Nuclear medicine: uptake on somatostatin-receptor imaging such as Indium-111 Octreoscan and Gallium-68 Dotatate PET/CT, however not specific as thymoma and thymic carcinoma may also demonstrate uptake	Plasmacytoid cells with “salt and pepper” chromatin pattern. Cytoplasm can be granular. Positive for neuroendocrine markers (chromogranin, synaptophysin and CD56)

Lymphoproliferative			
Hodgkin lymphoma	(I) Most common 2nd–4th decades. (II) Female predilection. (III) Arises from thymus and/or lymph nodes	(I) CT: large mass in thymic region often involving contiguous prevascular, paratracheal and subaortic, often also lower cervical and supraclavicular lymph nodes (3); may directly invade pulmonary parenchyma. (II) MRI: adenopathy is T2 hyperintense. (III) Nuclear medicine: FDG-PET used for staging and monitoring. (IV) Calcification rare in untreated lymphoma	(I) Nodular sclerosis type is the most common in the mediastinum. (II) Reed-Sternberg cells are the hallmark for the diagnosis
Primary mediastinal (thymic) large B-cell lymphoma	(I) Young adults in 3rd–4th decades. (II) Female predilection (3)	CT: large mass that may infiltrate pericardium, pleura, pulmonary parenchyma, chest wall	(I) Presence of irregular fibrosis is the hallmark of the diagnosis. (II) The tumor is confined to the mediastinum. (III) Similar IHC profile to large B cell lymphoma originating from other locations
T-lymphoblastic lymphoma (T-LBL)	(I) Adolescents and young adults. (II) Male predilection (3)	CT: large rapidly growing mass involving thymus, extracapsular mediastinal soft tissue, mediastinal lymph nodes	(I) Small to medium size lymphocytes with round nuclei and small nucleoli; numerous mitotic figures are present. (II) Tumor cells are positive for TdT by IHC

Table 1 (*continued*)

Lesion type	Clinical and laboratory findings	Imaging findings	Histopathology features
Germ cell tumors (GCT)			
Teratoma	(I) Equal gender predilection (3). (II) Often asymptomatic; may have symptoms in relation to lesion size; trichoptysis or expectoration of other tumoral contents via fistula with bronchi can occur rarely. (III) Association with Klinefelter syndrome. (IV) No elevation in beta-HCG or alpha-fetoprotein (AFP)	(I) CT: mass containing components of varying attenuation including fluid, soft tissue, calcium and/or fat; fat-fluid level highly specific (8), bone or tooth diagnostic. (II) MRI: T1 fat saturation sequence to identify macroscopic fat; calcification may cause susceptibility artifact	(I) Tumor composed of epithelial, mesenchymal and neural tissue; not all components need to be present for the diagnosis. (II) There is no specific IHC for the diagnosis
Seminomatous GCT	(I) Almost exclusively in men. (II) 3rd–4th decade. (III) Elevated beta-HCG in approximately one third of patients; LDH may be elevated (3)	(I) CT: often homogeneous circumscribed mass with mild enhancement (9). (II) Pulmonary metastases common	(I) Large cells with prominent nuclei, often associated with lymphocytes. (II) Granulomatous reaction can be present. (III) Tumor cells are positive for SALL4, OCT4, D2-40 and CD117
Non seminomatous GCT	(I) Primarily children, young men. (II) Elevated AFP in 80%, beta-hCG in 30%; LDH may be elevated (3). (III) Association with Klinefelter syndrome, hematologic malignancies	(I) CT: heterogeneous, irregularly marginated mass with areas of hemorrhage, necrosis, invasion (9). (II) Pulmonary metastases common	(I) Yolk sac tumor, choriocarcinoma, and embryonal carcinoma are high grade malignant epithelial neoplasms. (II) The diagnosis is confirmed by specific IHC stains and correlation with serum markers
Miscellaneous anterior mediastinal lesions			

			markers
Miscellaneous anterior mediastinal lesions			
Thymic hyperplasia	(I) True (rebound) thymic hyperplasia as sequela of physiologic stressors such as illness, injury, chemo/ radiotherapy (10). (II) Thymic lymphoid hyperplasia most often in setting of systemic immunologic conditions including hyperthyroidism, autoimmune disease such as myasthenia gravis, collagen vascular disease, HIV (11)	(I) CT: may be homogeneously enlarged thymic soft tissue or heterogeneous due to interspersed fat. (II) MRI: chemical shift imaging demonstrates loss of signal on opposed phase T1-weighted sequence due to presence of microscopic fat, characteristic of thymic hyperplasia. (III) Nuclear medicine: No uptake on somatostatin receptor imaging as seen in thymic epithelial neoplasms; may demonstrate physiologic, low level FDG-avidity	(I) Histologic section shows normal thymic structures, lobules are interspersed with adipose tissue. (II) Well-developed lymphoid follicles are seen in follicular hyperplasia
Thymolipoma	(I) Often large mass in young demographic. (II) Uncommonly in association with myasthenia gravis (12); case reports of thymoma arising within thymolipoma (13-15)	CT: adipose with intermixed thymic soft tissue; encapsulated and often conforming to anterior mediastinal structures; may have tumor pedicle and most often located at inferior aspect prevascular compartment (12)	Circumscribed tumor composed of mature fat admixed with islands of normal thymic tissue
Thyroid	Anterior mediastinal thyroid tissue may be due to substernal extension of goiter, or less commonly ectopic thyroid tissue discontinuous from cervical thyroid	(I) CT: often the same attenuation as cervical thyroid tissue (II) Nuclear Medicine: Tc-99m pertechnetate, I-123 or I-131 scans may characterize tissue as thyroid	(I) Irregular sized thyroid follicles containing colloid. (II) Cells are positive for TTF-1 and PAX-8 by IHC
Ectopic parathyroid	Elevated PTH/hypercalcemia can occur	(I) CT and MRI: often hypervascular. (II) Nuclear Medicine: Tc-99m Sestamibi parathyroid scintigraphy	(I) Sheets of bland cells with clear and/ or oncocytic cytoplasm admixed with fat; delicate fibrous bands can be seen. (II) Cells are positive for parathyroid hormone by IHC

SVCS : Clinical Presentations

Symptoms

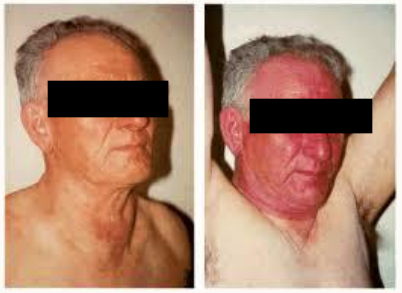
- Dyspnea,orthopnea,cough: lying down may aggravate the symptoms
- Face and neck swelling

  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



Life-threatening manifestations of SVCS

❑True emergency conditions of SVCs

- **Airway compromise** from laryngeal edema
  : upper airway obstruction >>> stridor

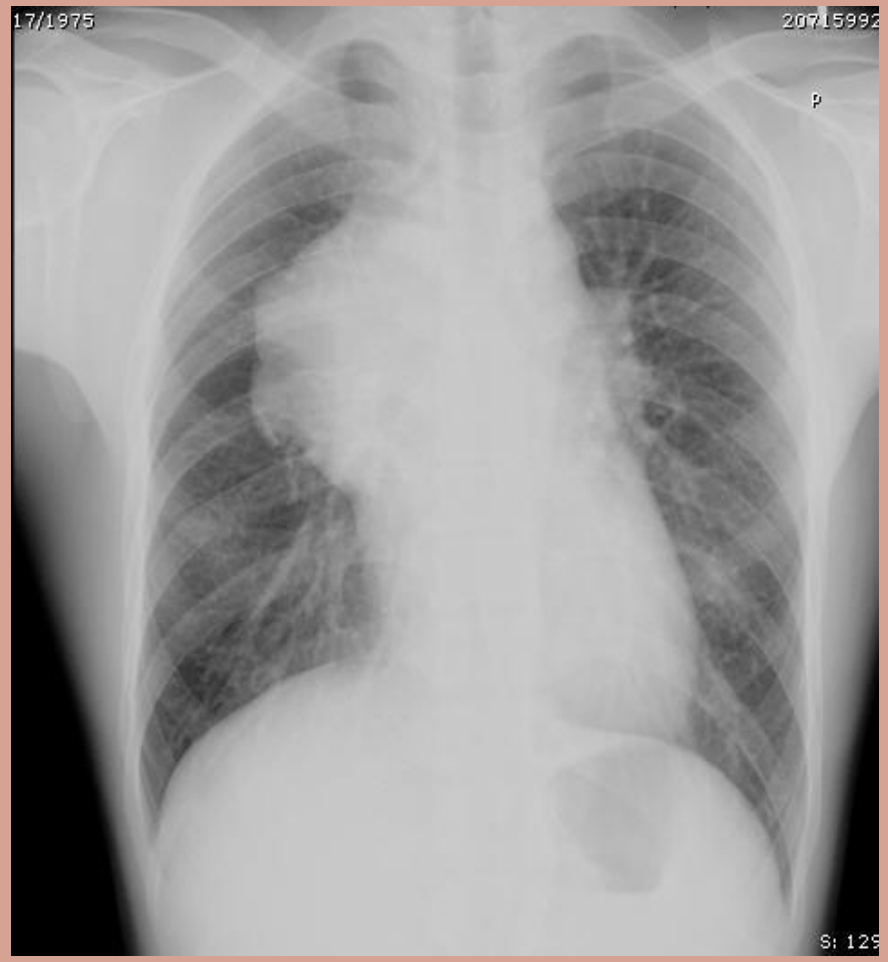
- **Cardiovascular collapse**
  : syncope without precipitating factors, hypotension

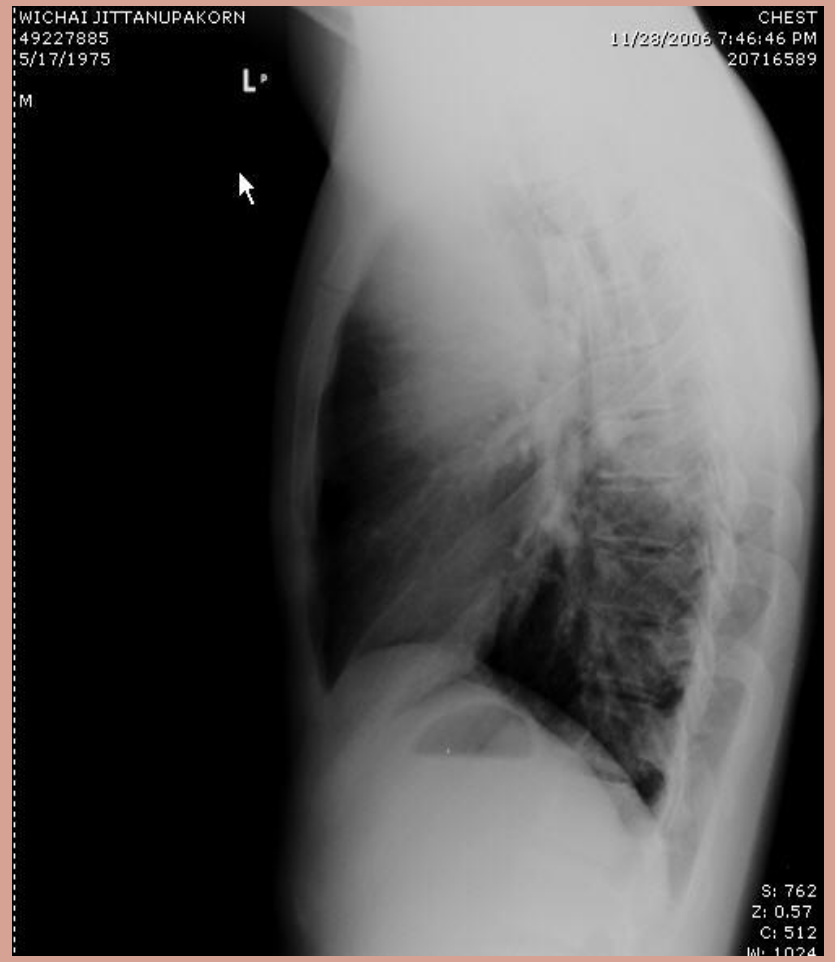
- **Neurologic abnormalities** from increased intracranial pressure and cerebral edema
  : severe headache, blurred vision,
  alteration of conscious and seizures

SVCS : Diagnosis

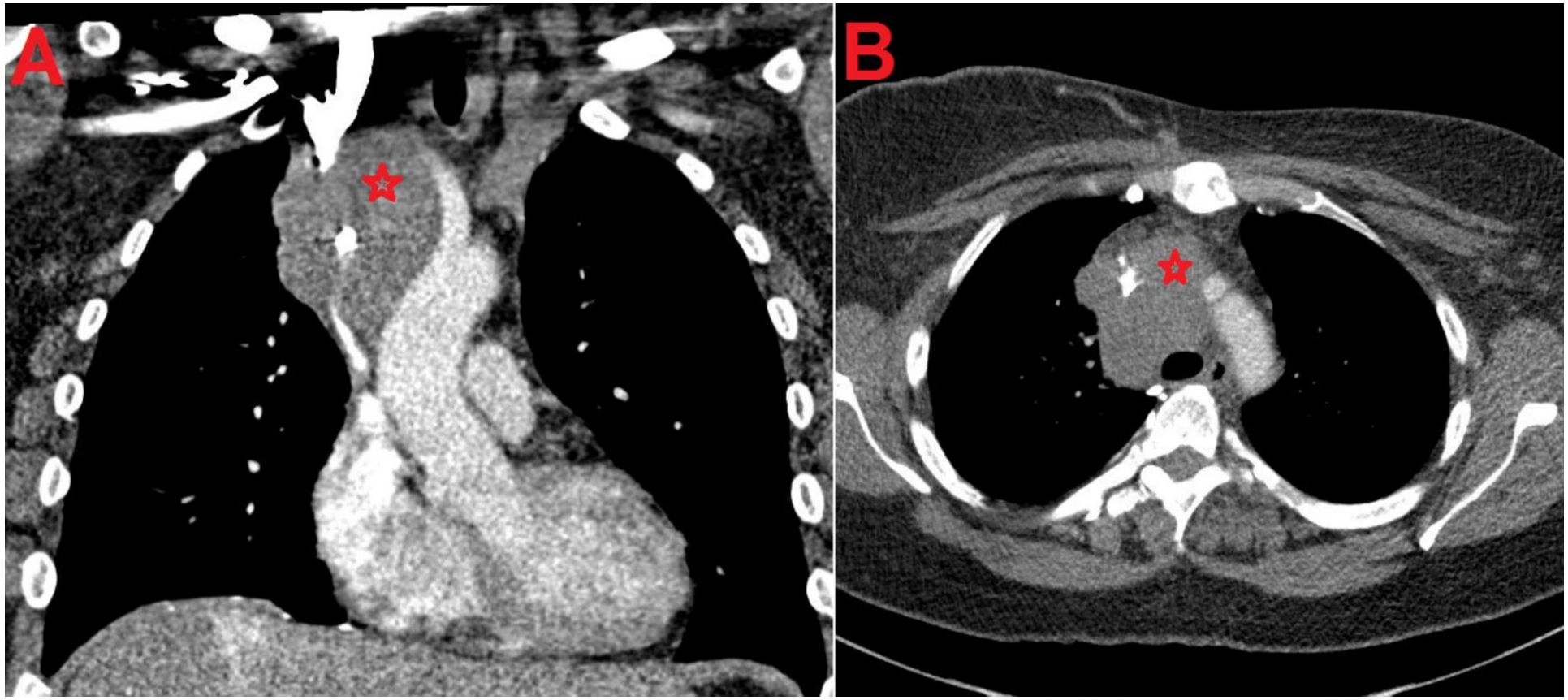
- **Clinical diagnosis**
- **CXR PA and lateral**
  - Most have abnormal chest film
  - Most common abnormalities are widening mediastinal
- **CT chest with contrast**
  - Most useful
  - Confirm diagnosis
  - Identify etiology
    >>> external compression, thrombosis

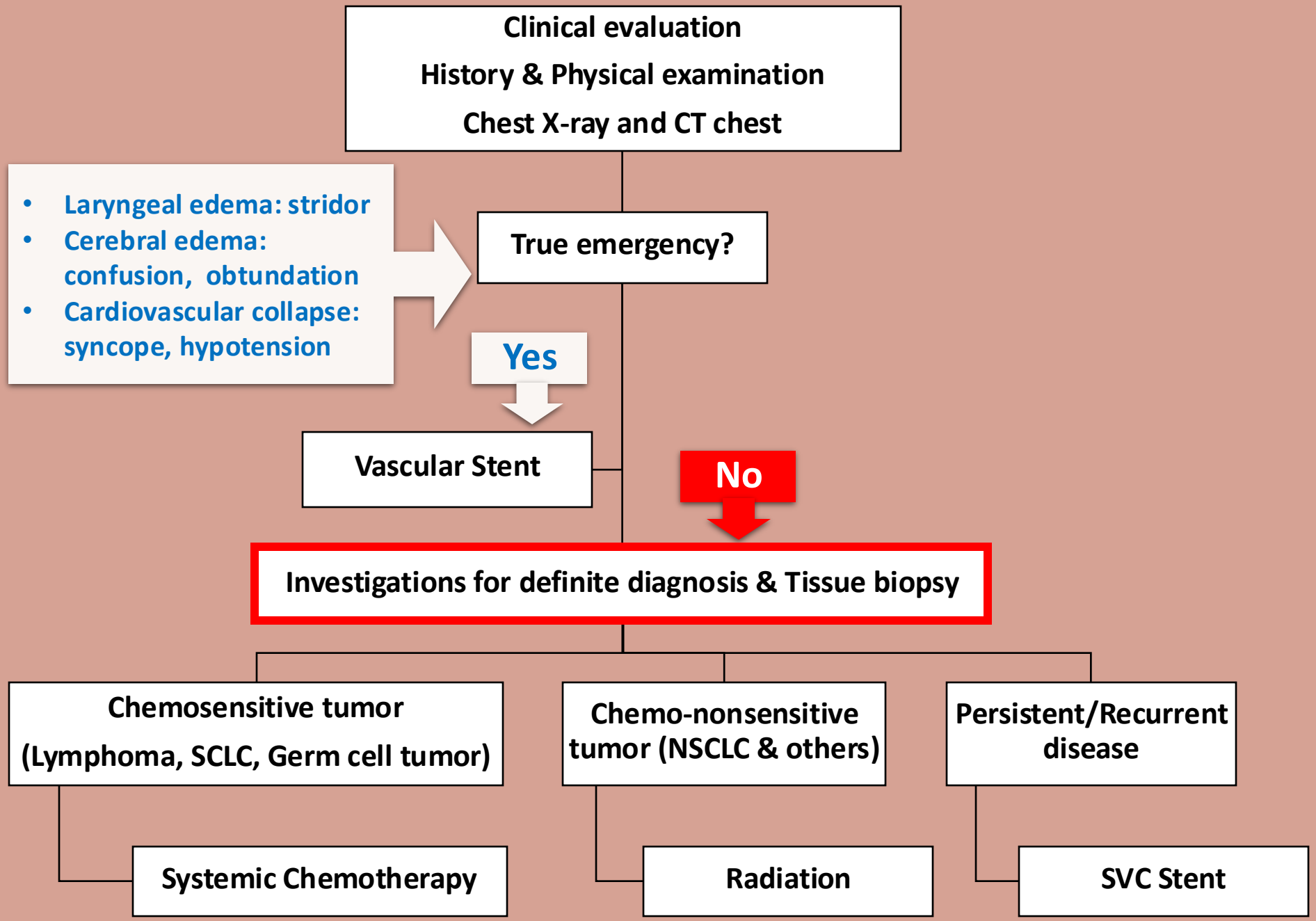
Imaging : Chest X-Ray





Imaging : CT Chest




Clinical evaluation
History & Physical examination
Chest X-ray and CT chest
True emergency?
Laryngeal edema: stridor
Cerebral edema: confusion, obtundation
Cardiovascular collapse: syncope, hypotension
Yes
Vascular Stent
No
Investigations for definite diagnosis & Tissue biopsy
Chemosensitive tumor (Lymphoma, SCLC, Germ cell tumor)
Chemo-nonsensitive tumor (NSCLC & others)
Persistent/Recurrent disease
Systemic Chemotherapy
Radiation
SVC Stent

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 : 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 of Malignancy

Hypercalcemia of Malignancy

10-20% of cancer patients have hypercalcemia during the disease course

Definition	Corrected serum calcium > 11.0 mg/dl (2.75 mmol/L)

Therapeutic intervention is generally needed when serum calcium > 12.0 mg/dl or symptomatic

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, ovarian dysgerminoma

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

Incidence by tumor type

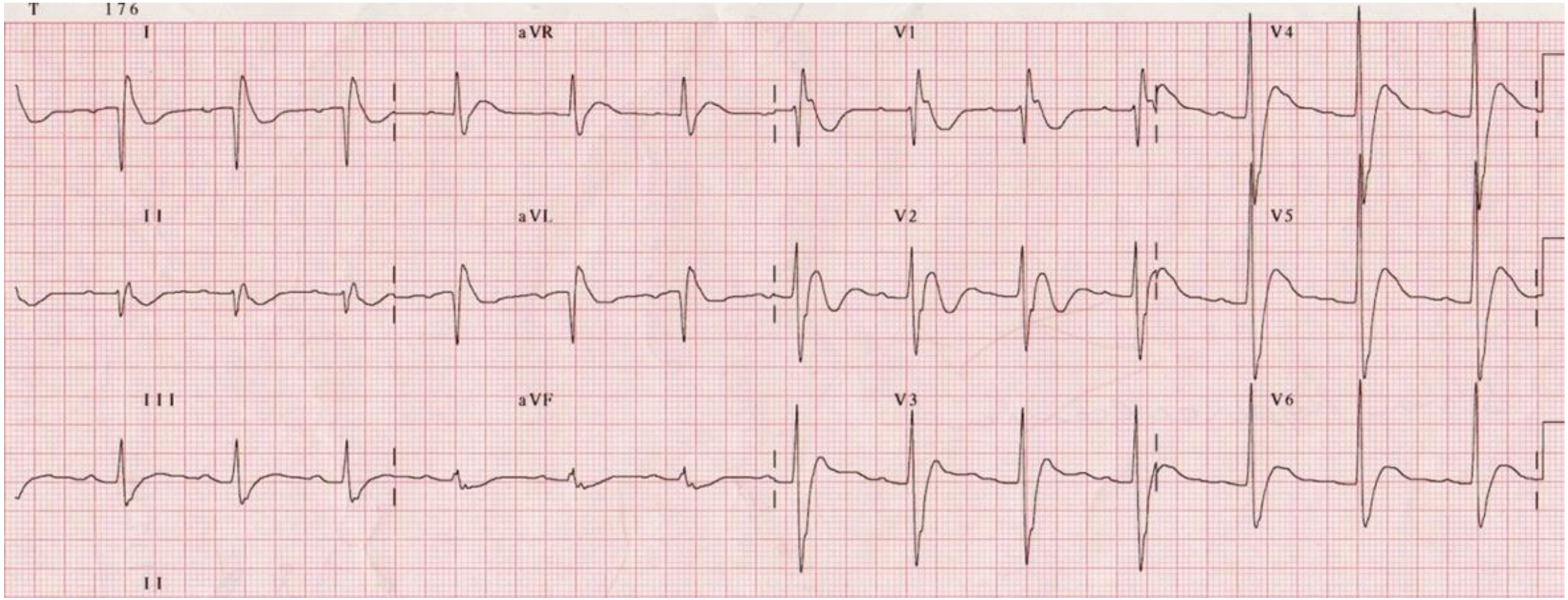
Tumor Type	%Hypercalcemia
Lung	27.0
Breast	25.0
Multiple Myeloma	7.3
Head & Neck	6.9
Unknown Primary	4.7
Lymphoma/leukemia	4.3
Renal	4.3
Gastrointestinal	4.1

Hypercalcemia : Clinical Presentations

Symptoms associated with hypercalcemia by organ systems

General	CNS	Cardiac	GI	Renal
Dehydration	Weakness	Bradycardia	Nausea and vomiting	Polyuria
Anorexia	Hypotonia	Short QT interval	Constipation	Nephrocalcinosis
Pruritus	Proximal myopathy	Prolonged PR interval	Ileus	–
Weight loss	Mental status changes	Wide T wave	Pancreatitis	–
Fatigue	Seizure Coma	Atrial or ventricular arrhythmia	Dyspepsia	–

- Non-specific : Mimic S&S of cancer
- Symptom ∝ degree and rate of rise of serum calcium
- Spectrum ranging from few or no symptoms to severe obtundation and coma


T 176
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

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
- Classic symptom “stone bone moan groan”

If diagnosis hypercalcemia >>>

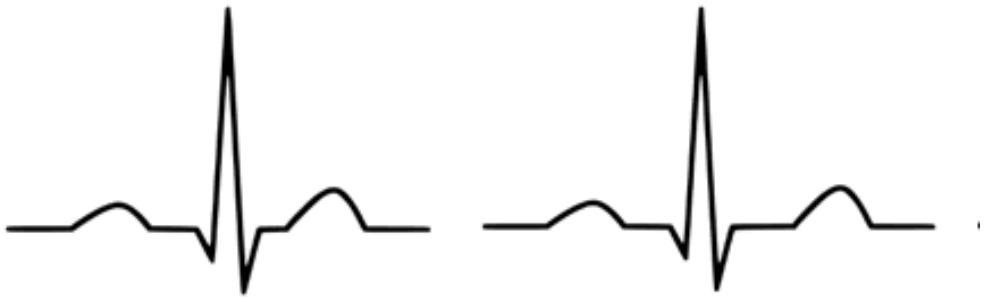
- Don’t forget to do EKG
- (short QT interval < 300 ms)

Hypercalcemia : Diagnosis

All case	Serum Calcium	Corrected cal = 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



HYPERcalcaemia Normal

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

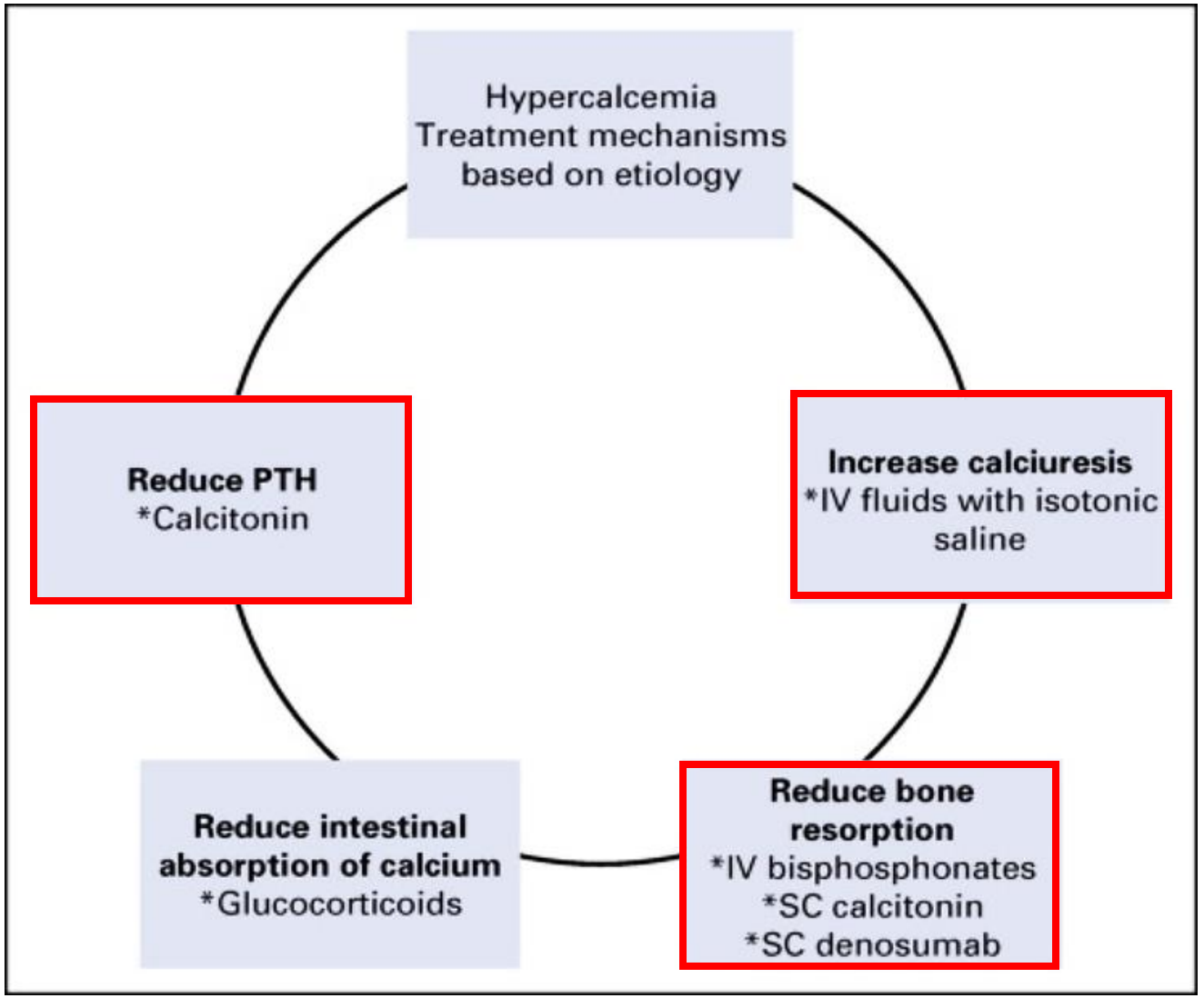
Known history of malignancy, staging, prognosis

Etiology of hypercalcemia

Management of Hypercalcemia

- Treatment or not?
- Factor to be considered
  - Symptomatic vs asymptomatic
  - First or recurrent episode
  - Performance status
  - Quality of life
  - Prognosis of primary cancer
  - Further effective specific treatment of primary cancer
  - Etiology of hypercalcemia

Management 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, 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

Bisphosphonate and renal impairment

- Factors to prevent nephrotoxicity from bisphosphonate
  - Adequate hydration
  - Adjust dose along creatinine clearance
  - Increase time of intravenous infusion

Creatinine clearance (mL/min)	Recommended dose for zoledronic acid (3–4 weekly)
>60	4 mg over 15 min
50–60	3.5 mg over 15–30 min
40–49	3.3 mg over 15–30 min
30–39	3 mg over 15–30 min
<30	Not recommended

Creatinine clearance (mL/min)	Recommended infusion time for pamidronate 90 mg (3–4 weekly)
>60	2–4 h
30–60	Reduce dose or infuse over 4–6 h
<30	Not recommended unless life-threatening hypercalcaemia

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

Common cancer management

Lung cancer

Colon cancer

Breast cancer

Germ cell tumor

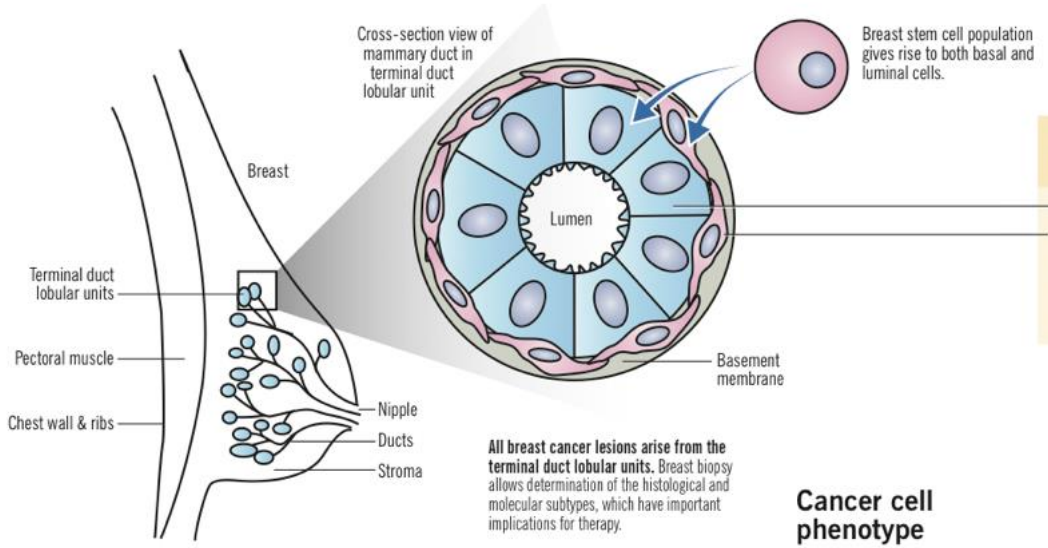
Others


Breast cancer

Metastatic Breast cancer

Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jenna Rebelo



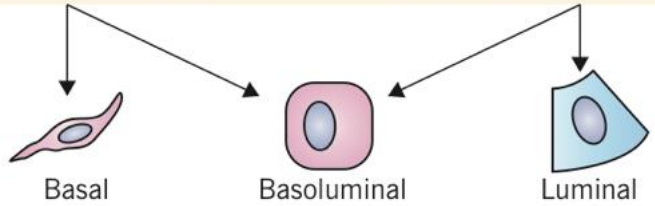
All breast cancer lesions arise from the terminal duct lobular units. Breast biopsy allows determination of the histological and molecular subtypes, which have important implications for therapy.

Normal breast stem cells or progenitor cells transform into breast cancer cells. The cancer cells are similar in phenotype to the normal basal and luminal cells of the ductal structure.

Basal or myoepithelial cells
- Contractile cells for milk ejection
- *Estrogen receptor* –
- Progesterone receptor –

Luminal or epithelial cells
- Respond to hormonal stimulation for milk production
- *Estrogen receptor* +
- Progesterone receptor +/–

Cancer cell phenotype

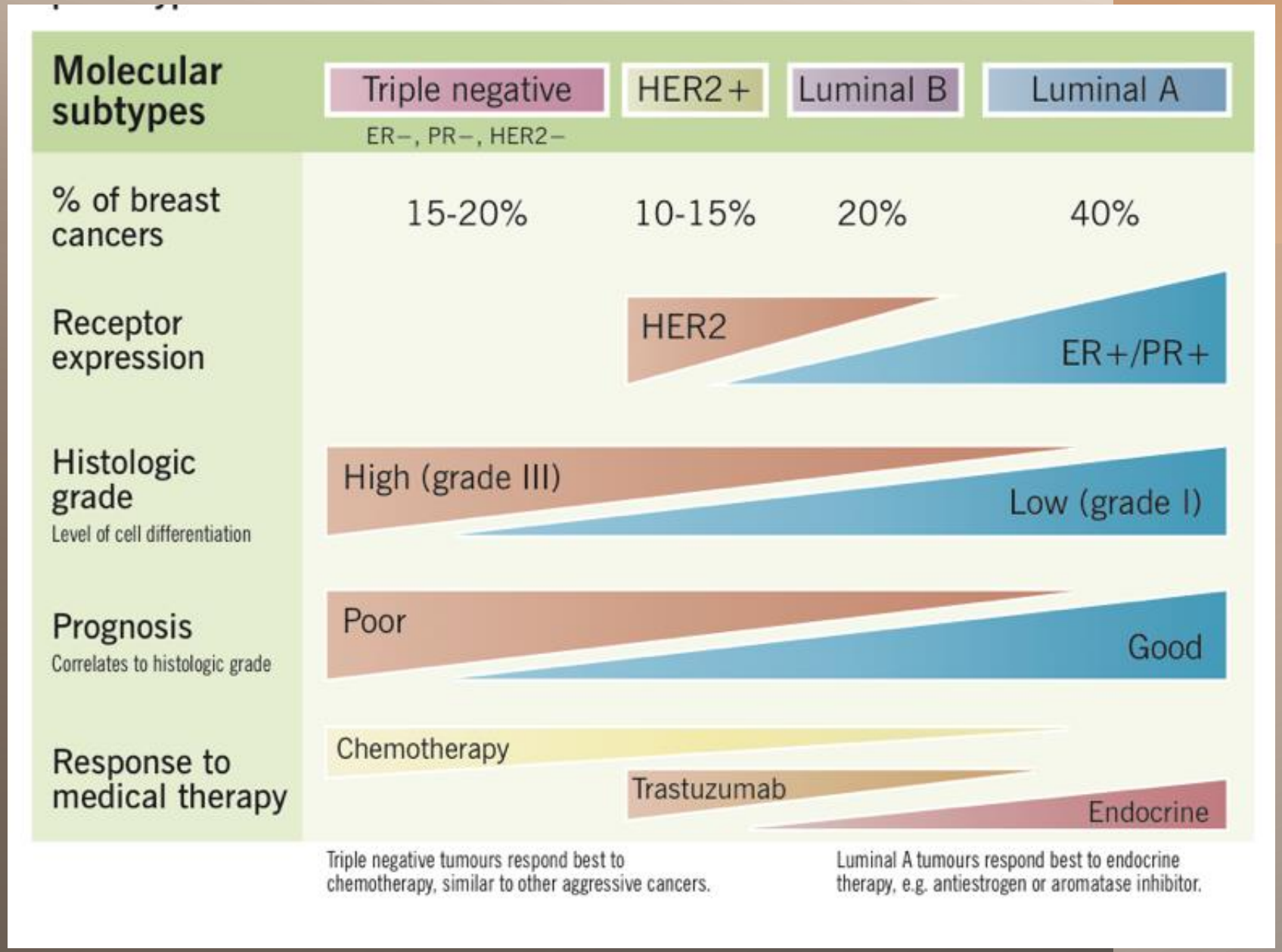


Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	**Ductal carcinoma in situ (DCIS)** 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	**Lobular carcinoma in situ (LCIS)** 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	**Invasive ductal carcinoma (IDC)** 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	**Invasive lobular carcinoma (ILC)** 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

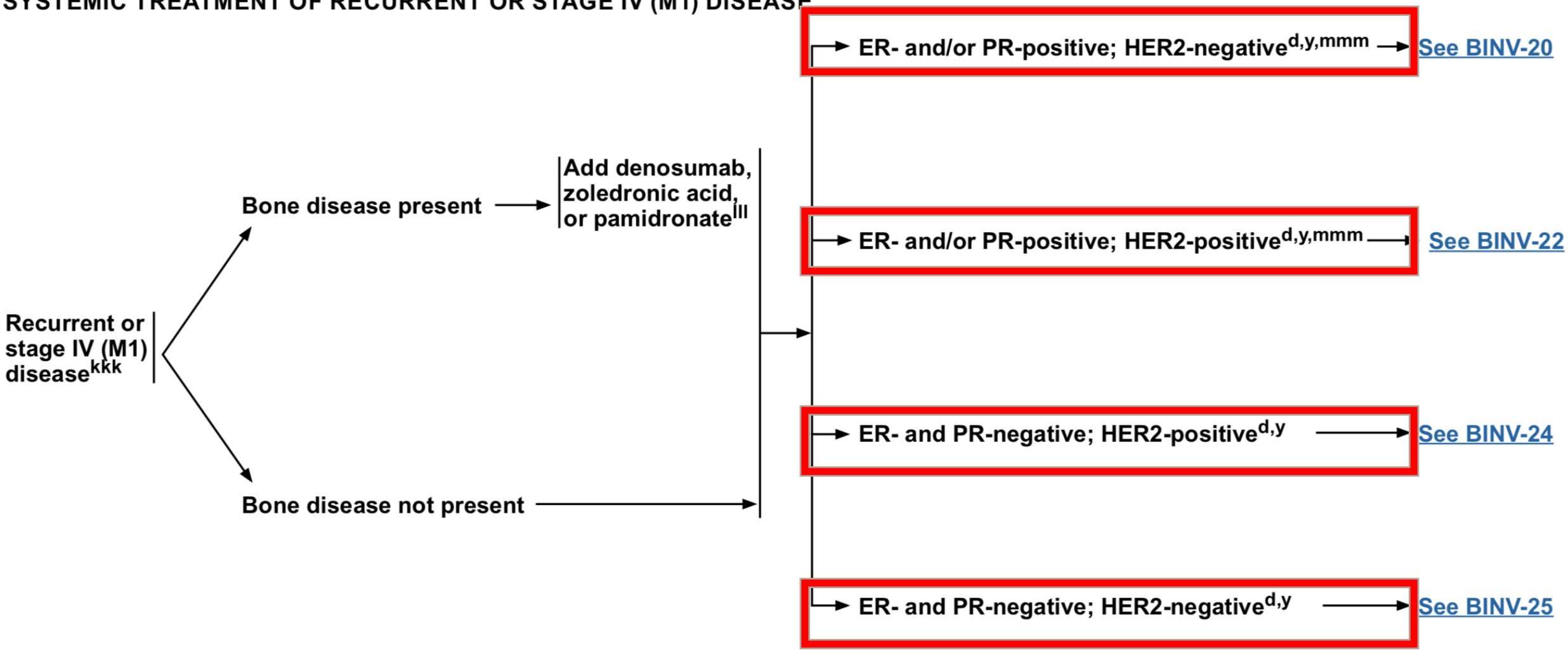
Molecular subtypes	Triple negative (ER–, PR–, HER2–)	HER2+	Luminal B	Luminal A
% of breast cancers	15-20%	10-15%	20%	40%
Receptor expression		HER2		ER+/PR+
Histologic grade Level of cell differentiation	High (grade III)			Low (grade I)
Prognosis Correlates to histologic grade	Poor			Good
Response to medical therapy	Chemotherapy	Trastuzumab		Endocrine

Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.


Molecular subtypes
Triple negative
ER−, PR−, HER2−
HER2+
Luminal B
Luminal A
% of breast cancers
15-20%
10-15%
20%
40%
Receptor expression
HER2
ER+/PR+
Histologic grade
Level of cell differentiation
High (grade III)
Low (grade I)
Prognosis
Correlates to histologic grade
Poor
Good
Response to medical therapy
Chemotherapy
Trastuzumab
Endocrine
Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.
Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE



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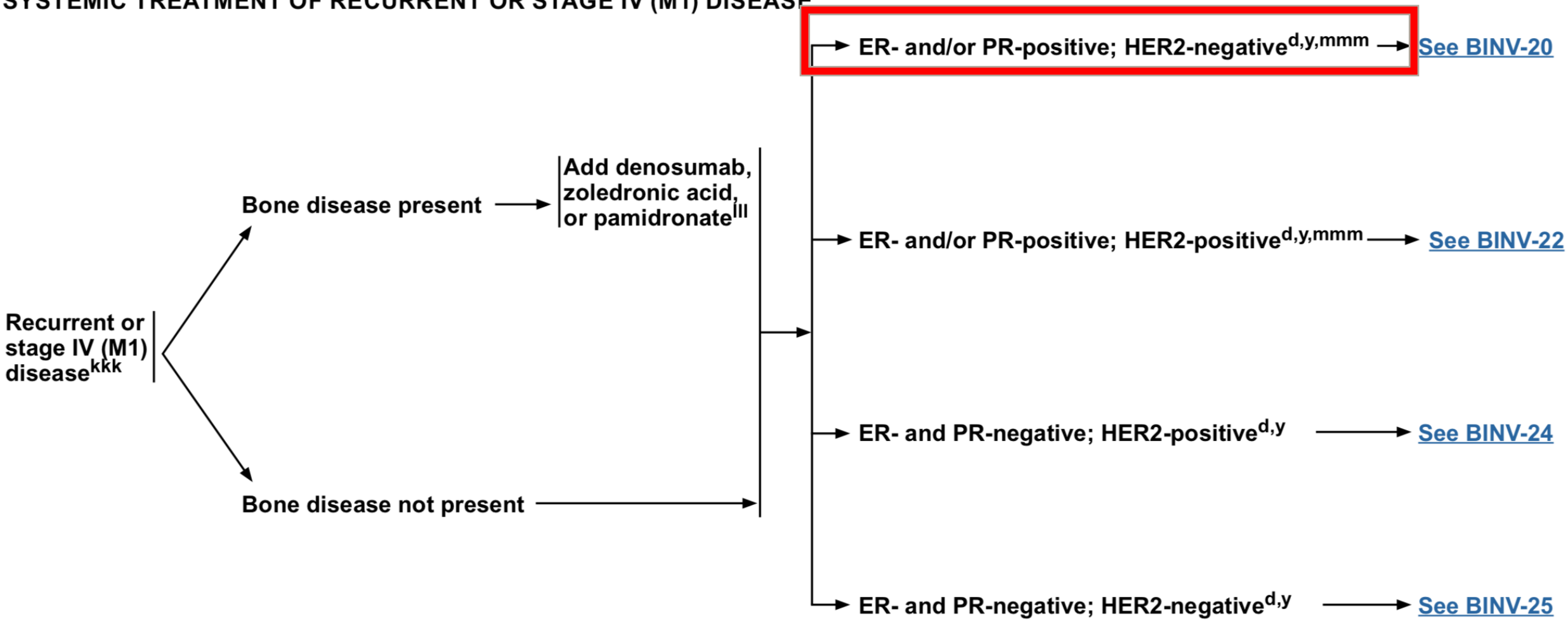
Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE



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Invasive Breast Cancer

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens
First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective estrogen receptors modulator (tamoxifen or toremifene)
- Steroidal aromatase inactivator (exemestane)

Preferred Regimens
Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[c]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f]
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Selective ER down-regulator (fulvestrant)
- Selective estrogen receptors modulator (tamoxifen or toremifene)

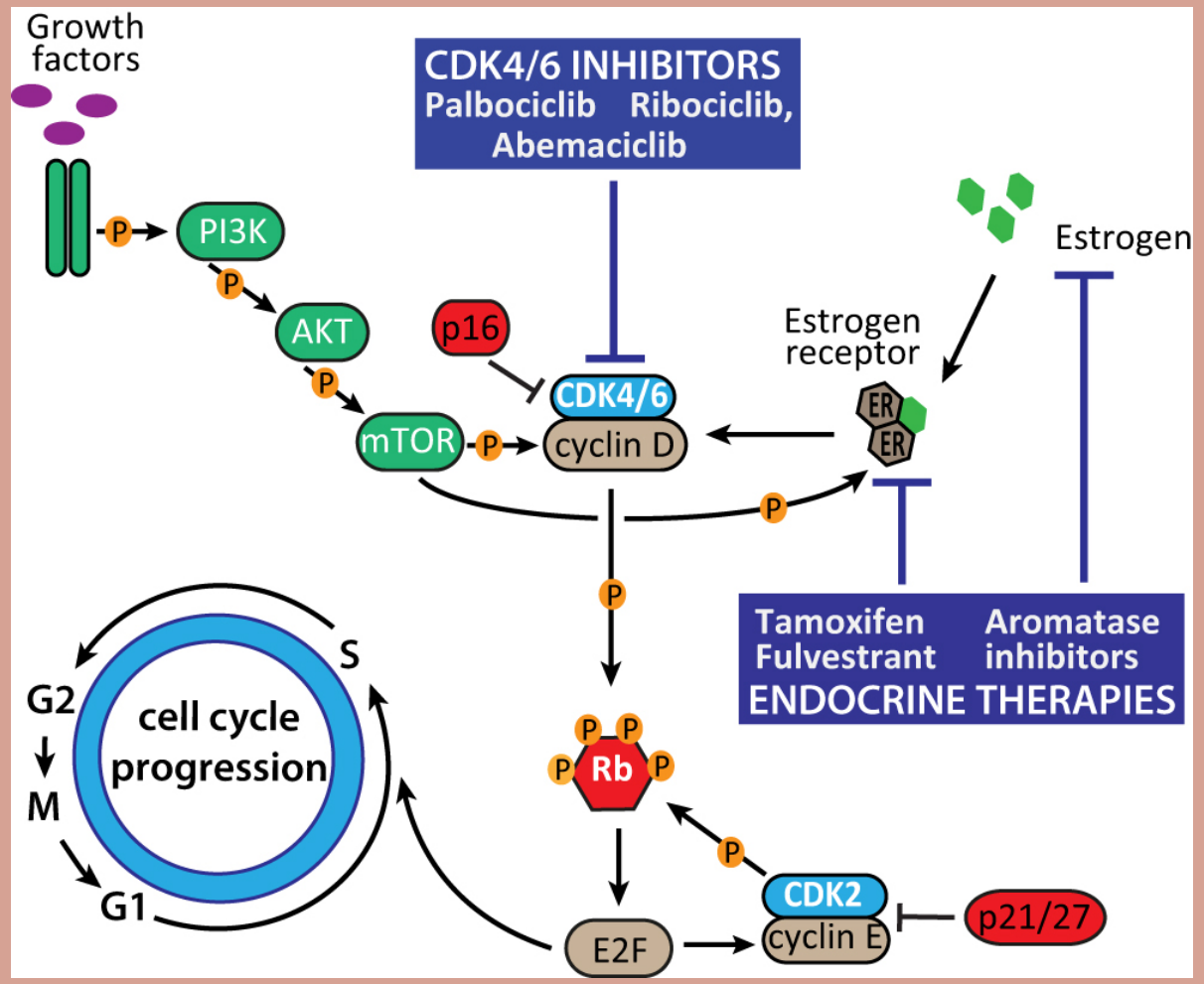
Useful in Certain Circumstances[d]

- Megestrol acetate
- Estradiol
- Abemaciclib[c,e]

HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

Why G1-to-S checkpoint is an ideal therapeutic target ?



- HR-positive and HER2 –neg presents different degrees that make itself susceptible for CDK4/6 inhibitor.
- Cyclin D1 is highly expressed in ER-Positive BC with or without concomitant amplification of cyclin D1 Gene (CCND1).
- ER signaling pathway is able to activate CCND1 Gene promotor.
- Cyclin D1 can also stimulate ER transcriptional activity in CDK 4-independent manner.
- Cyclin E expression and Rb mutation are very rare in ER-Positive BC.

Regulation of cell cycle in ER+ breast cancer. The key pathways in promoting entry into the cell cycle in ER+ breast cancer and the nodes to which current therapies are targeted.

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Invasive Breast Cancer

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Discussion

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE[a]

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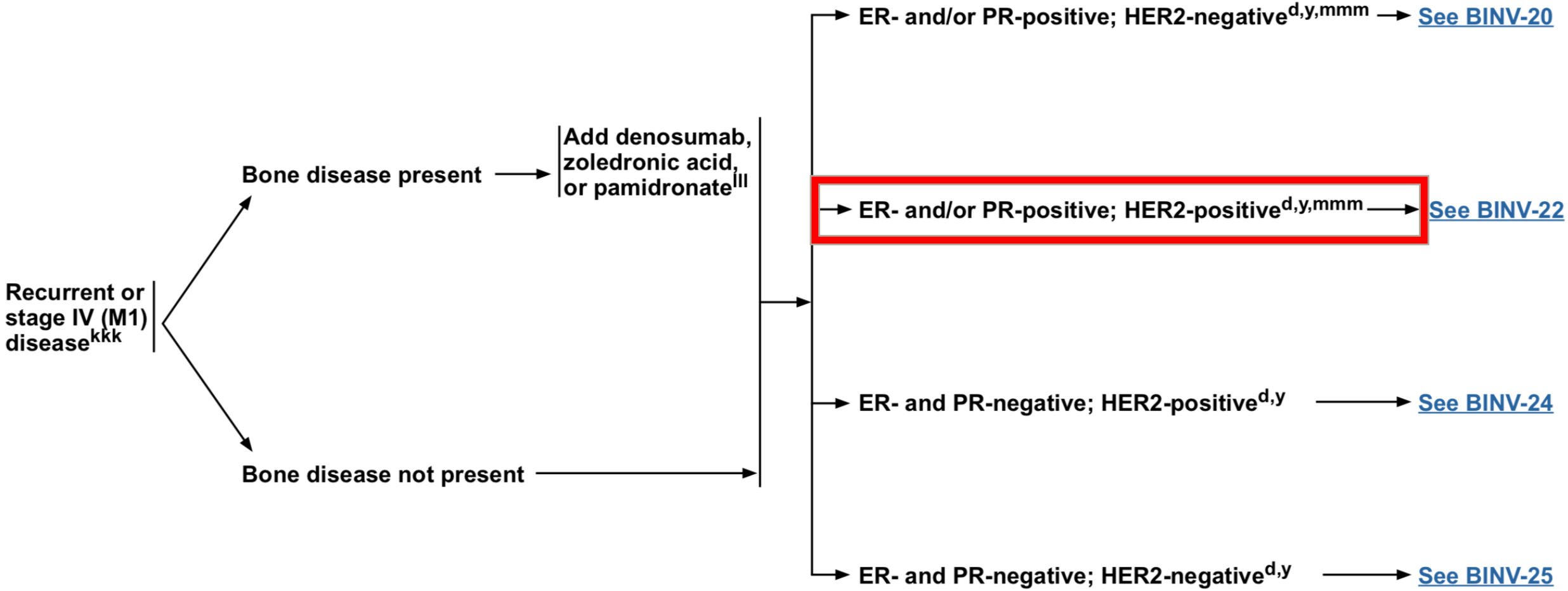
- Estradiol
- Abemaciclib[c,e]

HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

Viseral crisis > Chemotherapy

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE



SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER- and/or PR-POSITIVE; HER2-POSITIVE[d]

Systemic therapy + HER2-targeted therapy[ooo,ppp]
or
Endocrine therapy[uuu] ± HER2-targeted therapy (if premenopausal,[nnn] consider ovarian ablation or suppression)[ppp,vvv]
or
Other HER2-targeted therapies[ooo]

→ **Continue therapy until progression[rrr] or unacceptable toxicity** → **Progression**
See BINV-23

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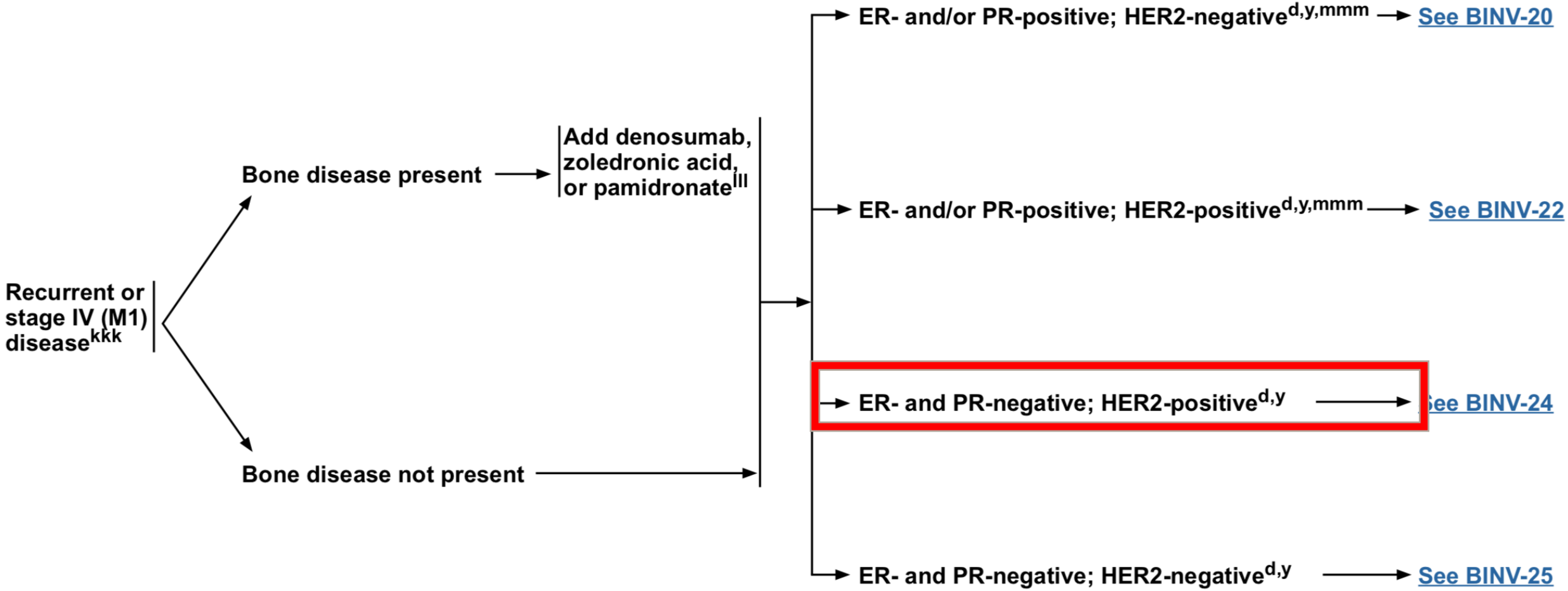
Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE



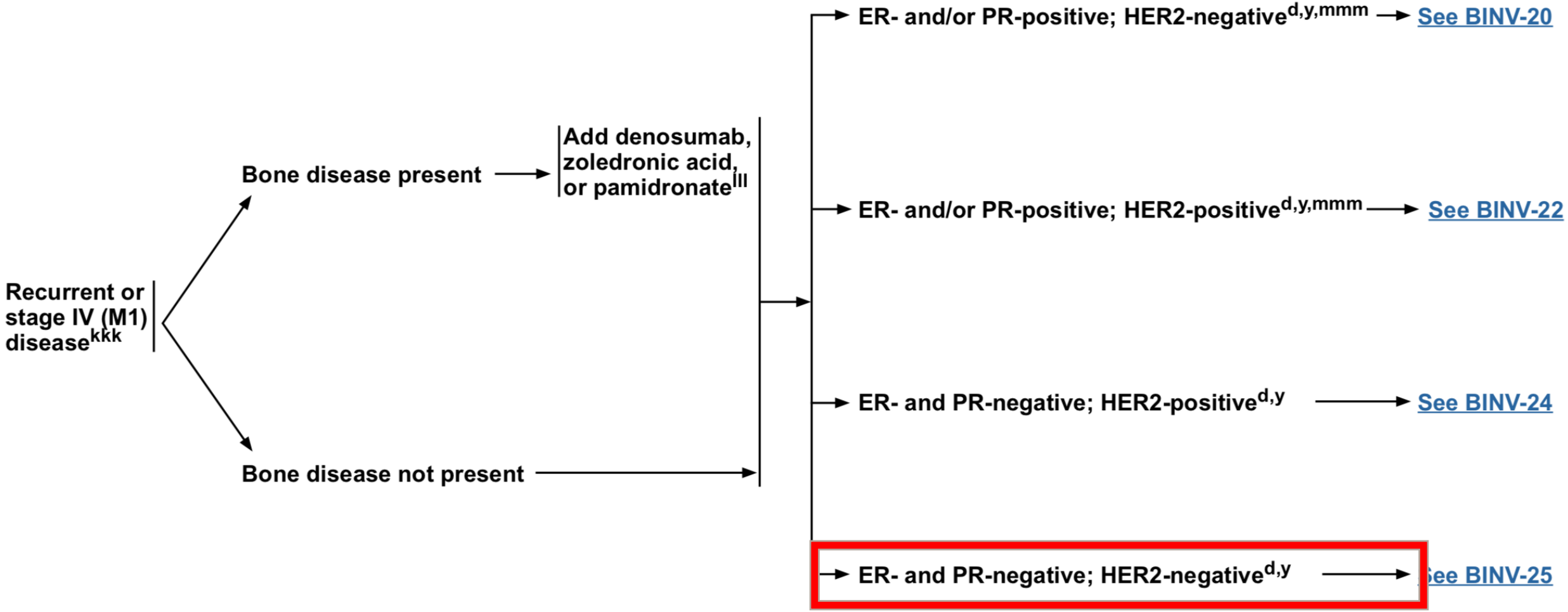
[d] See Principles of Disease Treatment (BINV-A)

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

NCCN Guidelines
Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE



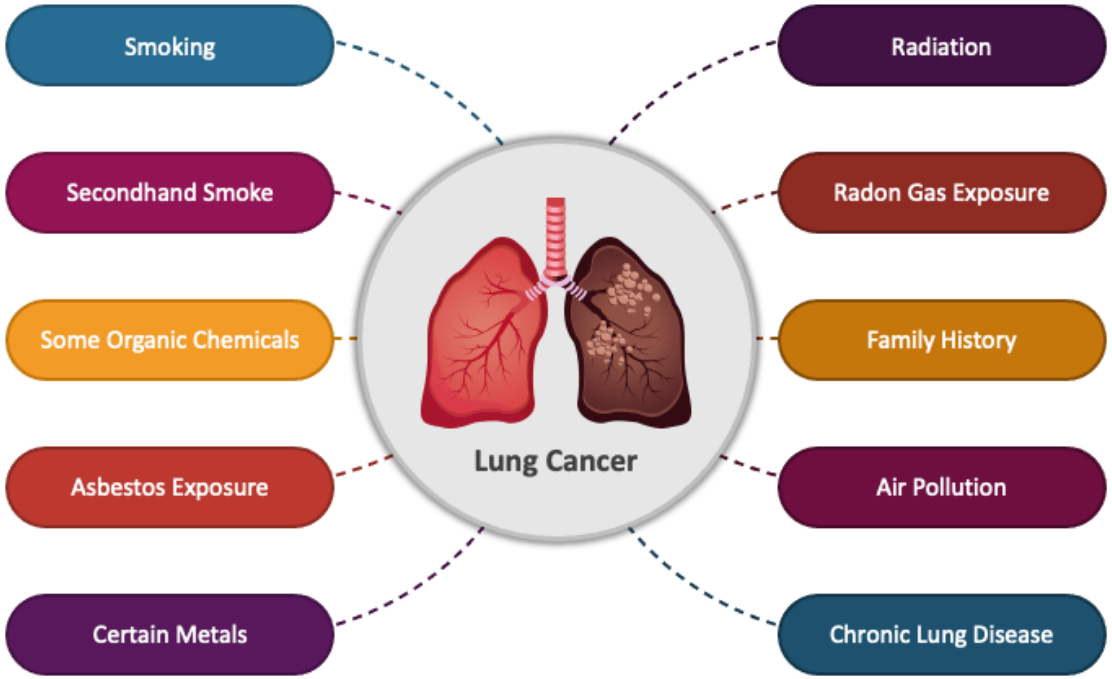
Lung cancer

LUNG CANCER

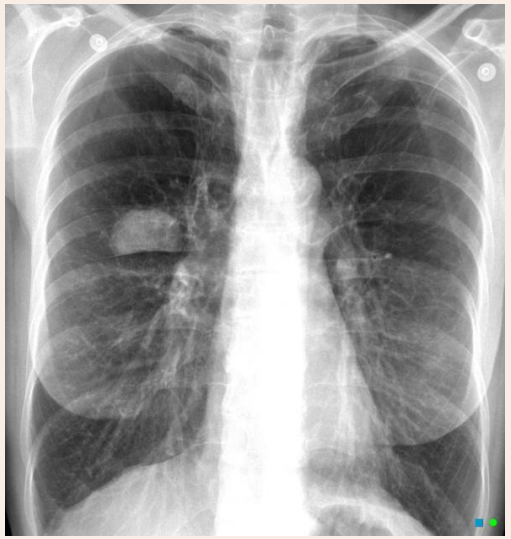
Symptoms of Lung Cancer

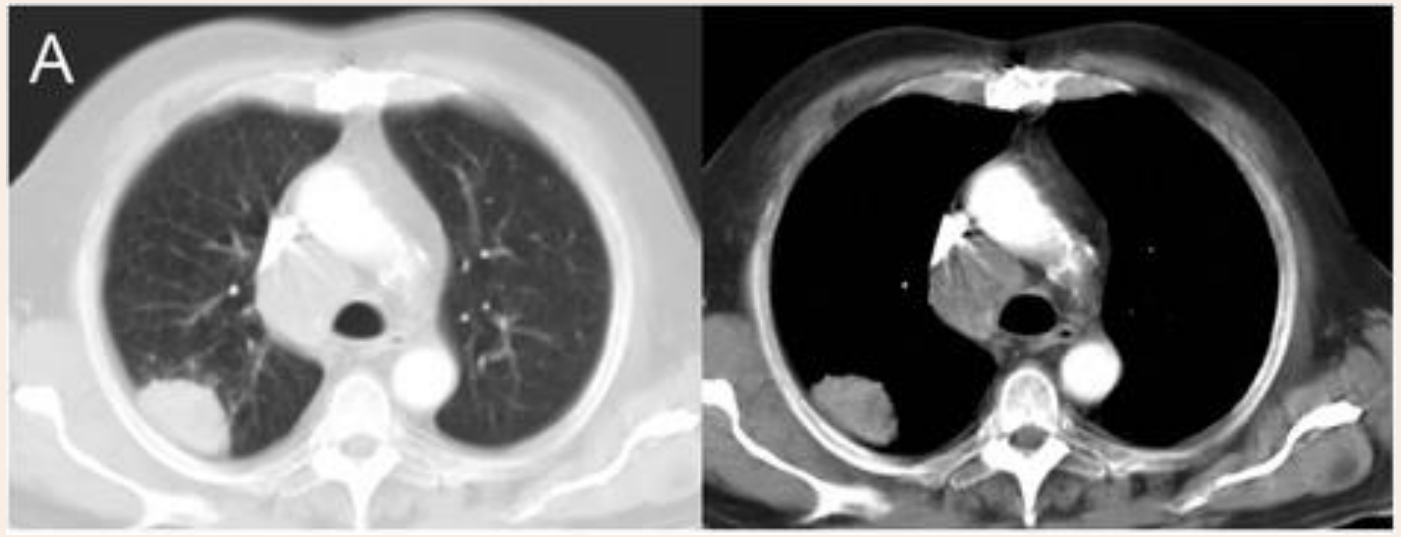
LUNG CANCER

Lung Cancer Risk Factors



Investigation

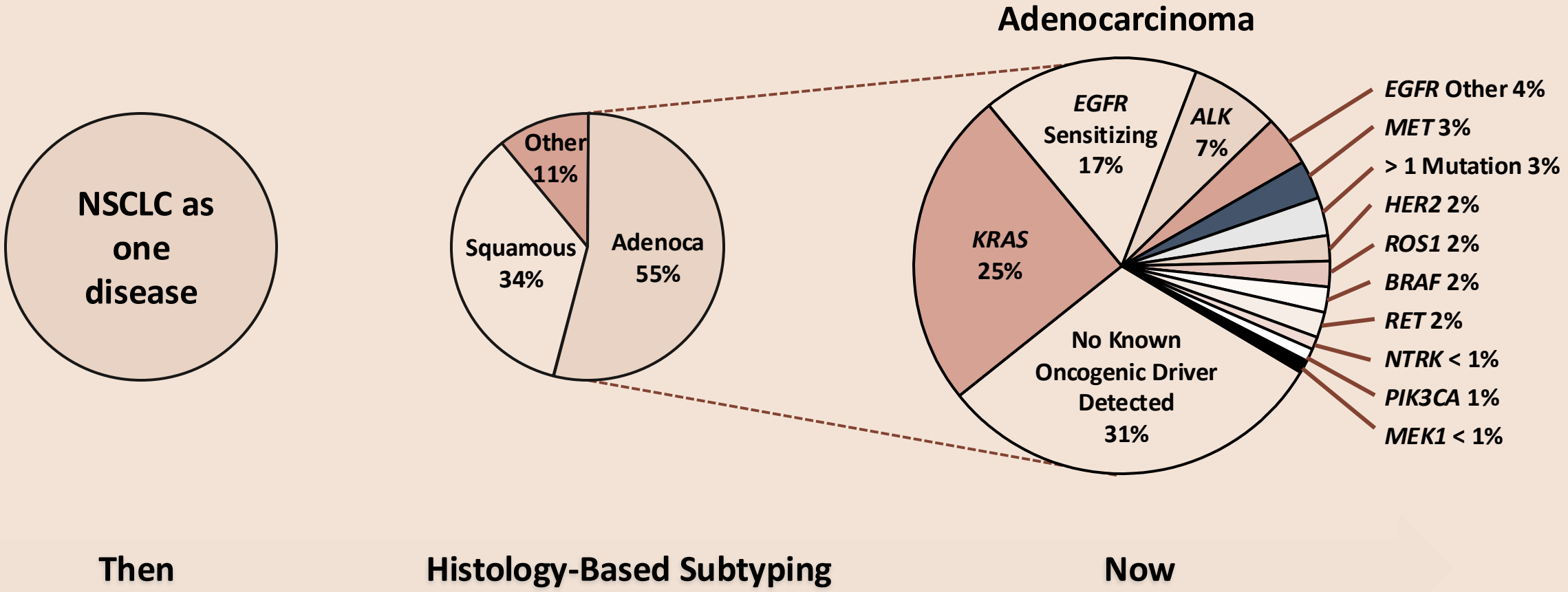




If no obvious M1 suspected form CT scan

PET scan + MRI brain or Bone scan + MRI brain

Non-Small-Cell Lung Cancer: Not One Disease, but Many!



Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Slide credit: clinicaloptions.com

Biopsy: Establish Diagnosis, Determine Histologic Subtype, Biomarker Testing

- Histologic subtyping
  - Squamous or nonsquamous?[1]

Nonsquamous

- *EGFR/ALK/ROS1/BRAF* V600E[4]
- Broad molecular testing by next-generation sequencing is preferred to detect a wider range of mutations[4,5]

Squamous

- Broad testing still recommended
- At very least, consider molecular testing in young, never, or light smokers or if biopsy specimen is small or has mixed histology[2]

Determination of PD-L1 expression indicated in all NSCLC[4]

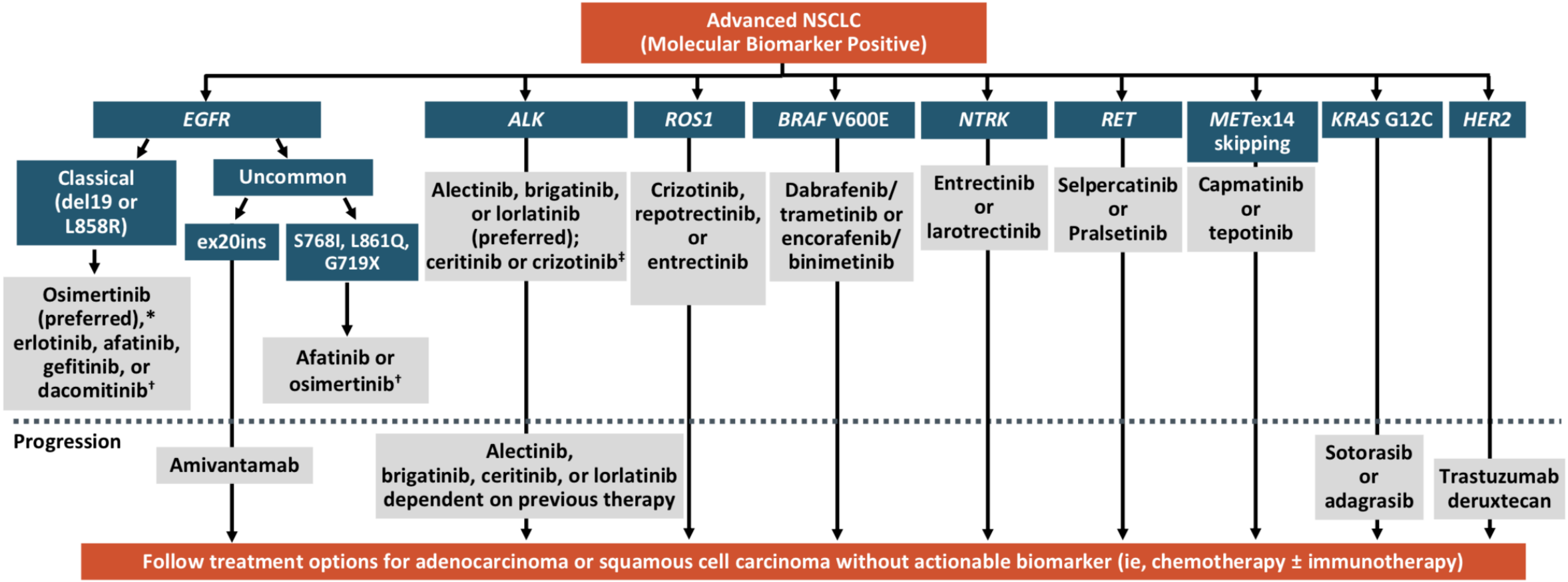
1. Masters. J Clin Oncol. 2015;33:3488. 2. Lindeman. J Thorac Oncol. 2013;8:823. 3. Bernabé. Eur J Cancer. 2017;81:66.
4. Pennell. ASCO Educ Book. 2019;39:351. 5. Kalemkerian. JCO. 2018;36:911. 6. Bernicker. J Oncol Pract. 2017;13:221.

Management of Patients With Advanced NSCLC and an Actionable Alteration

Although there are a variety of molecular NSCLC subtypes, oncogene-addicted NSCLC share some typical hallmarks and similarities:

- Oncogenic driver alterations are mutually exclusive.
- Treatment outcome with targeted therapies is superior to conventional chemotherapy.
- TKIs, selected by a predictive targetable oncogenic driver alteration, yield a high objective response rate (ORR).
- Responses to TKIs occur timely after onset of therapy, usually within 4–6 weeks.
- Emergence of secondary resistance to targeted therapy is inevitable and usually occurs within 12–24 months.

Targeted Therapy in Advanced NSCLC With Actionable Driver Mutations (2024)

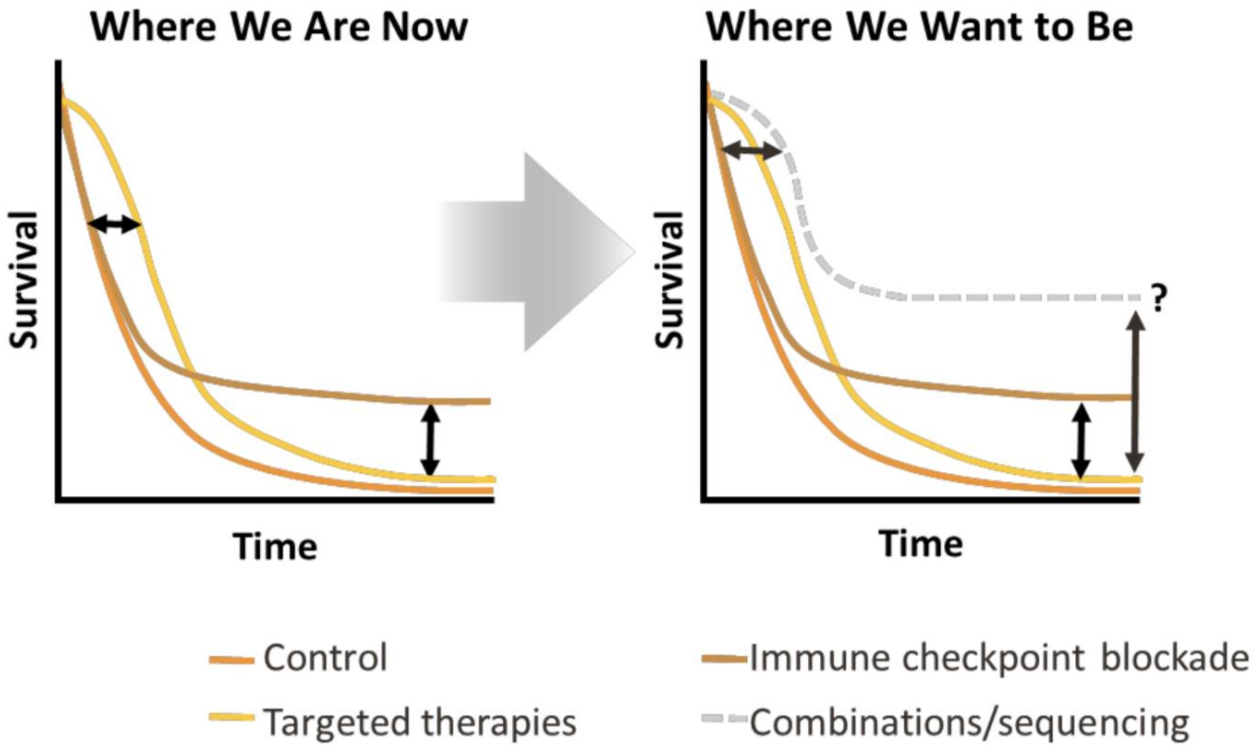


*Osimertinib also approved as second-line therapy for *EGFR* T790M–positive disease after an earlier-generation EGFR TKI. †Afatinib, dacomitinib, erlotinib (alone or in combination with ramucirumab or bevacizumab), gefitinib, and osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q. Osimertinib also a preferred option for *EGFR* G719X, S768I, L861Q per NCCN guidelines. ‡Or as second-line after CT.

Adagrasib PI. Afatinib PI. Alectinib PI. Amivantamab PI. Capmatinib PI. Ceritinib PI. Crizotinib PI. Dabrafenib PI. Dacomitinib PI. Entrectinib PI. Erlotinib PI. Gefitinib PI. Lorlatinib PI. Larotrectinib PI. Osimertinib PI. Pralsetinib PI. Selpercatinib PI. Sotorasib PI. Trametinib PI. Trastuzumab deruxtecan PI. NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2024.

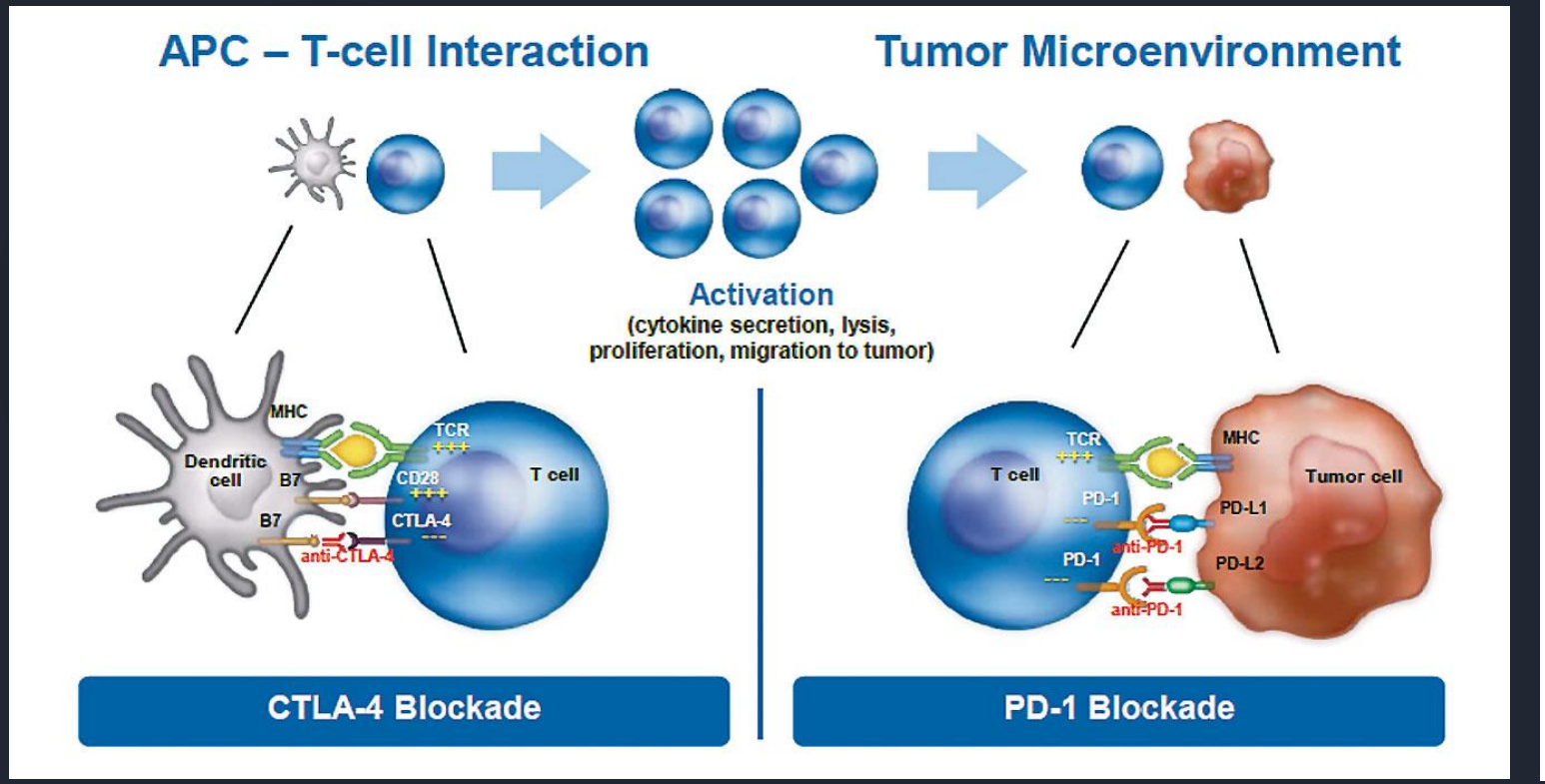
Optimal Use of ICI Therapy in Advanced NSCLC in the Absence of a Targetable Mutation

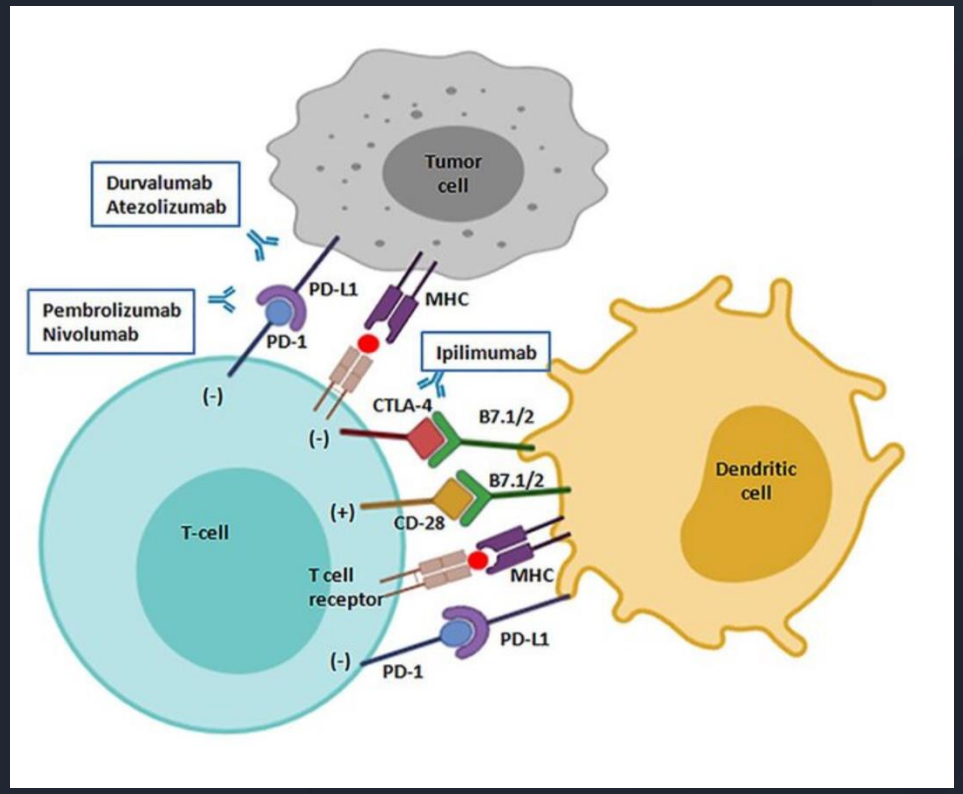
Boosting the Potential for Immune Response With Combination Therapies



Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

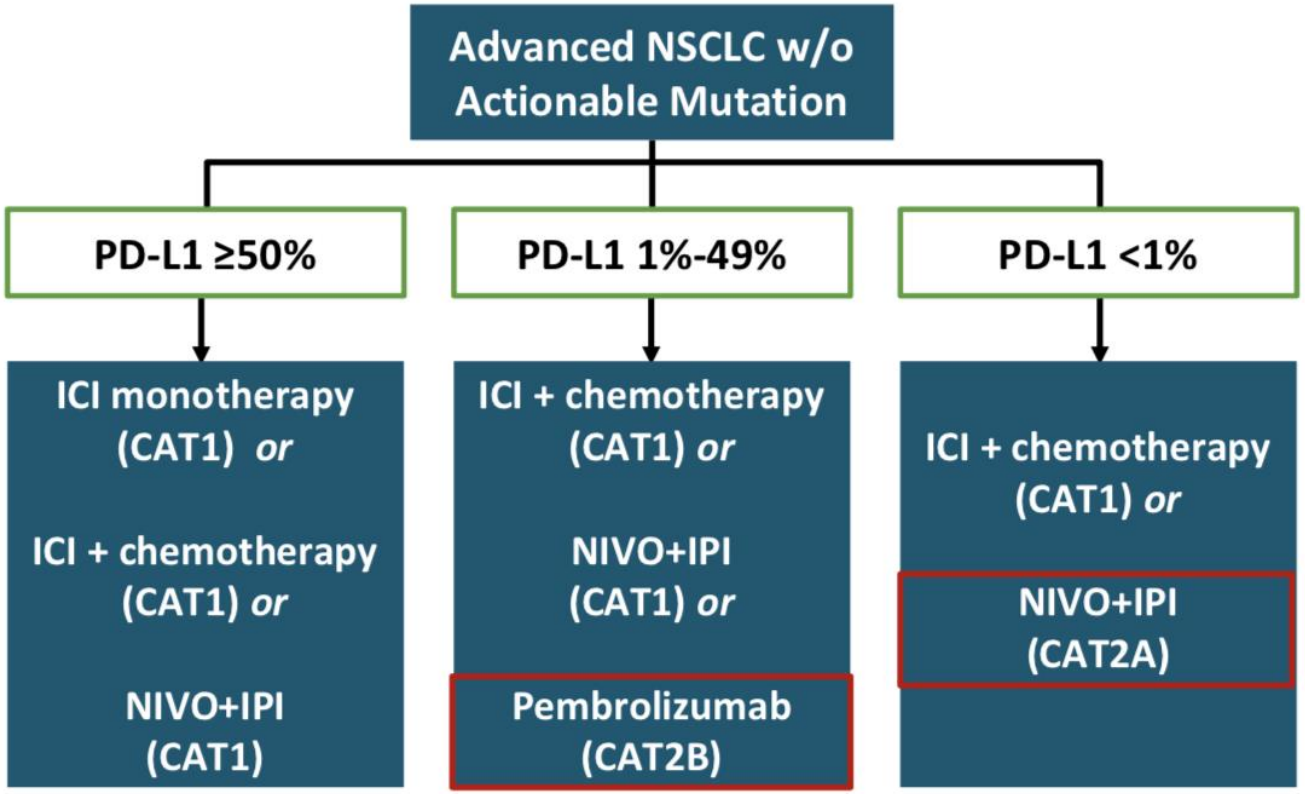
Immune Checkpoint Blockage

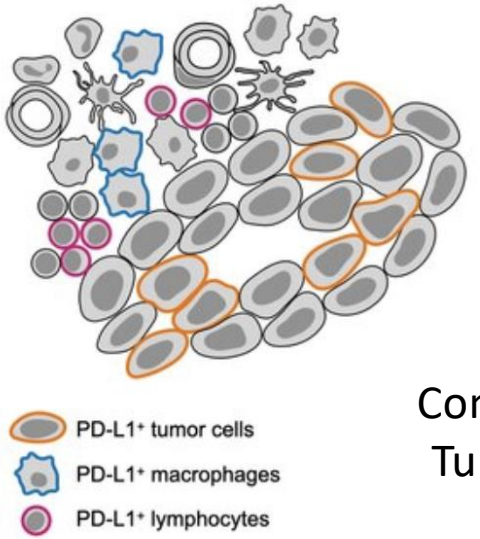




- *Ther Adv Med Oncol* 2021, Vol. 13: 1–18

First-line Treatment Options for Advanced NSCLC Without Actionable Driver Mutations





$$\text{CPS} = \frac{\#\text{ PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\#\text{ viable tumor cells}} \bullet 100$$

$$\text{TPS} = \frac{\#\text{ PD-L1 positive tumor cells}}{\#\text{ viable tumor cells}} \bullet 100$$

Combined positive score (CPS).
Tumor proportion score (TPS)

"The current version of NCCN guidelines for NSCLC is version 3.2024."

NCCN. Clinical practice guidelines in oncology: NSCLC. v2.2024.

Stage III NSCLC (Unresectable)

NCCN Guidelines Version 5.2024
Non-Small Cell Lung Cancer

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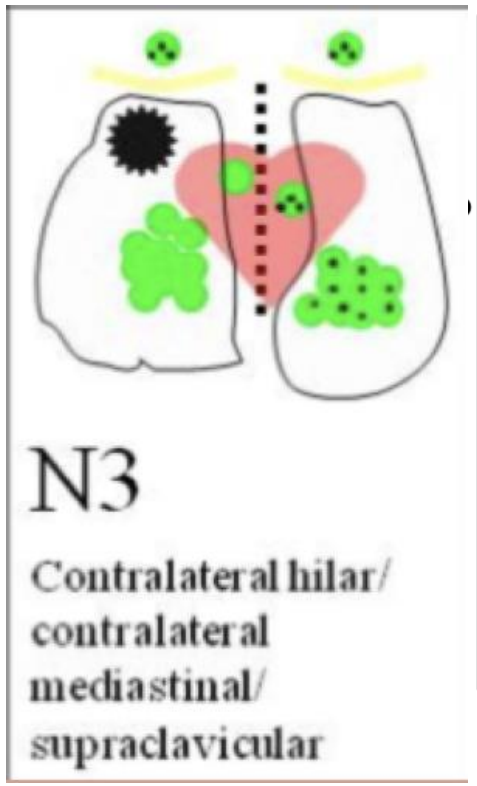
N3

Stage IIIB (T1–2, N3)
Stage IIIC (T3, N3)



N3 negative → See Initial treatment for stage I–IIIA (NSCL-9)

N3 positive → Definitive concurrent chemoradiation[l,t] (category 1) → Durvalumab[t,u] (category 1) → Surveillance (NSCL-16)

Metastatic disease → See Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)

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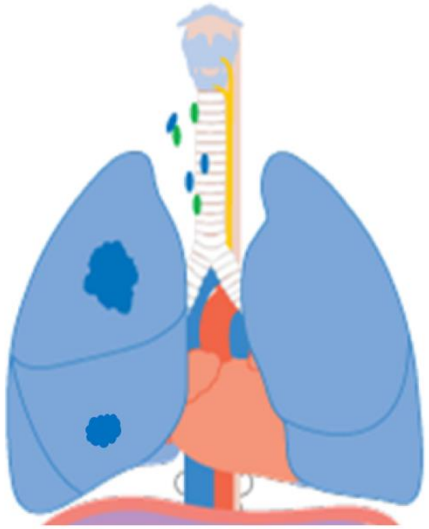
CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT

T4

Stage IIIB (T4, N2)
Stage IIIC (T4, N3)



Contralateral mediastinal node negative

- **Ipsilateral mediastinal node negative (T4, N0–1)** → See Treatment for Stage IIIA (NSCL-7)
- **Ipsilateral mediastinal node positive (T4, N2)** → **Definitive concurrent chemoradiation[l,t] (category 1)** → **Durvalumab[t,u] (category 1)** → Surveillance (NSCL-16)

Contralateral mediastinal node positive (T4, N3) → **Definitive concurrent chemoradiation[l,t] (category 1)** → **Durvalumab[t,u] (category 1)** → Surveillance (NSCL-16)

Metastatic disease → See Treatment for Metastasis limited sites (NSCL-14) or

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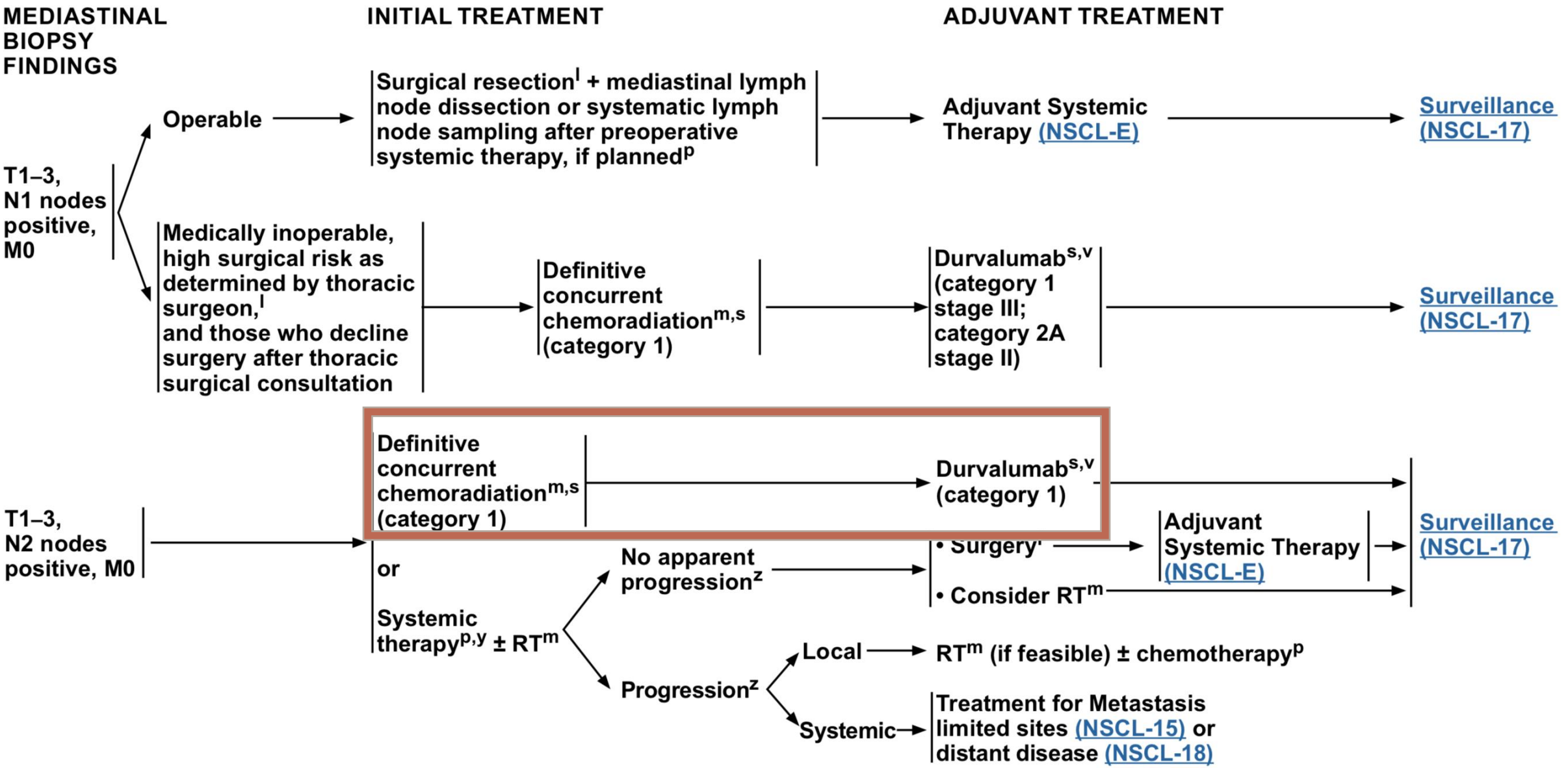

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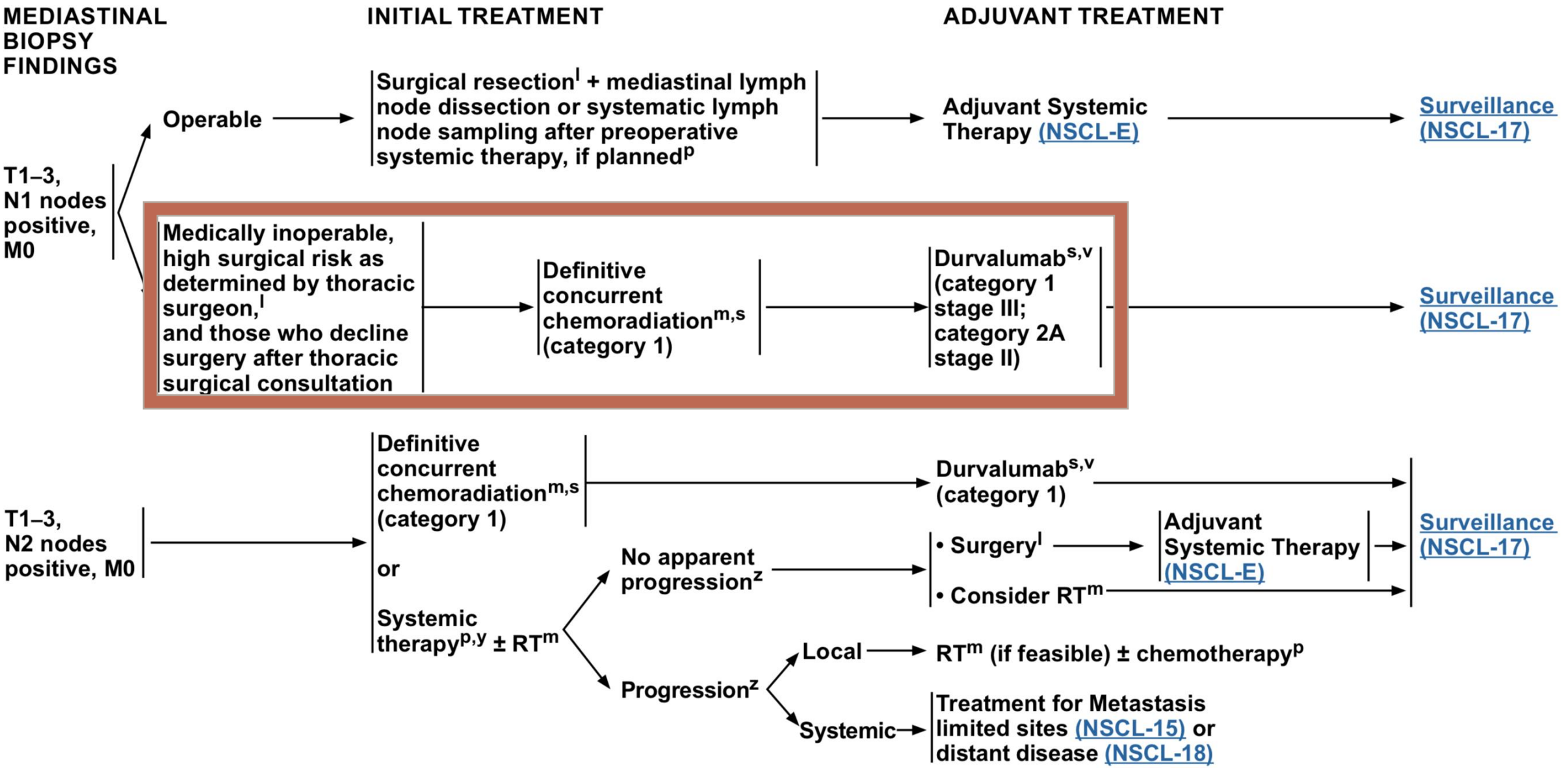
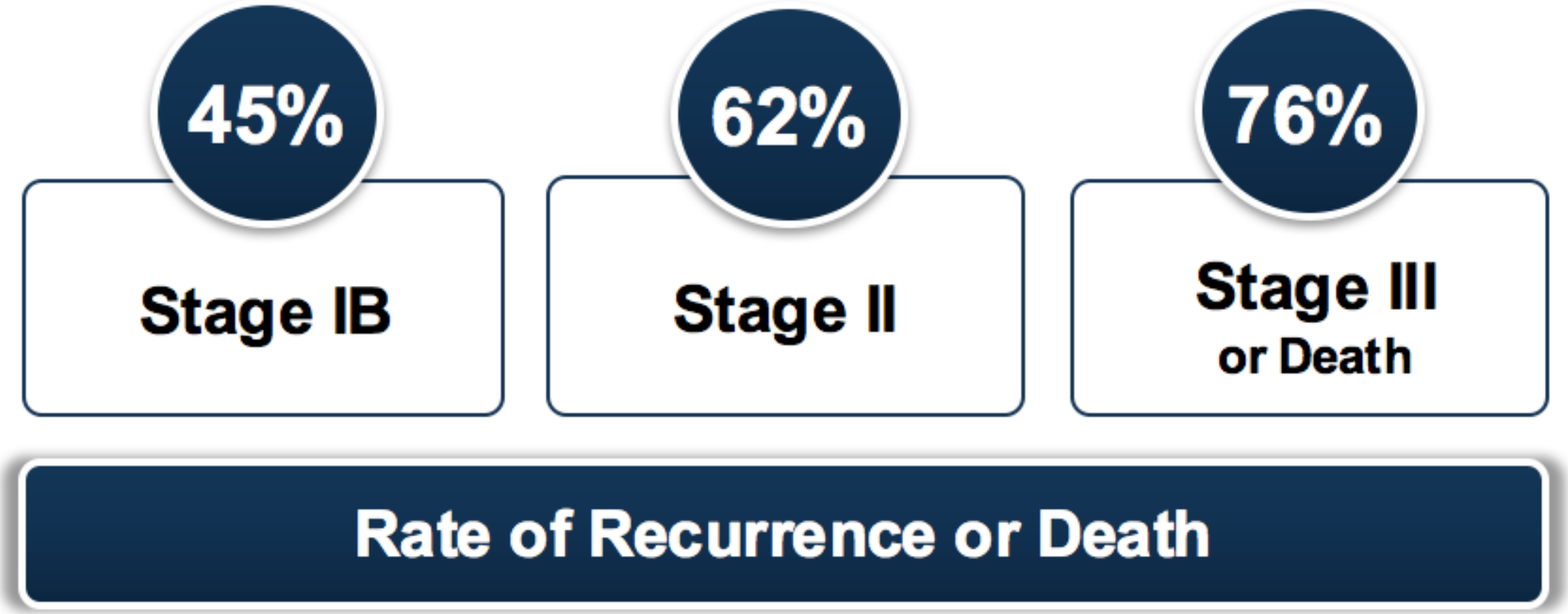


Resectable NSCLC

The Majority of Patients Who Receive Adjuvant Chemotherapy Will Experience Recurrence Within 5 Years



Pignon J-P et al. *J Clin Oncol*. 2008;26:3552-3559.

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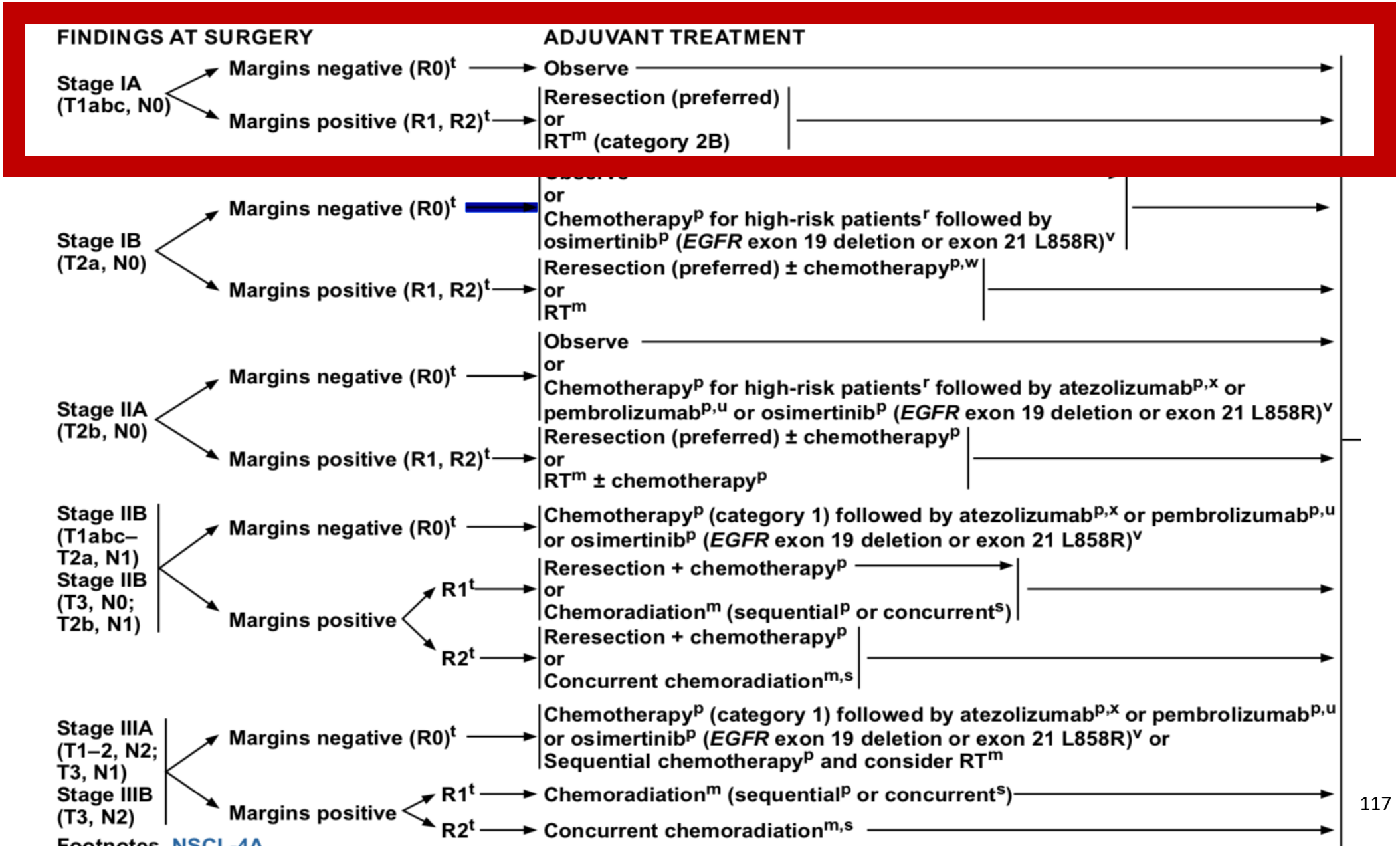
NCCN G
Ta



Footnotes NSCL-4A

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

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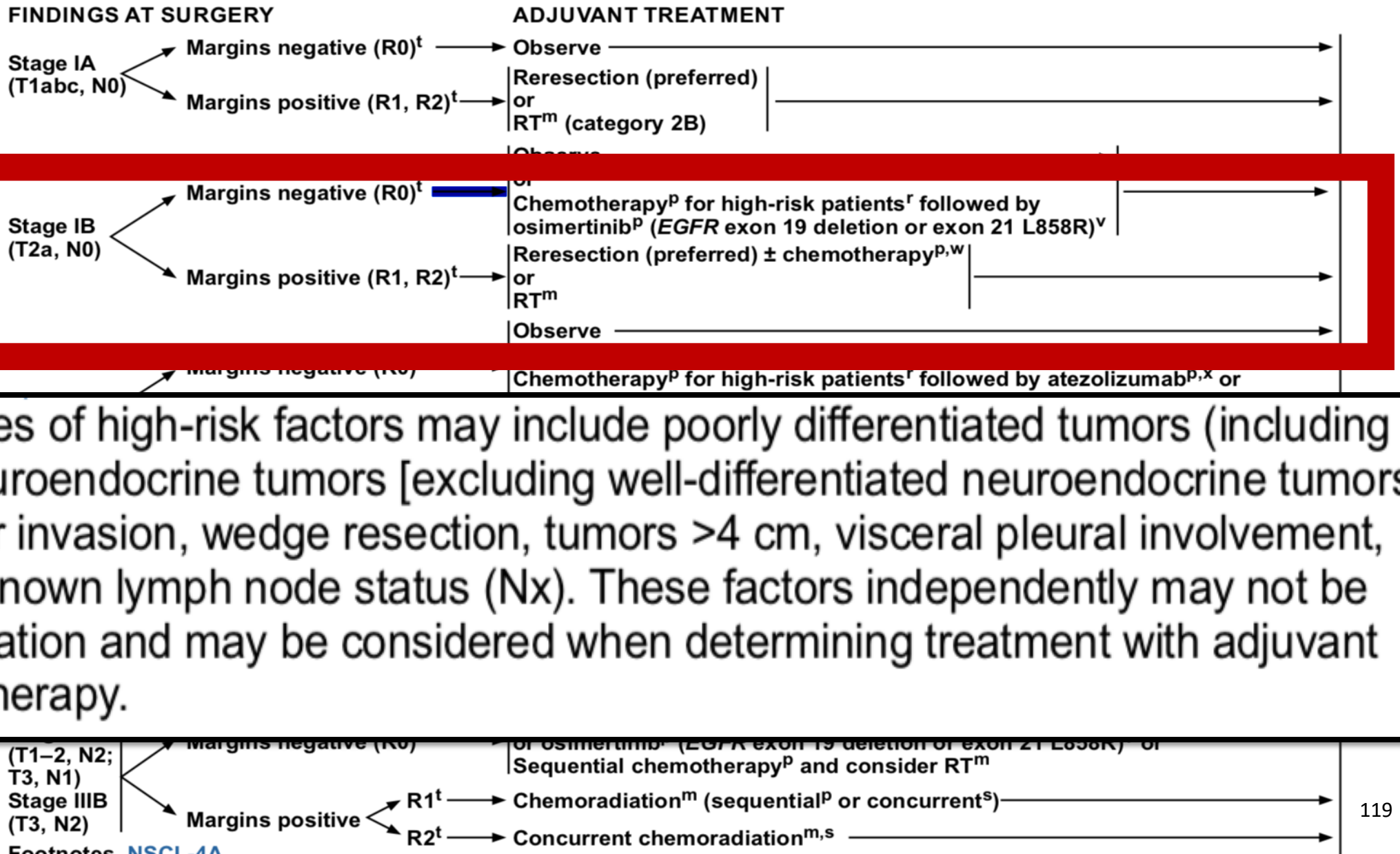

Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

NSCLC Staging : 8th AJCC

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

T		Primary Tumor
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	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

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NCCN G
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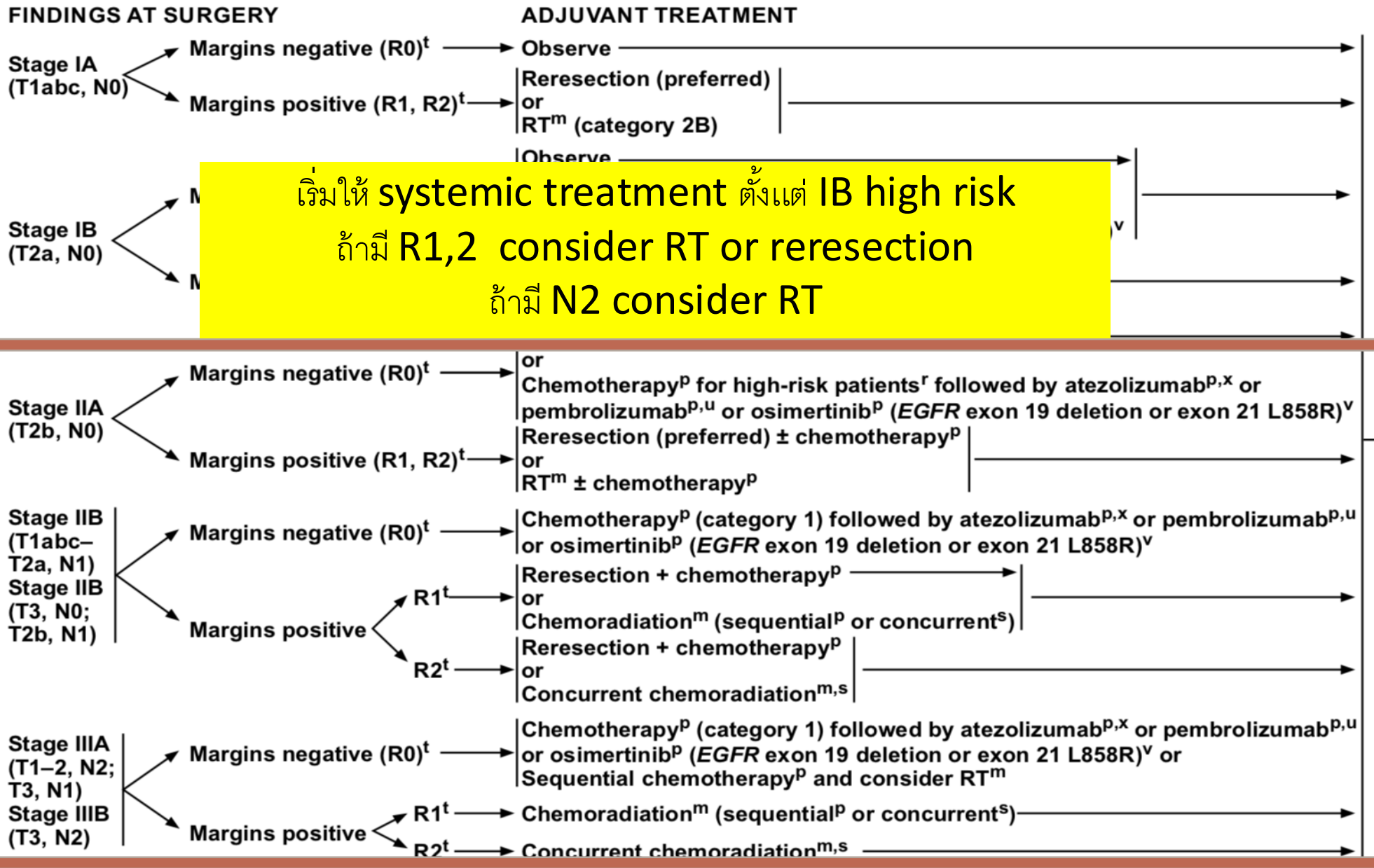


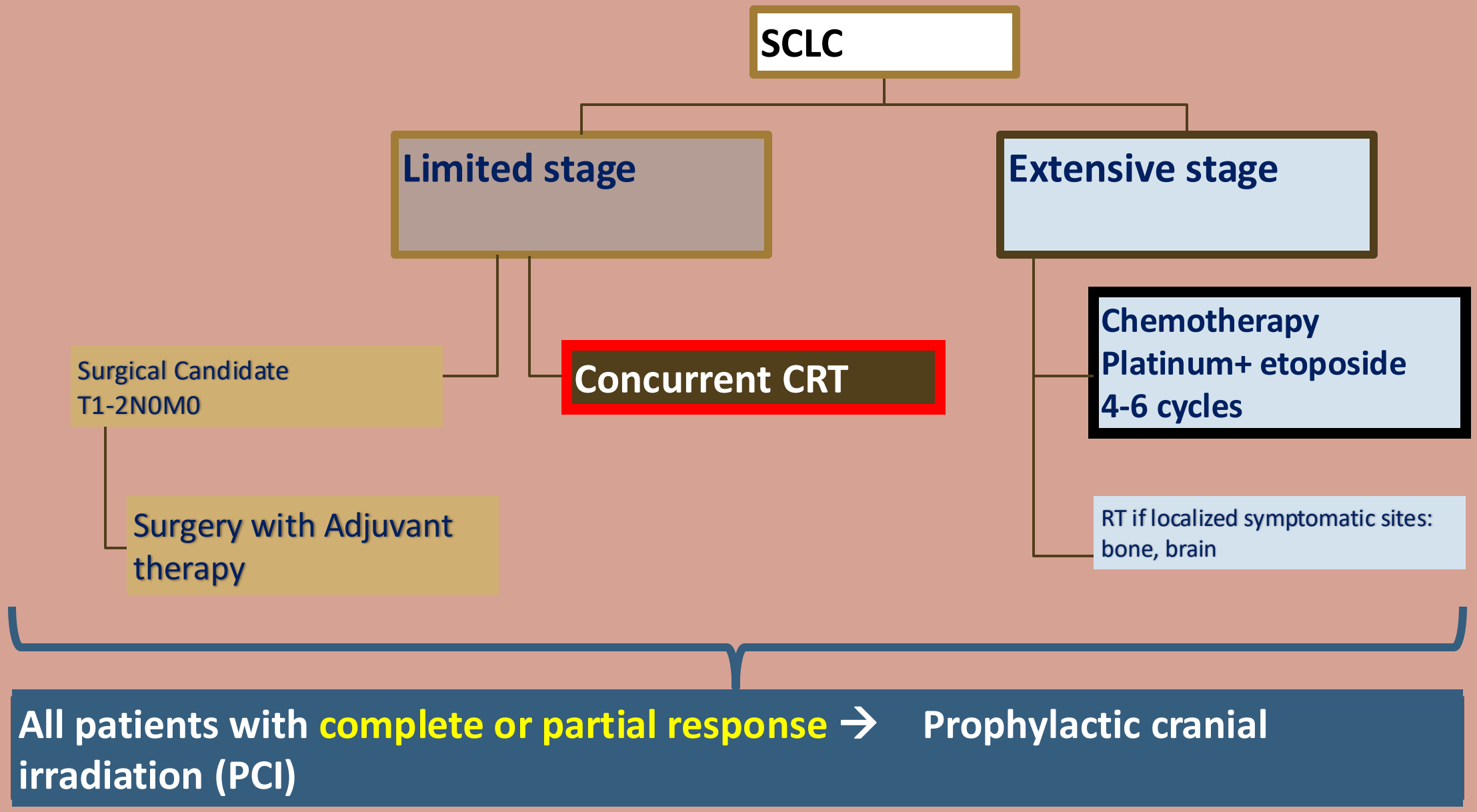
Small Cell lung Cancer

Staging System

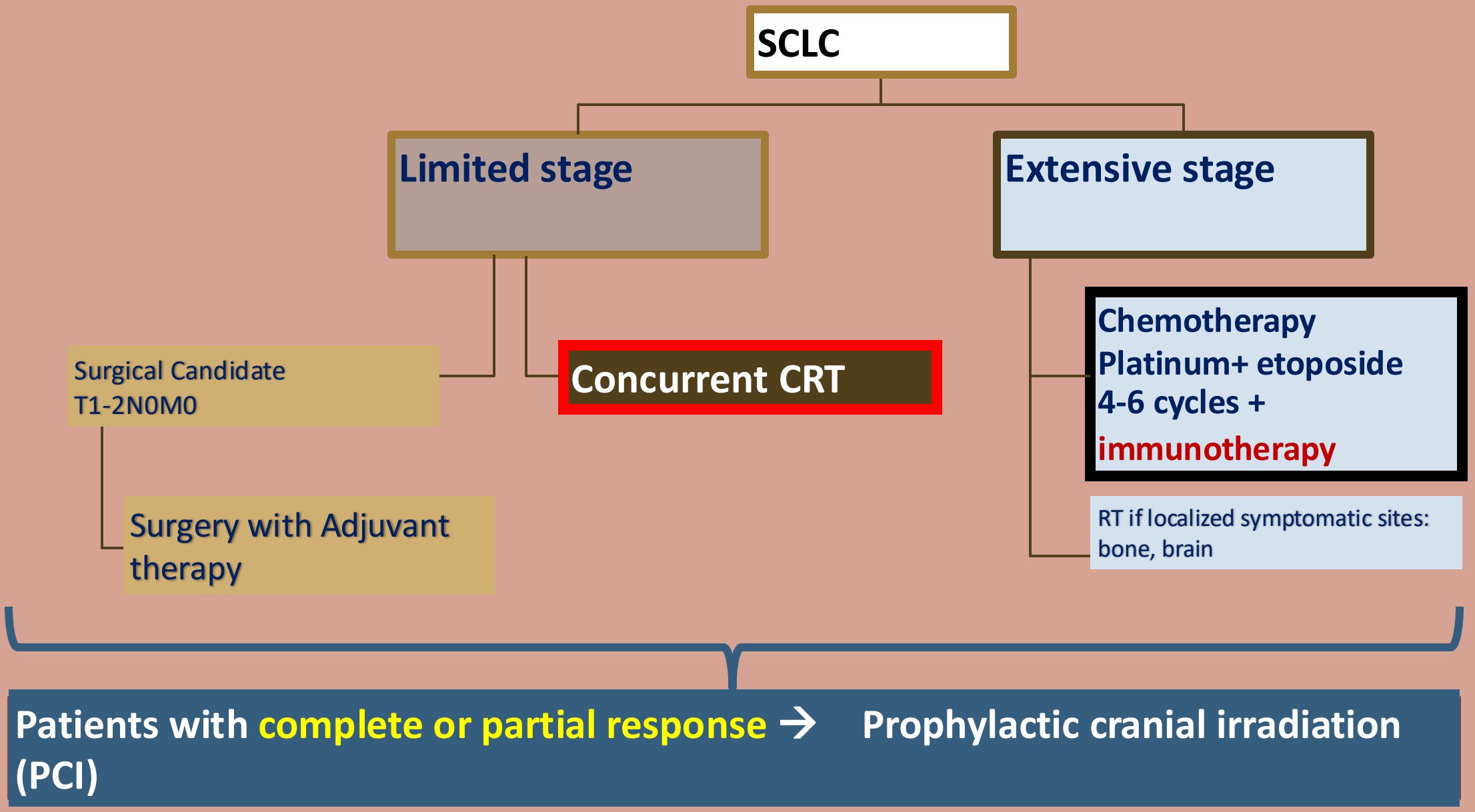
- The Veterans Lung Study Group (LD-ED)
  - Simplicity
  - Limited-stage (30%)
    - dz confined to ipsilateral hemithorax which can be safely encompassed within RT field
    - contralateral mediastinal and ipsilateral SCLN – LD
    - contralateral hilar and SCLN- controversy

- **TNM staging (LD = T1-3, N0-3, M0)**
  - more ass. with prognosis in AJCC 8th
  - **TNM classification (as NSCLC)- useful for selecting T1-2, N0 for surgery and RT plan**

Treatment Of Small Cell Lung Cancer



Treatment Of Small Cell Lung Cancer



PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of systemic therapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens

- **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]**
- **Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]**

Other Recommended Regimens

- **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]**
- **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]**

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimen

- **Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1, every 21 days (category 1, for all)[b,5]**
- **Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]**
- **Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]**

Other Recommended Regimens

- **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[7]**
- **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]**
- **Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]**
- **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]**

Useful In Certain Circumstances

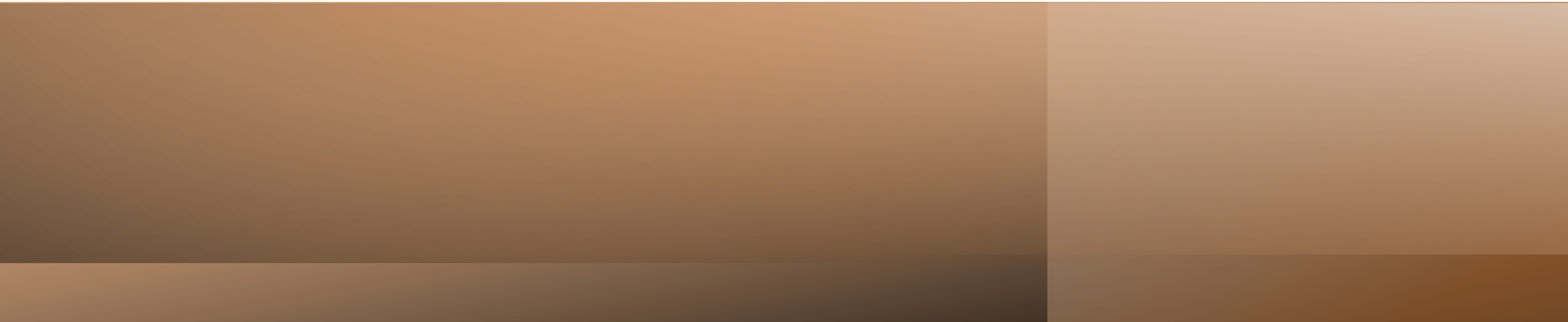
- **Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]**
- **Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]**
- **Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]**

[a] Cisplatin contraindicated or not tolerated.
[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

Subsequent Systemic Therapy (SCL-E 2 of 4)
Response Assessment (SCL-E 3 of 4)
References (SCL-E 4 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Management of Colorectal cancer



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Colon Cancer

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CLINICAL PRESENTATION[a]

WORKUP[j]

Early

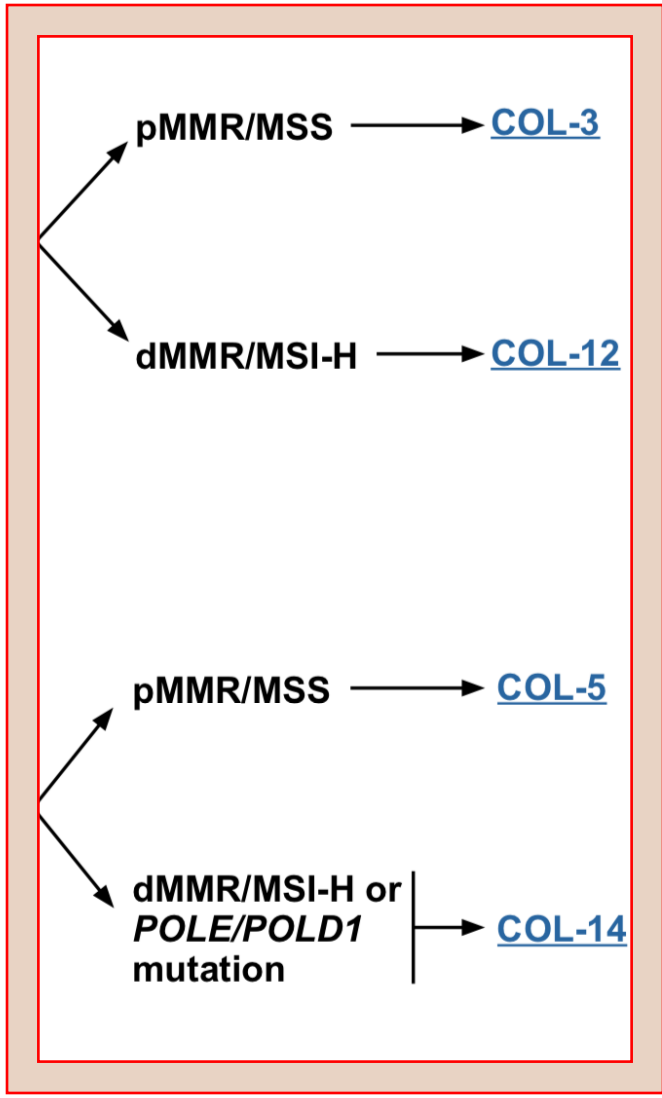
Colon cancer appropriate for resection (non-metastatic)[i]

- Biopsy
- MMR/MSI testing[e]
- Pathology review[f]
- Colonoscopy
- Consider abdomen/pelvis MRI[b,k]
- Complete blood count (CBC), chemistry profile, carcinoembryonic antigen (CEA)
- C/A/P CT[b]
- Enterostomal therapist as indicated for preoperative marking of site, teaching
- FDG-PET/CT scan is not indicated[b]
- Fertility risk discussion/counseling in appropriate patients

Metastasis

Suspected or proven metastatic adenocarcinoma

- Colonoscopy
- C/A/P CT[b]
- CBC, chemistry profile, CEA
- Molecular testing, including[l,m]:
  - *RAS* and *BRAF* mutations; HER2 amplifications; MMR or MSI status (if not previously done)
  - Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK*.
- Biopsy, if clinically indicated
- Consider FDG-PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases[b]
  - Consider MRI of liver for liver metastases that are potentially resectable[b]
- If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases



Work up

CLINICAL PRESENTATION[a]

WORKUP[j]

Early

Colon cancer appropriate for resection (non-metastatic)[i]

- Biopsy
- MMR/MSI testing[e]
- Pathology review[f]
- Colonoscopy
- Consider abdomen/pelvis MRI[b,k]
- Complete blood count (CBC), chemistry profile, carcinoembryonic antigen (CEA)
- C/A/P CT[b]
- Enterostomal therapist as indicated for preoperative marking of site, teaching
- FDG-PET/CT scan is not indicated[b]
- Fertility risk discussion/counseling in appropriate patients

→ pMMR/MSS → COL-3

→ dMMR/MSI-H → COL-12

Metastasis

Suspected or proven metastatic adenocarcinoma

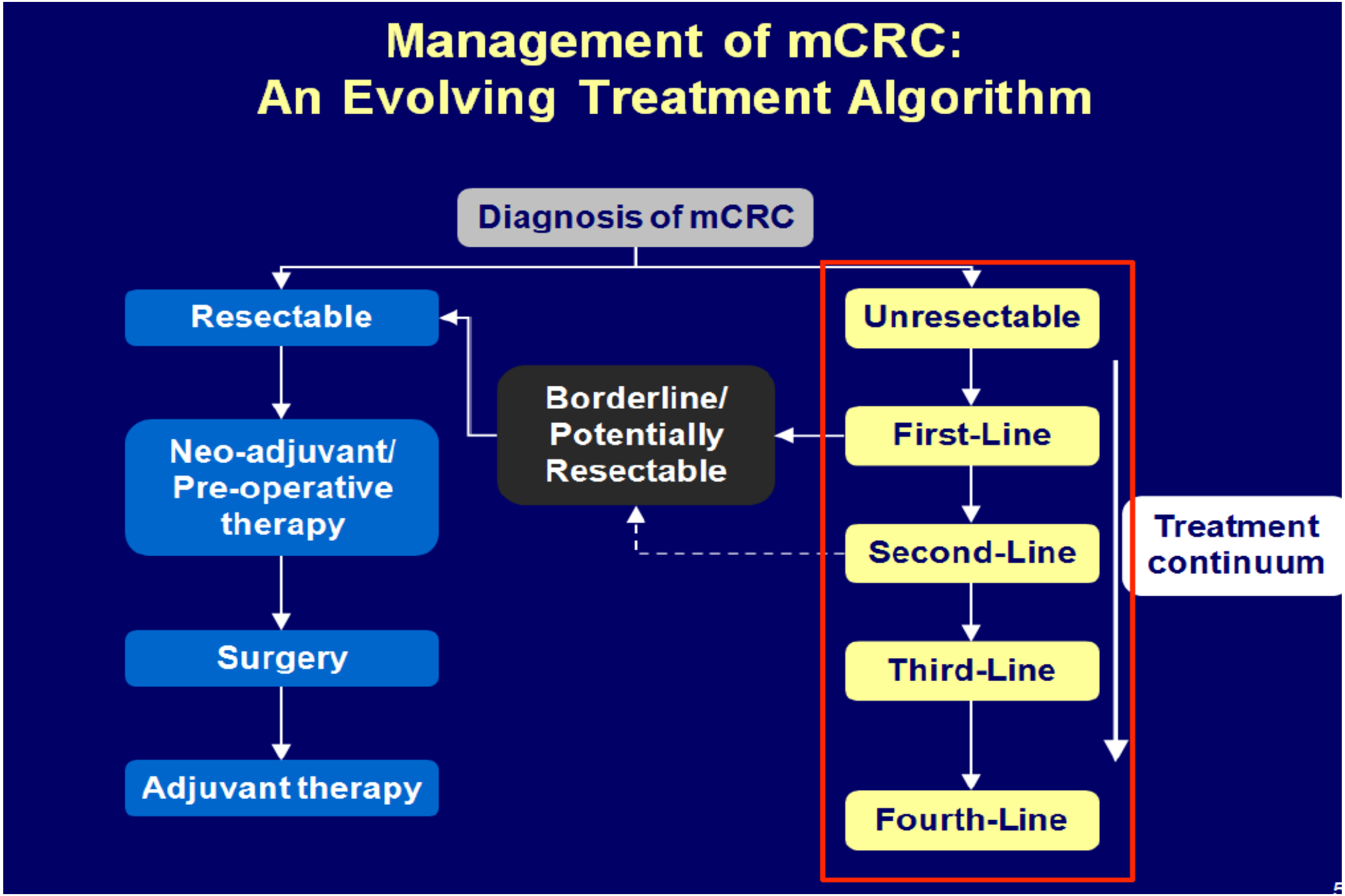
- Colonoscopy
- C/A/P CT[b]
- CBC, chemistry profile, CEA
- Molecular testing, including[l,m]:
  - *RAS* and *BRAF* mutations; HER2 amplifications; MMR or MSI status (if not previously done)
  - Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK*.
- Biopsy, if clinically indicated
- Consider FDG-PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases[b]
  - Consider MRI of liver for liver metastases that are potentially resectable[b]
- If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases

→ pMMR/MSS → COL-5

→ dMMR/MSI-H or *POLE/POLD1* mutation → COL-14

2. Evaluate for Resection

Management of mCRC: An Evolving Treatment Algorithm



3. Systemic treatment

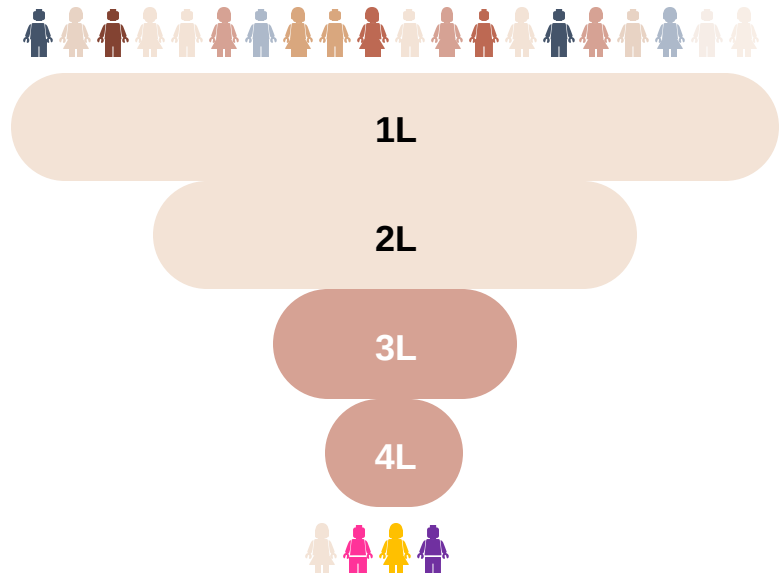
What Influences Treatment Choices in mCRC

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location



Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2
- NTRK
- RET

Patient preference

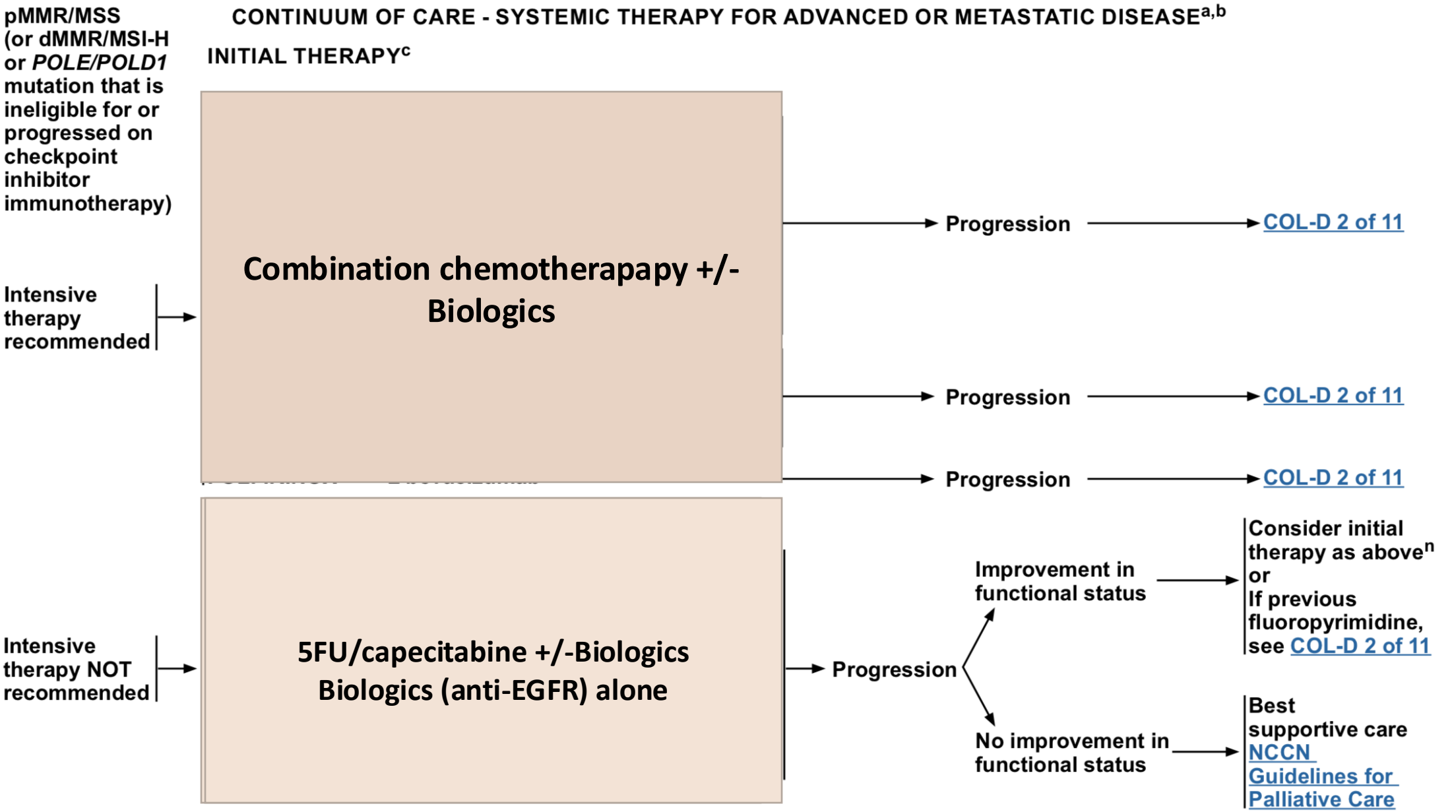
- Quality of life
- Toxicity profile

Availability and affordability

Therapy tailored according to individual patient needs

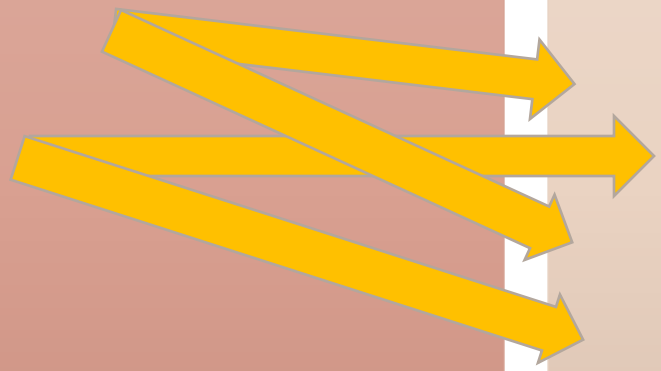
Modified from Van Cutsem. Ann Oncol. 2016;27:1386.

Slide credit: clinicaloptions.com


pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]
INITIAL THERAPY[c]
Intensive therapy recommended
Combination chemotherapapy +/- Biologics
Progression
COL-D 2 of 11
Progression
COL-D 2 of 11
Progression
COL-D 2 of 11
Intensive therapy NOT recommended
5FU/capecitabine +/-Biologics
Biologics (anti-EGFR) alone
Progression
Improvement in functional status
Consider initial therapy as above[n] or If previous fluoropyrimidine, see COL-D 2 of 11
No improvement in functional status
Best supportive care
NCCN Guidelines for Palliative Care

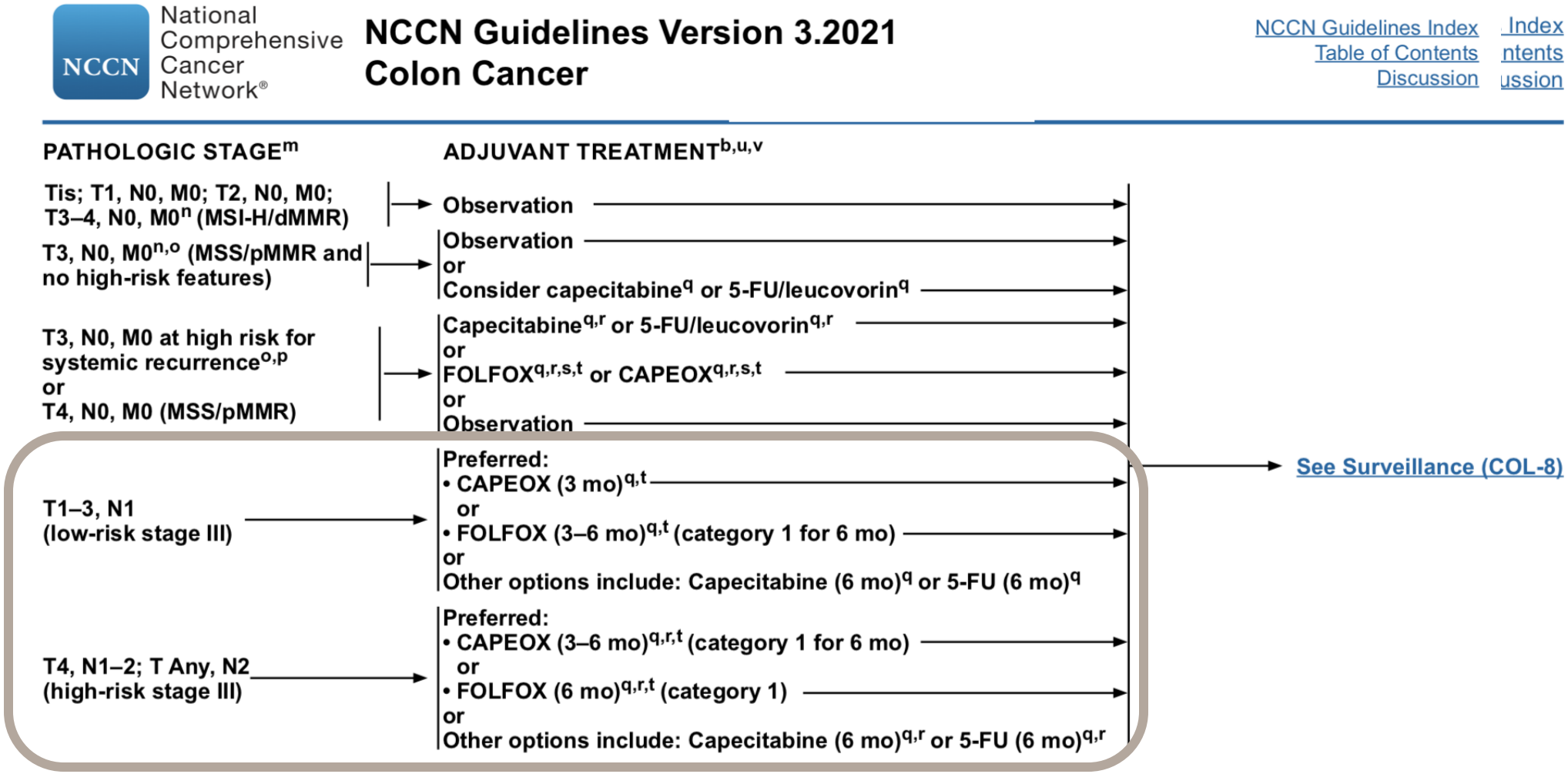
1st line mCRC with BIOLOGICS

- Chemotherapy
  - Combination
    - FOLFOX/XELOX/FLOX
    - FOLFIRI/IFL
  - Single
    - 5FU/LV
    - Capecitabine



- Targeting Agent
  - Antiangiogenesis
    - Bevacizumab
    - Aflibercept
  - Anti-EGFR (only in KRAS-WT)**
    - Cetuximab
    - Panitumumab

Adjuvant chemotherapy of Stage III Colon cancer



Intracranial germ cell tumours (ICGCT)

@Neudrawlogy

PARINAUD'S SYNDROME

What?

Light-near dissociation (tectal pupils)

Eyelid retraction (Collier's sign)

Convergence retraction nystagmus

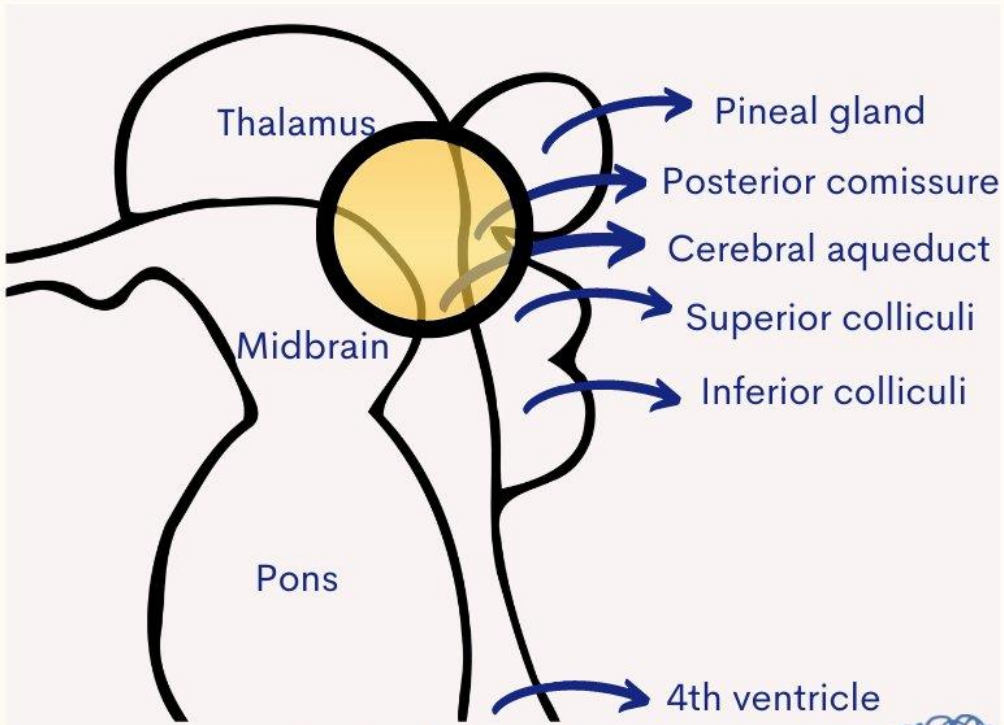
Impaired up gaze

Why?

- Pineal region tumors
- Multiple sclerosis
- Hydrocephalus -> "setting sun" sign
- Vascular disease (stroke)

Where?

DORSAL MIDBRAIN AND PRETECTAL AREA



Sagital view, brainstem

Central Nervous System Germinoma

Neurologic Symptoms	Endocrine Symptoms	Ophthalmologic Symptoms
headaches nausea projectile vomiting papilledema lethargy hemiparesis ataxia	diabetes insipidus GH insufficiency hypogonadism secondary hypothyroidism hypocortisolaemia (secondary adrenal insufficiency) menstrual irregularities precocious puberty	Parinaud's syndrome visual field deficits acuity deficits

Abbreviations: GH: growth hormone.

Biological Markers

AFP-serum or CSF

in embryonal, endodermal sinus or malignant teratoma

-if positive excludes a pure germinoma

B-HCG

10IU-70IU in 10-20% pure germinomas

>1000IU choriocarcinoma

- **Diagnosis**
- Need for biopsy controversial
- Recommended for pineal tumors
- Suprasellar – biopsy considered essential
- If elevated tumor marke-any AFP orβ-HCG more then 100 some consider adequate to diagnose "malignant" GCT

System Germinoma. *J. Pers. Med*. **2021**,*11*,661.

Central Nervous System Germinoma

Neurologic Symptoms	Endocrine Symptoms	Ophthalmologic Symptoms
headaches	diabetes insipidus	Parinaud's syndrome
nausea	GH insufficiency	visual field deficits
projectile vomiting	hypogonadism	acuity deficits
papilledema	secondary hypothyroidism	
lethargy	hypocortisolaemia (secondary	
hemiparesis	adrenal insufficiency)	
ataxia	menstrual irregularities	
	precocious puberty	

Abbreviations: GH: growth hormone.

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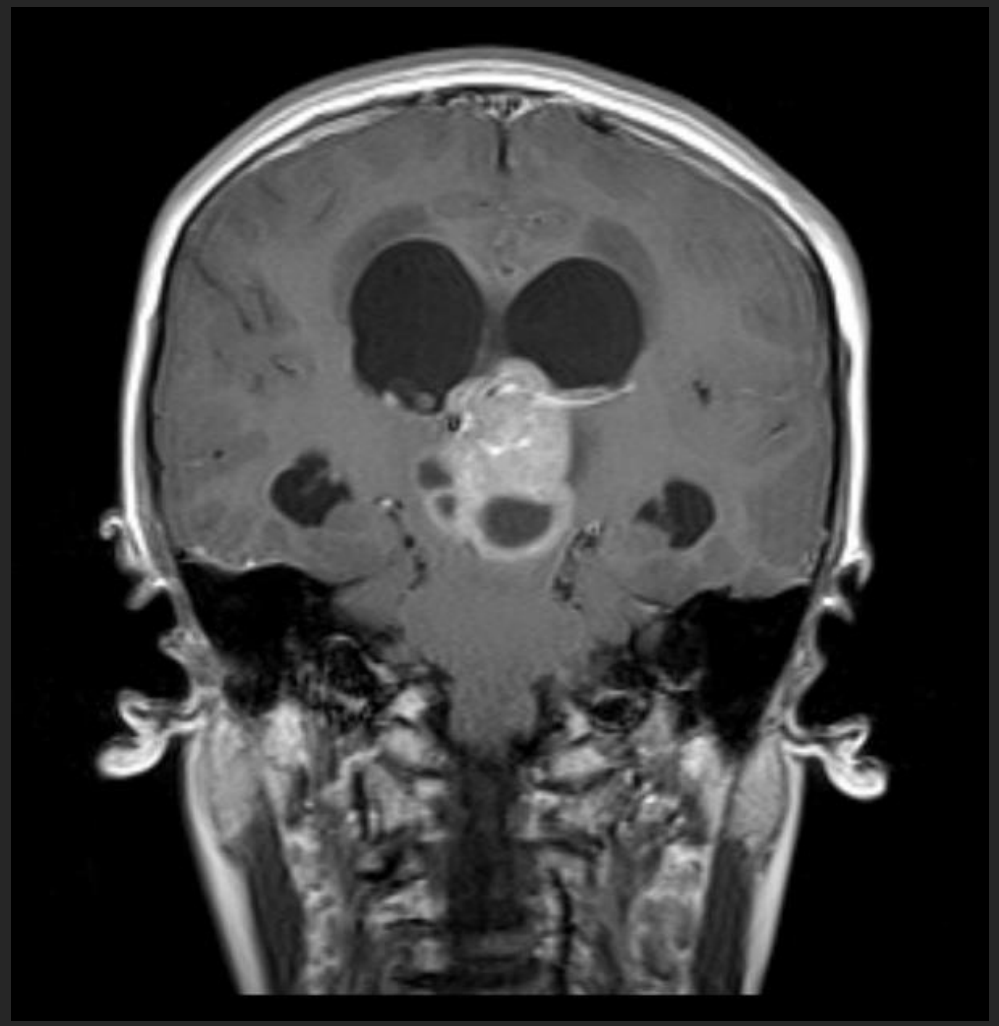
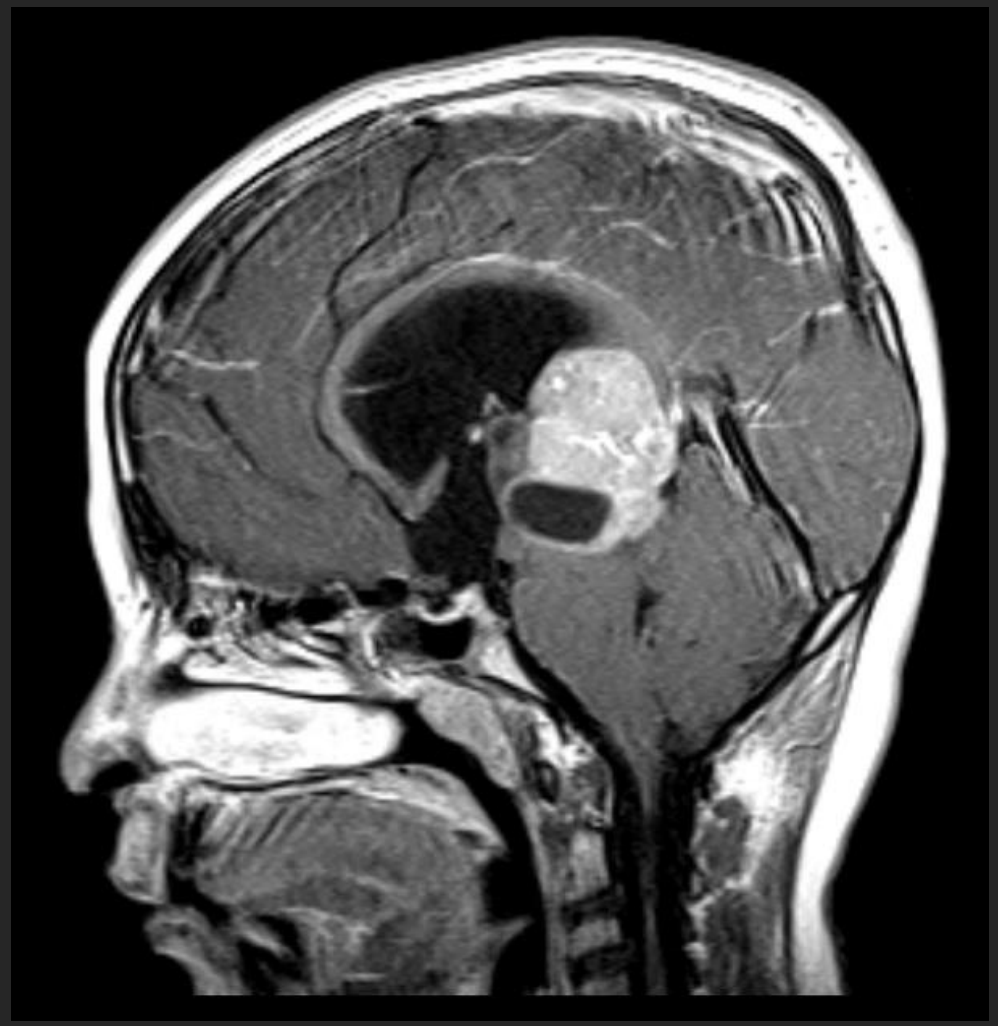
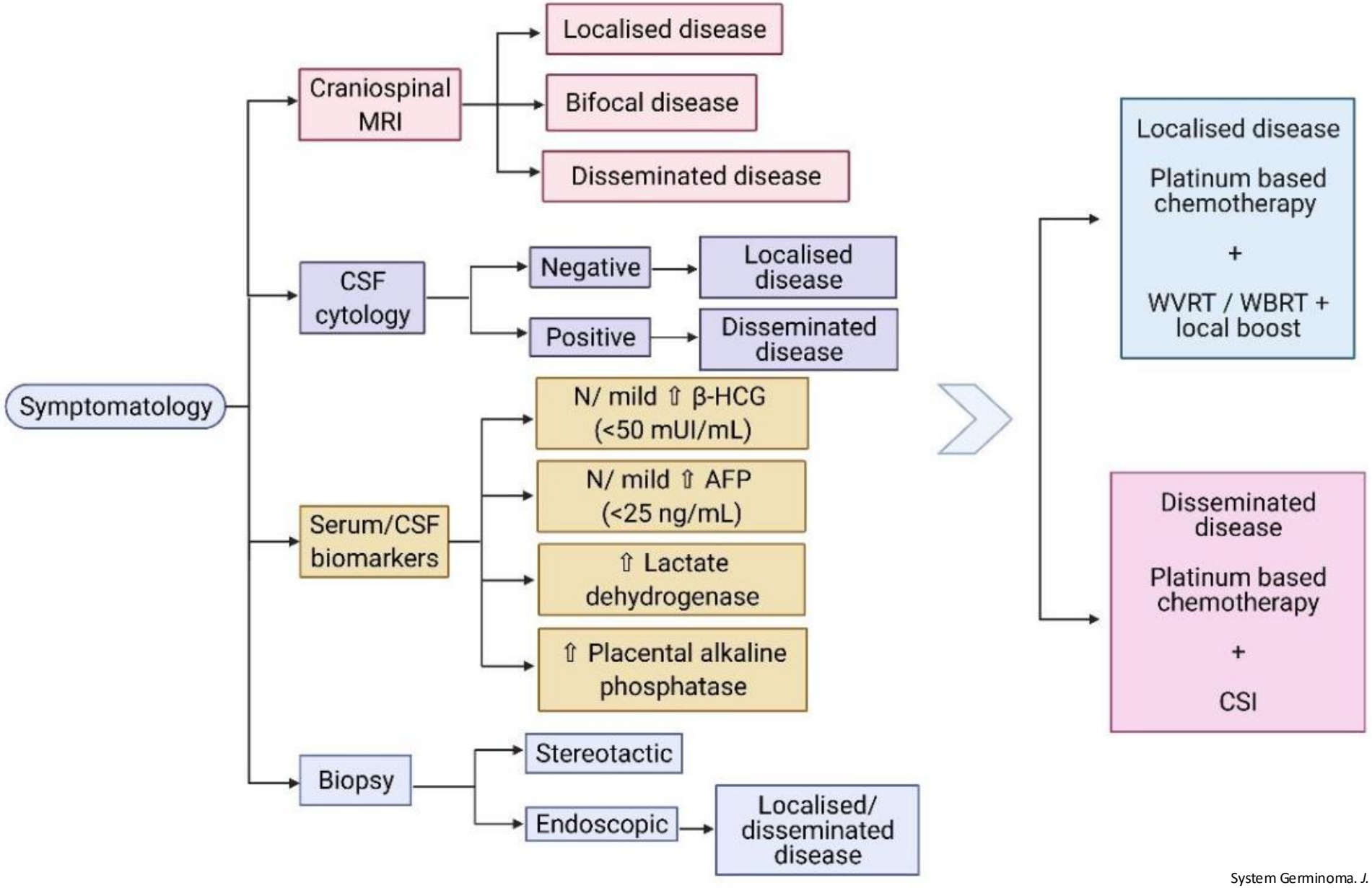




A large enhancing mass is centered on the pineal region. It is heterogeneous with areas of cystic change. There is marked compression of the tectum with resulting obstructive hydrocephalus.

https://radiopaedia.org/cases/pineal-germinoma

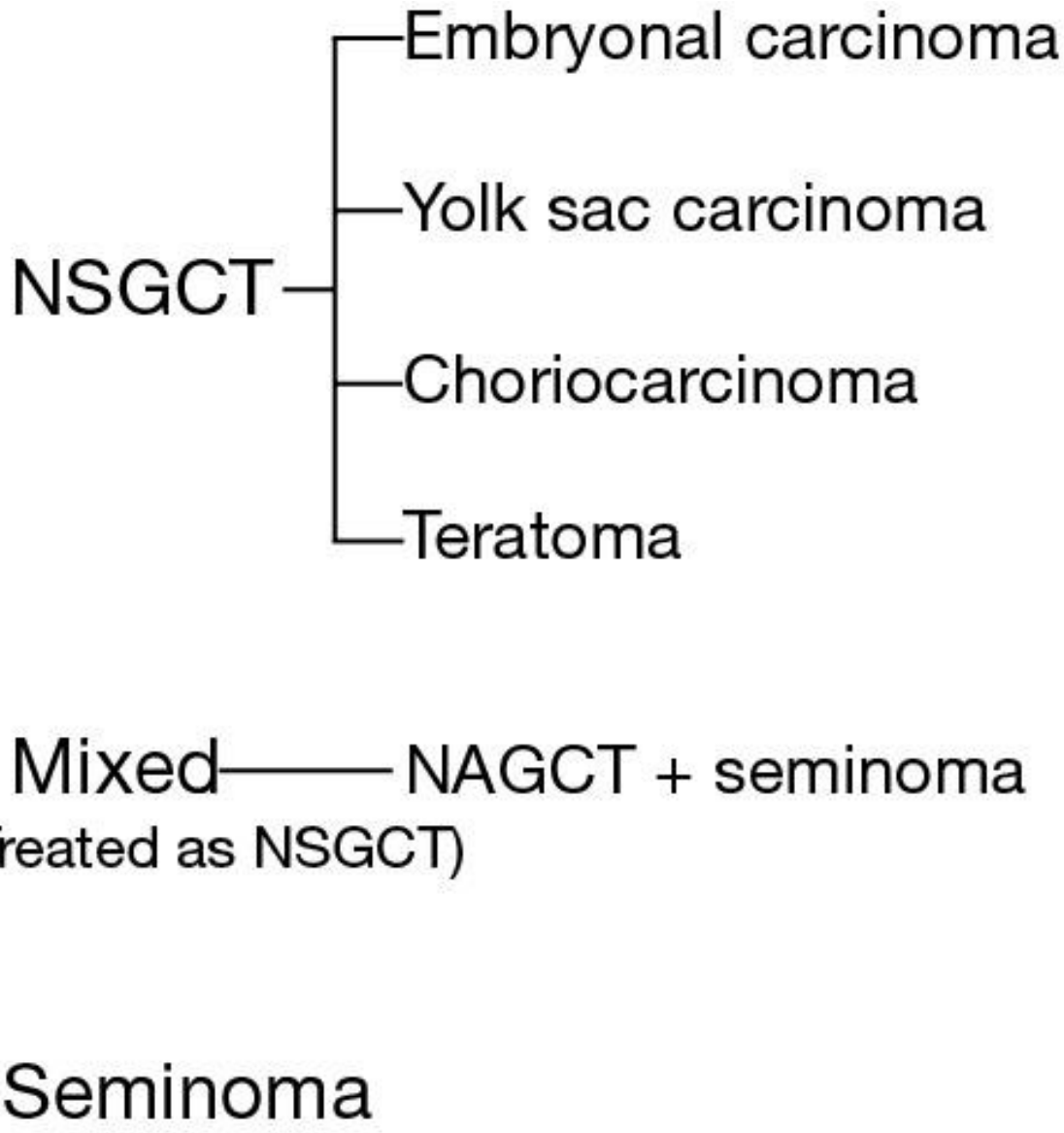


System Germinoma. *J. Pers. Med*. **2021**,*11*,661.

Primary Mediastinal Germ Cell Tumors

PMGCTs

- GCTs mainly originate from the gonads. However, 2–5% of cases arise in the midline structures,
- Mediastinum GCT is the most common site in adults aged between 25 and 35.
- PMGCTs account for 15–20% of all anterior mediastinal tumors.
- Non- seminoma is more frequent than seminoma in PMGCTs representing 60–70% of cases.
- Mature teratoma is the most frequent histology among non-seminoma PMGCTs and is usually managed with surgery.
- Immature teratomas are rarer aggressive tumors with poorer outcomes



iomedicines **2023**, *11*, 487.

Table 2. Immunohistochemistry in germ cell tumors.

	Seminoma	Immature Teratoma	Yolk Sac Tumor	Embryonal Carcinoma	Choriocarcinoma
Positive Markers	SALL4 OCT 3–4 NANOG c-kit PLAP	SALL4 SOX2 Cytokeratins EMA	SALL4 Glypican-3 Cytokeratins AFP	SALL4 OCT 3–4 CD30 SOX2 Cytokeratins NANOG	HCG Cytokeratins Glypican-3 SALL4 EMA
Negative Markers	CD30 Glypican-3 SOX2	OCT 3–4 CD30 c-kit NANOG SOX2	CD30 c-kit SOX2 NANOG OCT 3–4	c-kit Glypican-3	OCT 3–4 c-kit CD30 SOX2 NANOG

Good-prognosis group 5-year PFS 90% 5-year survival 96%	
Non-seminoma	*All of the following criteria:* Testis/retroperitoneal primary No non-pulmonary visceral metastases Age AFP < 1000 ng/mL hCG < 5000 IU/L (1000 ng/mL) LDH < 2.5 × ULN
Seminoma	*All of the following criteria:* Any primary site No non-pulmonary visceral metastases Age Normal AFP Any hCG Any LDH
Intermediate-prognosis group 5-year PFS 78% 5-year survival 89%	
Non-seminoma	*Any of the following criteria:* Testis/retroperitoneal primary No non-pulmonary visceral metastases Age AFP 1000–10,000 ng/mL or hCG 5000–50,000 IU/L or LDH 2.5–10 × ULN
Seminoma	*All of the following criteria:* Any primary site Non-pulmonary visceral metastases Age Normal AFP Any hCG Any LDH
Poor-prognosis group 5-year PFS 54% 5-year survival 67%	
Non-seminoma	*Any of the following criteria:* Mediastinal primary Non-pulmonary visceral metastases Age AFP > 10,000 ng/mL or hCG > 50,000 IU/L (10,000 ng/mL) or LDH > 10 × ULN
Seminoma	No patients classified as "poor-prognosis"

Seminoma

Radiation therapy has been the treatment of choice

→ does not control systemic metastasis

First-line chemotherapy: cisplatin-based combination chemotherapy regimens,BEP (bleomycin, etoposide, and cisplatin)

Follow-up: clinical and serial radiographic If local growth of a residual mass is demonstrated during long-term follow-up →

second-line cisplatin-based + surgery and/or radiation

NON-SEMINOMATOUS GERM CELLS

- Appropriate therapy: 4 cycles of cisplatin-based chemotherapy (BEP)
- . When any reduction of Careful monitoring of pulmonary diffusing capacitypulmonary function is noted, Bleomycin is decreased or discontinued.
- Serum tumor markers levels normalize and surgery is planned after adequate functional and hematologic recovery
- Patients with persistently elevated serum tumor marker levels were treated with second-line chemotherapy before considering surgery

Additional Slide

- Paraneoplastic Syndrome
- IHC for occult primary

Paraneoplastic Syndrome

Mayo Clin Proc. 2010;85(9):838-854

Paraneoplastic Endocrine Syndrome

Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options[c]	References
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia: mild, sodium 130-134 mEq/L; moderate, sodium, 125-129 mEq/L; severe, sodium <125 mEq/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	Small cell lung cancer, mesothelioma, bladder, ureteral, endometrial, prostate, oropharyngeal, thymoma, lymphoma, Ewing sarcoma, brain, GI, breast, adrenal	Restrict fluids (usually <1000 mL/d) and encourage adequate salt and protein intake Demeclocycline, 300-600 mg orally twice daily Conivaptan, 20-40 mg/d IV Tolvaptan, ~10-60 mg/d orally Hypertonic (3%) saline at <1-2 mL/kg/h	5-7
Hyper-calcemia	Altered mental status, weakness, ataxia, lethargy, hypertonia, renal failure, nausea/vomiting, hypertension, bradycardia	Hypercalcemia: mild, calcium 10.5-11.9 mg/dL; moderate, calcium 12.0-13.9 mg/dL; severe, calcium ≥14.0 mg/dL Low to normal (<20 pg/mL) PTH level Elevated PTHrP level	Breast, multiple myeloma, renal cell, squamous cell cancers (especially lung), lymphoma (including HTLV-associated lymphoma), ovarian, endometrial	Normal saline, 200-500 mL/h Furosemide, 20-40 mg IV (use with caution and only after adequate fluid resuscitation) Pamidronate, 60-90 mg IV Zoledronate, 4 mg IV Prednisone, 40-100 mg/d orally (for lymphoma, myeloma) Calcitonin, 4-8 IU/kg SC or IM every 12 h Mithramycin, 25 µg/kg IV (often requires multiple doses) Gallium nitrate, 100-200 mg/m^2/d IV continuous infusion for 5 d Hemodialysis	4, 8, 9
Cushing syndrome	Muscle weakness, peripheral edema, hypertension, weight gain, centripetal fat distribution	Hypokalemia (usually <3.0 mmol/L), elevated baseline serum cortisol (>29.0 µg/dL), normal to elevated midnight serum ACTH (>100 ng/L) not suppressed with dexamethasone	Small cell lung cancer, bronchial carcinoid (neuroendocrine lung tumors account for ~50%-60% of cases of paraneoplastic Cushing syndrome), thymoma, medullary thyroid cancer, GI, pancreatic, adrenal, ovarian	Ketoconazole, 600-1200 mg/d orally Octreotide, 600-1500 µg/d SC or octreotide LAR, 20-30 mg IM monthly Aminoglutethimide, 0.5-2 g/d orally Metyrapone, ~1.0 g/d orally Mitotane, 0.5-8 g/d orally Etomidate, 0.3 mg/kg/h IV Mifepristone, 10-20 mg/kg/d orally Adrenalectomy	10-14
Hypo-glycemia	Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma	For non–islet cell tumor hypoglycemia: low glucose, low insulin (often <1.44-3.60 µIU/mL), low C-peptide (often <0.3 ng/mL), elevated IGF-2:IGF-1 ratio (often >10:1) For insulinomas: low glucose, elevated insulin, elevated C-peptide, normal IGF-2:IGF-1 ratio	Mesothelioma, sarcomas, lung, GI	Glucose (oral and/or parenteral) Dexamethasone, 4 mg 2 or 3 times daily Prednisone, 10-15 mg/d Diazoxide, 3-8 mg/kg/d orally divided in 2 or 3 doses Glucagon infusion, 0.06-0.3 mg/h IV Octreotide, ~50-1500 µg/d SC or octreotide LAR, 20-30 mg IM monthly (often with corticosteroids) Human growth hormone, 2 U/d SC (often with corticosteroids)	4, 15-20

Paraneoplastinc Neurologic Symptom

***Mayo Clin Proc*. 2010;85(9):838-854**

Syndrome	Clinical presentation	Associated antibodies[b]	Diagnostic studies	Associated cancers	Treatment options[b]	References
Limbic encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	anti-Hu (typically with small cell lung cancer) anti-Ma2 (typically testicular cancer) anti-CRMP5 (anti-CV2) anti-amphiphysin	EEG: epileptic foci in temporal lobe(s); focal or generalized slow activity FDG-PET: increased metabolism in temporal lobe(ss) MRI: hyperintensity in medial temporal lobe(s) CSF analysis: pleocytosis, elevated protein, elevated IgG, oligoclonal bands	SCLC (~40%-50% of LE patients), testicular germ-cell (~20% of LE patients), breast (~8% of LE patients), thymoma, teratoma, Hodgkin lymphoma	IVIG, 400-1000 mg/d to total 2-3 g Methylprednisolone, up to 1 g/d IV Prednisone, 1 mg/kg per day orally Plasma exchange Cyclophosphamide, ~2 mg/kg/d orally Rituximab, 375 mg/m^2 IV per dose	27-44
Paraneoplastic cerebellar degeneration	Ataxia, diplopia, dysphagia, dysarthria; prodrome of dizziness, nausea, vomiting	anti-Yo anti-Hu anti-CRMP5 (anti-CV2) anti-Ma anti-Tr anti-Ri anti-VGCC anti-mGluR1	FDG-PET: increased metabolism (early stage) and then decreased metabolism (late stage) in cerebellum MRI: cerebellar atrophy (late stage)	SCLC, gynecologic, Hodgkin lymphoma, breast	IVIG, 400-1000 mg/d to total 2-3 g Methylprednisolone, up to 1 g/d IV Plasma exchange Cyclophosphamide, ~2 mg/kg/d orally Rituximab, 375 mg/m^2 IV per dose	27, 28, 30, 33, 35, 36, 38-56
Lambert-Eaton myasthenia syndrome (LEMS)	Lower extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in MG); later in course, autonomic symptoms (ptosis, impotence, dry mouth) in most patients	anti-VGCC (P/Q type)	EMG: low compound muscle action potential amplitude; decremental response with low-rate stimulation but incremental response with high-rate stimulation	SCLC (~3% of patients have LEMS), prostate, cervical, lymphomas, adenocarcinomas	3,4-DAP, maximum of 80 mg/d orally Guanidine, ~575 mg/d orally (with pyridostigmine) Pyridostigmine, ~240-360 mg/d orally (with guanidine) Prednisolone, 60-100 mg orally every other day Azathioprine, up to 2.5 mg/kg/d orally IVIG, 400-1000 mg/d to total 2-3 g Plasma exchange	27, 30, 44, 57-66

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Limbic encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	anti-Hu (typically with small cell lung cancer) anti-Ma2 (typically testicular cancer) anti-CRMP5 (anti-CV2) anti-amphiphysin	EEG: epileptic foci in temporal lobe(s); focal or generalized slow activity FDG-PET: increased metabolism in temporal lobe(ss) MRI: hyperintensity in medial temporal lobe(s) CSF analysis: pleocytosis, elevated protein, elevated IgG, oligoclonal bands	SCLC (~40%-50% of LE patients), testicular germ-cell (~20% of LE patients), breast (~8% of LE patients), thymoma, teratoma, Hodgkin lymphoma	IVIG, 400-1000 mg/d to total 2-3 g Methylprednisolone, up to 1 g/d IV Prednisone, 1 mg/kg per day orally Plasma exchange Cyclophosphamide, ~2 mg/kg/d orally Rituximab, 375 mg/m^2 IV per dose	27-44
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Paraneoplastic Neurologic Symptom

***Mayo Clin Proc*. 2010;85(9):838-854**

Myasthenia gravis (MG)	Fatigable weakness of voluntary muscles (ocular-bulbar and limbs), diaphragmatic weakness	anti-AchR	EMG: decremental response to repetitive nerve stimulation	Thymoma (in ~15% of MG patients)	Thymectomy Pyridostigmine, ~600 mg/d orally in divided doses Prednisone, ~1 mg/kg/d orally Azathioprine, up to 2.5 mg/kg/d orally (with corticosteroids) Cyclosporine A, ~3 mg/kg/d orally Tacrolimus, 3-4 mg/d orally Mycophenolate mofetil, 1-3 g/d orally Rituximab, 375 mg/m^2 IV per dose Cyclophosphamide, 50 mg/kg/d IV for 4 d Plasma exchange IVIG, 400-1000 mg/d to total 2-3 g

IHC for occult primary malignancy

POTENTIAL IMMUNOHISTOCHEMISTRY/IN SITU HYBRIDIZATION MARKERS FOR UNKNOWN PRIMARY CANCERS

Undifferentiated Panel: For Determining Most Likely Cell Lineage[3]

Markers*	Most Likely Cell Lineage
Pan-keratin (AE1/AE3 & CAM5.2)	Carcinoma
CK5/6, p63/p40	Squamous cell carcinoma
S100, SOX10	Melanoma and sarcoma
LCA± CD20± CD3±	Lymphoma
OCT3/4± SALL4±	Germ cell tumor
WT1, calretinin, mesothelin, D2-40	Mesothelial tumor

*These markers are not uniformly specific or sensitive and can be present on other tumors.

COMMONLY USED IMMUNOHISTOCHEMISTRY/IN SITU HYBRIDIZATION MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Adrenocortical carcinoma	CK7-/CK20-	SF-1 Melan A Inhibin	
Breast carcinoma	CK7+/CK20-	GATA3 GCDFP-15 (BRST2)± Mammaglobin±	ER/PR±
Endocervical adenocarcinoma	CK7+/CK20-	p16+ (strong diffuse staining) PAX8±	Vimentin- ER/PR± Human papillomavirus in situ hybridization
Endometrial adenocarcinoma	CK7+/CK20-	Vimentin PAX8	ER/PR± p16- (to distinguish from endocervical and uterine serous carcinoma)
Hepatocellular carcinoma	CK7-/CK20-	Arginase-1 HepPar-1 Glypican-3 CD10 and polyclonal CEA± (peri-canalicular pattern)	MOC31- (to distinguish from intrahepatic cholangiocarcinoma) Albumin in situ hybridization - (also for intrahepatic cholangiocarcinoma)
Lower gastrointestinal carcinoma, including small intestinal, appendiceal, and colorectal	CK7-/CK20+	CDX2 Villin SATB2	

COMMONLY USED IMMUNOHISTOCHEMISTRY/IN SITU HYBRIDIZATION MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Lung adenocarcinoma	CK7+/CK20-	TTF-1 NapsinA	
Mesothelioma	CK7+/CK20-	Calretinin WT1 CK5/6 D2-40 Mesothelin	p63- CEA- MOC31- BerEP4- TTF-1- (to distinguish from pulmonary adenocarcinoma)
Neuroendocrine carcinoma, including small cell carcinoma	CK7±/CK20± ("dot-like" pattern in Merkel cell carcinoma)	Chromogranin Synaptophysin	TTF-1± CDX-2± Mitotic rate and/or Ki-67 (for grade)
Non-seminomatous germ cell tumor	CK7-/CK20-	SALL4 OCT3/4±	CD30 Glypican-3 PLAP (for further subtyping)
Ovarian mucinous carcinoma	CK7+/CK20±	PAX8± CDX2±	SATB2-
Ovarian serous carcinoma	CK7+/CK20-	PAX8 WT1	p53 (abnormal) p16 (diffuse, strong)
Pancreaticobiliary carcinoma, including intrahepatic cholangiocarcinoma	CK7+/CK20±	CDX2± CK19	SMAD4 loss ± (pancreas, extrahepatic cholangiocarcinoma, and colorectal carcinomas) Albumin in situ hybridization - (also for intrahepatic cholangiocarcinoma)
Prostate carcinoma	CK7-/CK20-	PSA PSAP NKX3-1 P501S (prostein) ERG±	

COMMONLY USED IMMUNOHISTOCHEMISTRY/IN SITU HYBRIDIZATION MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Renal cell carcinoma	CK7±/CK20-	PAX2 PAX8 Carbonic anhydrase IX (CA9)± EMA± Vimentin± CD10± (membranous)	
Salivary gland carcinoma	CK7+/CK20-	CK5/6 p63	GATA3 AR HER2
Squamous cell carcinoma	CK7-/CK20-	CK5/6 p63 or p40 34βE12	p16 (strong diffuse staining) and/ or human papillomavirus in situ hybridization (HPV-associated carcinoma)
Thyroid carcinoma (follicular or papillary carcinomas)	CK7+/CK20-	TTF-1 PAX8 CK19±	Thyroglobulin
Thyroid carcinoma (medullary carcinoma)	CK7+/CK20-	TTF-1 PAX8 CK19±	Calcitonin, synaptophysin, chromogranin, and monoclonal CEA
Urothelial carcinoma	CK7+/CK20±	GATA3 p63 or p40 CK5/6± 34βE12 S100P Uroplakin II	
Upper gastrointestinal tract carcinoma, including esophagus and stomach	CK7+/CK20±	CDX-2± Villin±	

Long case examination

- Dyspnea
  - Malignant Pleural effusion
  - Malignant Pericardial effusion
  - Pulmonary embolism
- SVC sndrome
  - Ant mediastinal lesion
- Abdominal distension
  - Malignant ascites
  - Gut obstruction
    - GI cancer / carcinomatosis peritoneii
- Neurologic symptom
  - Cord compression
    - Bone metastasis
  - Multiple cranial neuropathy
  - Mid brain syndrome
    - Primary CNS tumor
  - Headache
    - CNS metastasis
  - Alteration of conciousness
    - Hypercalcemia
  - Seizure
- Hepatomegaly
  - Primary liver cancer
  - Liver met