IV Jornadas Hematológicas del Sur

URGENCIAS ONCOLÓGICAS

- Susana Calderón A.
- Medicina Interna-Hematología

INTRODUCCIÓN

Complicaciones que requieren evaluación y tratamiento urgentes

El incremento en la incidencia de neoplasias y mejoría en la sobrevida llevará a aumento de estos cuadros y llegada a atención primaria y/o s. de urgencia

La intervención oportuna puede ser vital y producir una disminución en la morbilidad y mortalidad

Emergencia oncológica: preguntar

- **Quién toma las decisiones**
- **Tipo de cáncer**
- **Tiempo desde el diagnóstico**
- **Tratamiento antineoplásico**
- **Pronóstico**
- **Exámenes recientes**
- **Medicación actual**

URGENCIAS ONCOLÓGICAS

METABÓLICAS:

Hipercalcemia

S. lisis tumoral

SSIADH (hiponatremia)

Hipoglicemia

HEMATOLÓGICAS:

Hiperleucocitosis

Hiperviscocidad

Neutropenia febril

Trombosis

NEUROLÓGICAS

S. compresión medular

Convulsiones

HIC

CARDIOVASCULARES

Derrame pericárdico maligno

S. de Vena Cava Superior

Thorvardurr R, et al Oncolic emergencies: diagnosis and Treatment, Mayo clinic 2006
Lewis, Mark et al Oncológica emergencies..CA cancer J Clin 2011;61:287-314

HIPERCALCEMIA

La complicación metabólica más frecuente

- ***Hipercalcemia (mg/dl)***
- ***leve < 12***
- ***Moderada 12-14***
- ***Severa >14***

HIPERCALCEMIA

↓ calcemia

Tratar e. subyacente

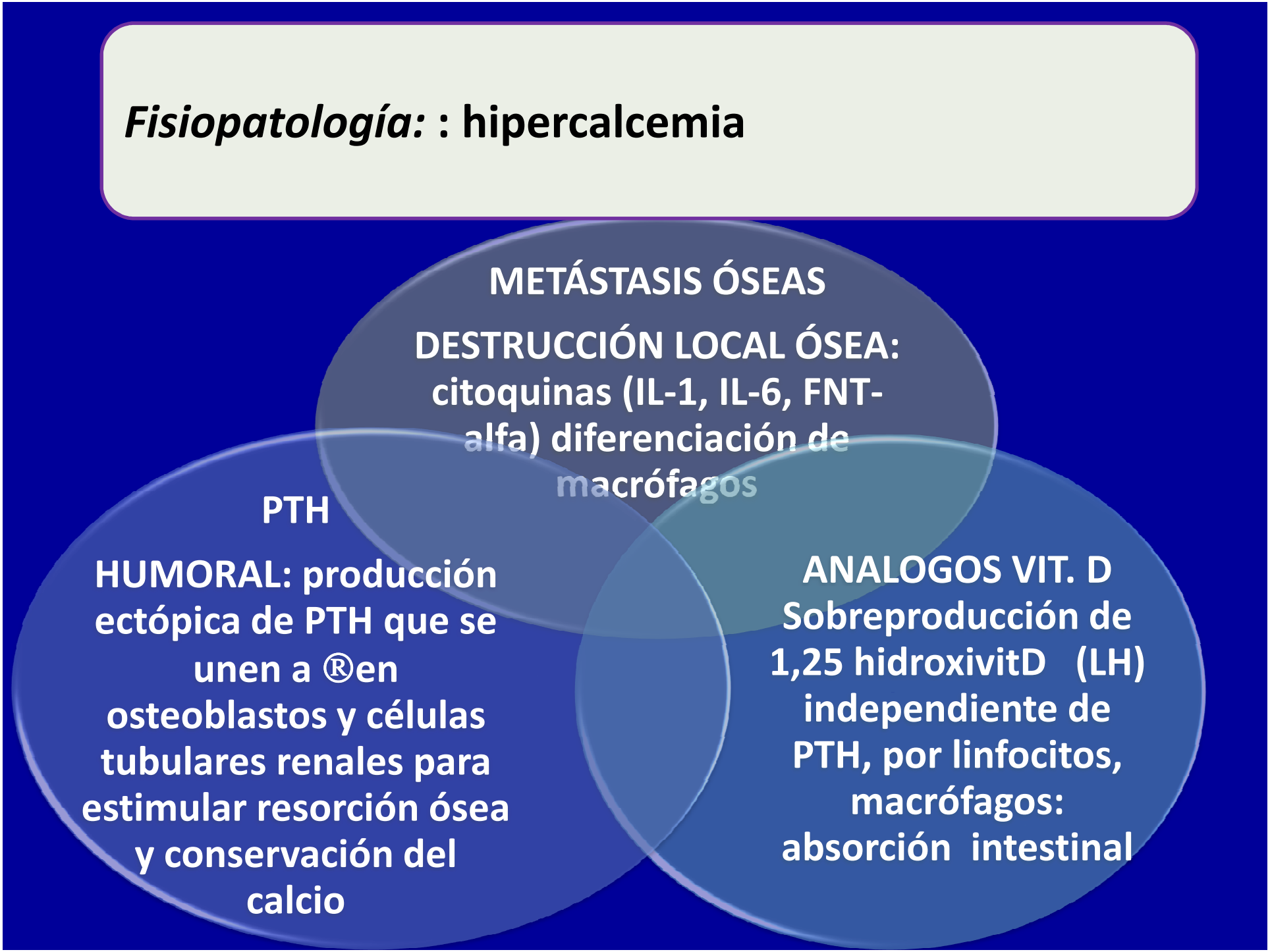
Hipercalcemia (mg/dl)
leve < 12
Moderada 12-14 Severa >14

↓ resorción ósea

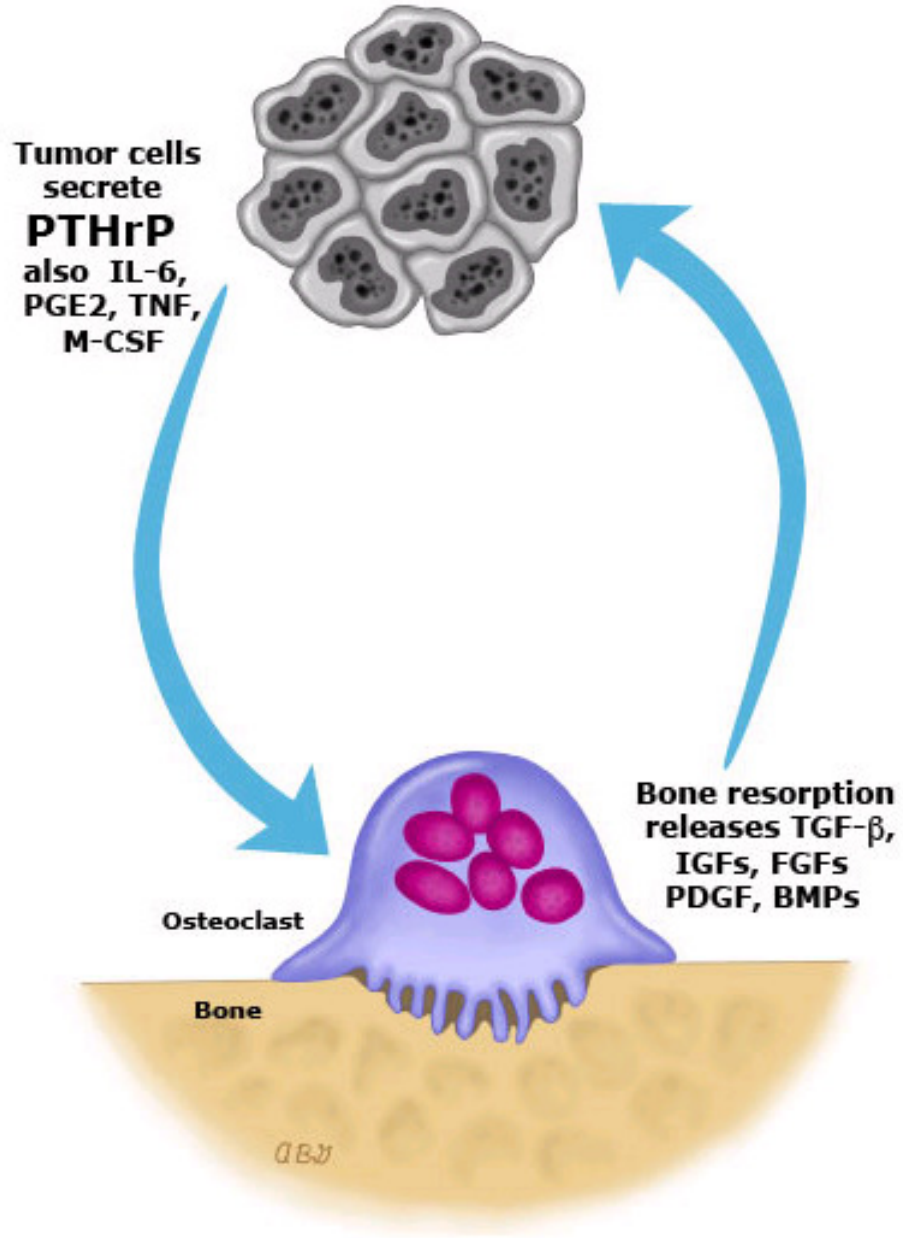
↓ absorción intestinal

↑ excreción urinaria

Fisiopatología: : hipercalcemia

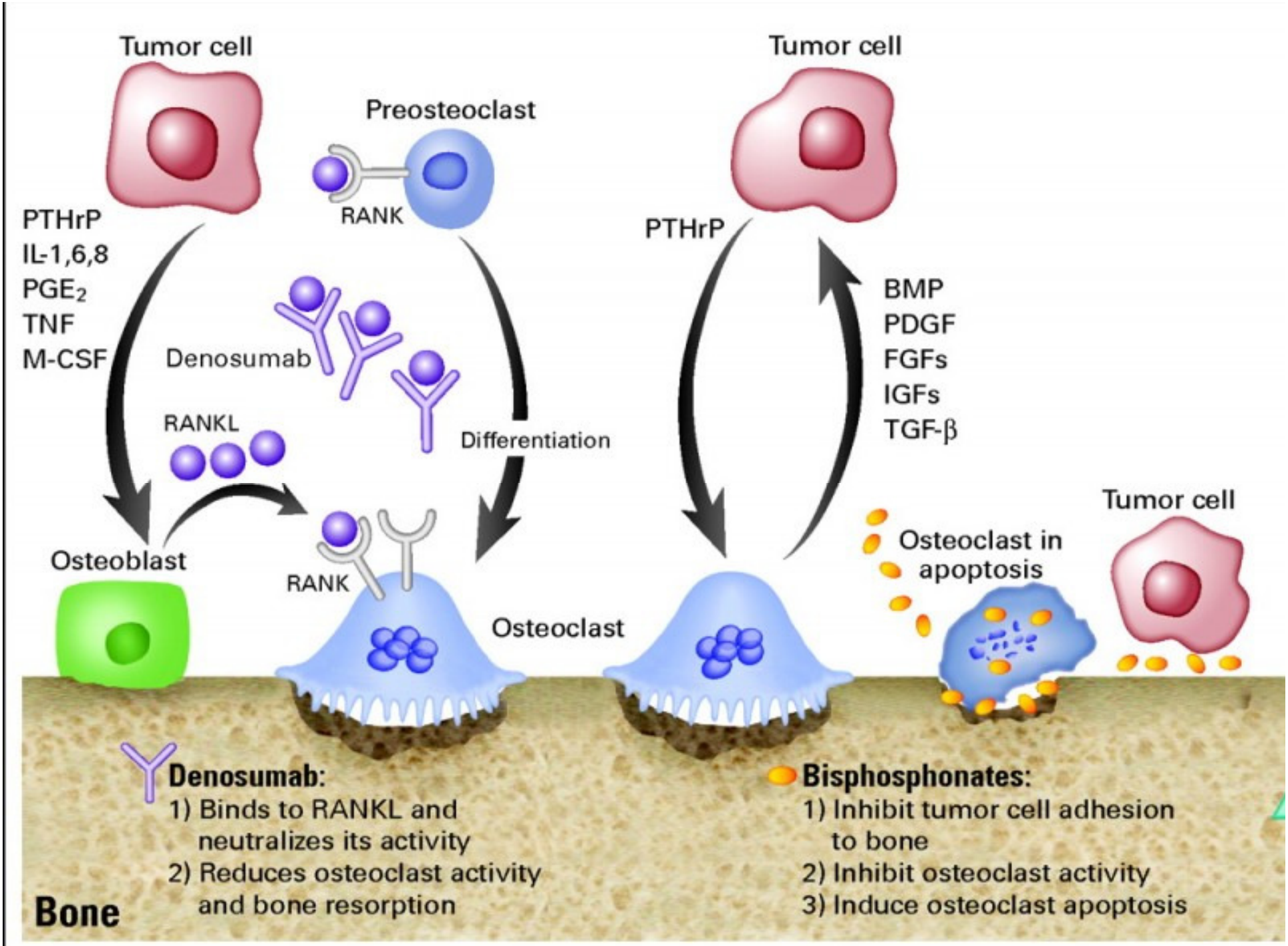


The vicious cycle of osteolytic metastasis



Tumor cells, in particular breast cancer, secrete parathyroid hormone related peptide (PTHrP) as the primary stimulator of osteoclastogenesis. In addition, tumor cells produce other factors that increase osteoclast formation including interleukin-6 (IL-6), prostaglandin E2 (PGE2), tumor necrosis factor (TNF), and macrophage colony-stimulating factor (M-CSF). These factors increase RANK ligand expression, which directly acts on osteoclast precursors to induce osteoclast formation and bone resorption. The bone resorption process releases factors such as transforming growth factor-beta (TGF-β), which increase PTHrP production by tumor cells as well as growth factors (eg, insulin-like growth factors [IGFs], fibroblast growth factors [FGFs], platelet-derived growth factor [PDGF], bone morphogenetic proteins [BMPs]) that increase tumor growth. This symbiotic relationship between bone destruction and tumor growth further increases bone destruction and tumor growth.

Modified from Roodman GD. Mechanisms of bone metastases. N Engl J Med 2004; 350:1655.


Tumor cell
Preosteoclast
RANK
PTHrP
IL-1,6,8
PGE2
TNF
M-CSF
Denosumab
RANKL
Differentiation
Osteoblast
RANK
Osteoclast
Tumor cell
PTHrP
BMP
PDGF
FGFs
IGFs
TGF-β
Osteoclast in apoptosis
Tumor cell
Denosumab:
1) Binds to RANKL and neutralizes its activity
2) Reduces osteoclast activity and bone resorption
Bisphosphonates:
1) Inhibit tumor cell adhesion to bone
2) Inhibit osteoclast activity
3) Induce osteoclast apoptosis
Bone

Renal
Polyuria
Polydipsia
Nephrolithiasis
Nephrocalcinosis
Distal renal tubular acidosis
Nephrogenic diabetes insipidus
Acute and chronic renal insufficiency
Gastrointestinal
Anorexia, nausea, vomiting
Bowel hypomotility and constipation
Pancreatitis
Peptic ulcer disease

Musculoskeletal
Muscle weakness
Bone pain
Osteopenia/osteoporosis
Neurologic
Decreased concentration
Confusion
Fatigue
Stupor, coma
Cardiovascular
Shortening of the QT interval
Bradycardia
Hypertension

rcalc

Exámenes

perfil bioquímico

Calcio, ELP, creatininemia, FA

Calcio corregido=Calcio+ (0,8x(4-albúmina))

Tratamiento

S. Fisiológico 200-400 (1000)ml/h

Furosemida 20-40 mg ev c/2-4 hrs

Bifosfonatos: pamidronato 60-90 mg en 4 hrs

Ácido zolendrónico 4 mg ev en 15 minutos

Prednisona 1-2 mg/kg vo

hidrocortisona 100 mg c/6 hrs ev

TABLE 1. Treatment of Hypercalcemia

MEDICATION	USUAL DOSE	POINTS TO REMEMBER
Normal saline	Rapid infusion 300-500 cc/h until euvolemic	Use caution in patients with heart failure
Furosemide	20-40 mg iv every 12-24 h	Only after adequate hydration
Pamidronate	60-90 mg iv	Adjust infusion time to creatinine clearance
Zoledronic acid	4 mg iv	Consider alternative treatment in patients with renal failure
Calcitonin	4-8 IU/kg sq or iv every 12 h	Tachyphylaxis occurs quickly
Steroids	Hydrocortisone, 100 mg iv every 6 h or prednisone, 60 mg orally daily	Role usually limited to lymphomas; anticipate hyperglycemia
Mithramycin and gallium		Of historical interest only
Denosumab	Under investigation	Currently approved only for the prevention of skeletal-related events from bone metastases

iv indicates intravenous; sq, subcutaneous.

Treatment of hypercalcemia

Intervention	Mode of action	Onset of action	Duration of action
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion
Calcitonin	Inhibits bone resorption via interference with osteoclast maturation Promotes urinary calcium excretion	4 to 6 hours	48 hours
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks
Gallium nitrate	Inhibits osteoclast-mediated bone resorption	3 to 5 days	2 weeks
Calcimimetics	Calcium sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy
Dialysis	Low or no calcium dialysate	Hours	During treatment

* Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

Data from: Shane E, Dinaz I. Hypercalcemia: pathogenesis, clinical manifestations, differential diagnosis, and management. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Sixth Edition). American Society of Bone and Mineral Research 2006; 179.

Malignancies associated with hypercalcemia

Osteolytic metastases:
Breast cancer
Multiple myeloma
Lymphoma
Leukemia
Humoral hypercalcemia (PTHrP):
Squamous cell carcinomas
Renal carcinomas
Bladder carcinoma
Breast cancer
Ovarian carcinoma
Non-Hodgkin lymphoma
CML
Leukemia
Lymphoma
1,25- dihydroxyvitamin D:
Lymphoma (Non-Hodgkin, Hodgkin, lymphomatosis/granulomatosis)
Ovarian dysgerminomas
Ectopic PTH sectretion:
Ovarian carcinoma
Lung carcinomas
Neuroectodermal tumor
Thyroid papillary carcinoma
Rhabdomyosarcoma
Pancreatic cancer

LEVE	• EVITAR DIURETICOS TIAZÍDICOS • HIDRATACIÓN 6-8 VASOS DE AGUA/D • DIETA CALCIO < 1000 MG/D
MODERADA	• SUERO FISIOLÓGICO • BIFOSFONATOS
SEVERA	• **SUERO FISOLÓGICO** • **CALCITONINA** • **BIFOSFONATOS** • **DIURÉTICOS DE ASA (?)** • **DIÁLISIS**

Sindrome de lisis tumoral

Lisis tumoral conjunto de alteraciones metabólicas que se produce en contexto de una gran carga tumoral junto con muerte celular masiva puede ocurrir ESPONTANEAS o posterior a tratamiento para neoplasias agresivas (hrs-días) (LLA, LMA, LNH Burkitt, neoplasia sólidos)

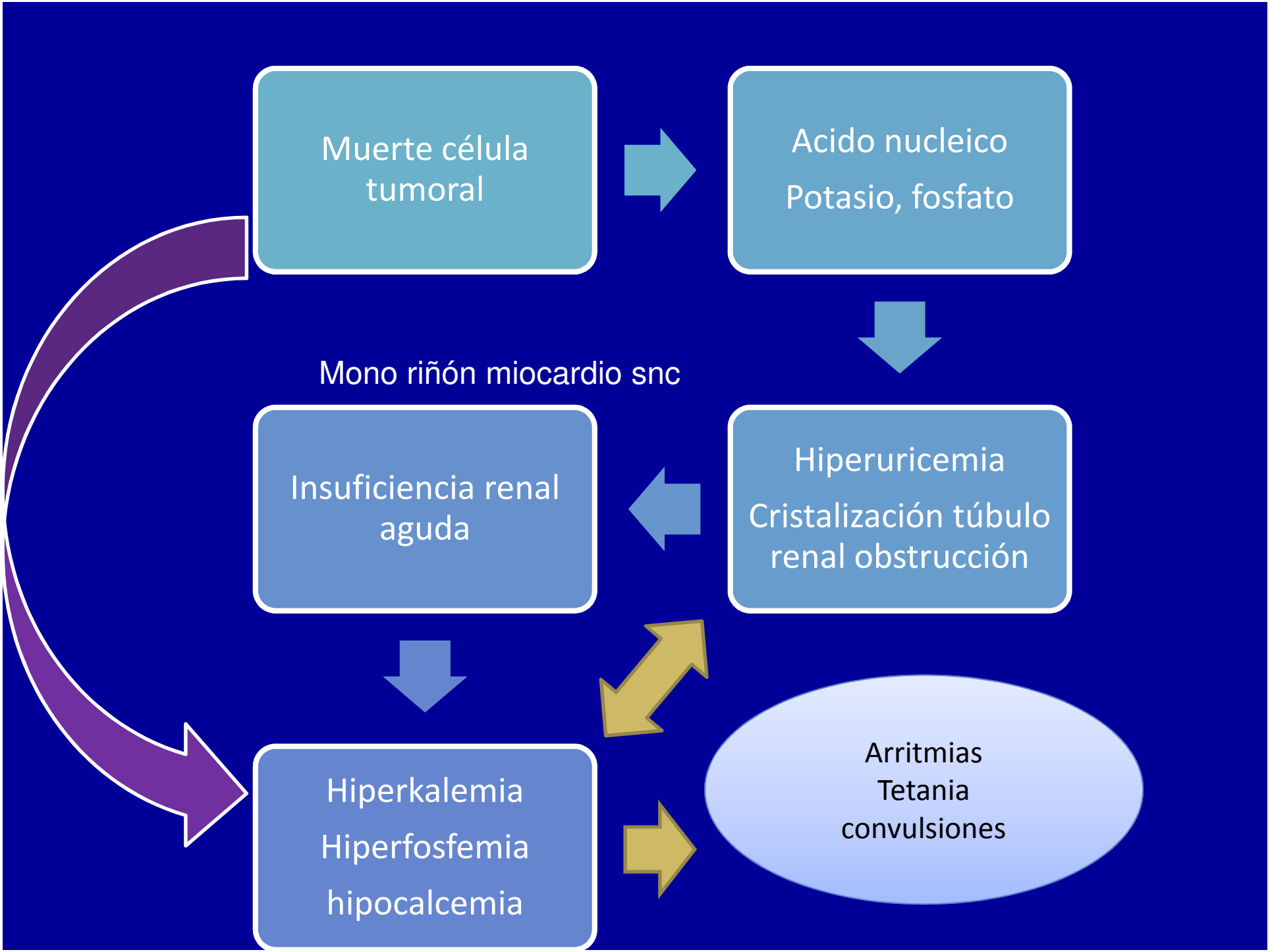

Muerte célula tumoral
Acido nucleico
Potasio, fosfato
Mono riñón miocardio snc
Insuficiencia renal aguda
Hiperuricemia
Cristalización túbulo renal obstrucción
Hiperkalemia
Hiperfosfemia
hipocalcemia
Arritmias
Tetania
convulsiones

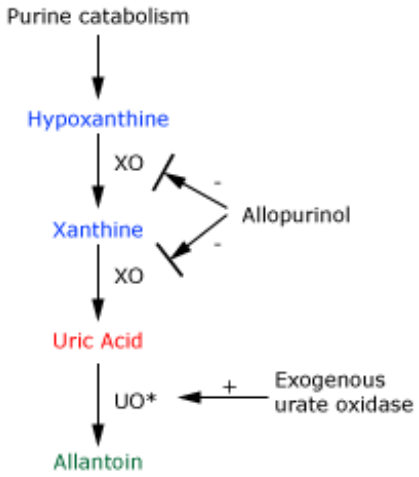
TABLE 2. Laboratory Definition of Tumor Lysis Syndrome Using the Cairo-Bishop Classification

LABORATORY TUMOR LYSIS SYNDROME
Uric acid $\geq$ 8 mg/dL ($\geq$ 476 μmol/L) or 25% increase from baseline
Potassium $\geq$ 6 mEq/L ($\geq$ 6 mmol/L) or 25% increase from baseline
Phosphorus $\geq$ 6.5 mg/dL ($\geq$ 2.1 mmol/L) or 25% increase from baseline
Calcium $\leq$ 7 mg/dL ($\leq$ 1.75 mmol/L) or 25% decrease from baseline
CLINICAL TUMOR LYSIS SYNDROME
Creatinine $\geq$ 1.5 times the upper limit of normal
Cardiac arrhythmia or sudden death
Seizure

NOTE. Two or more laboratory changes must be observed within 3 days before or 7 days after cytotoxic therapy.

Adapted from Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3–11, with permission from Blackwell Publishing Group.

Endogenous production of uric acid



rasburicasa

Purine catabolism results in the production of hypoxanthine and xanthine, which are metabolized to uric acid via the enzymatic action of xanthine oxidase (XO). This pathway can be blocked by the use of allopurinol, a hypoxanthine analog that competitively inhibits XO. After about two to three days, allopurinol therapy results in increased excretion of both hypoxanthine, which is more soluble than uric acid, and xanthine, which is less soluble than uric acid. A marked increase in xanthine excretion can occur when allopurinol is given for prevention of tumor lysis syndrome and may lead to acute renal failure or xanthine stones. Preformed uric acid is not altered by allopurinol. Urate oxidase (UO), present in most mammals, but not humans, oxidizes preformed uric acid to allantoin, which is 5 to 10 times more soluble than uric acid in acid urine. When exogenous urate oxidase (uricase, rasburicase) is administered, serum and urinary uric acid levels decrease markedly within approximately four hours.

* Urate oxidase (UO) is not normally present in humans.

Malignancies commonly diagnosed in patients perceived to be at high risk for developing tumor lysis syndrome

Malignancy	Pediatric (n = 682)		Adult (n = 387)		Total (n = 1069)	
	Number	Percent	Number	Percent	Number	Percent
Acute lymphoblastic leukemia	433	63	73	19	506	47
Acute myeloid leukemia	74	11	104	27	178	17
Chronic lymphocytic leukemia	0	0	37	10	37	3.5
Chronic myeloid leukemia	6	0.9	36	9	42	4
Non-Hodgkin's lymphoma	122	18	109	28	231	22
Hodgkin's disease	8	1.2	6	1.6	14	1.3
Multiple myeloma	0	0	15	3.9	15	1.4
Other hematologic malignancies	5	0.7	3	0.7	8	0.7
Solid tumors	34	5	4	1	38	3.6

Factores de Riesgo

- ***ALTA TASA PROLIFERACIÓN CELULAR***
- ***Quimiosensible***
- ***Tamaño bulky (10 cm) o GB > 50.000/mm3***
- ***LDH >2v VN, infiltración de órganos, (MO)***
- ***Hiperuricemia, hiperfosfemia previas***
- ***Neurotóxicos, nefropatía (crea 1,5: 36 V/S 2%)***
- ***Oliguria***
- ***Deshidratación***

Clínica:

inespecíficos, (refleja alteraciones metabólicas)

- **Nauseas, vómitos, diarrea, anorexia, Letargia, hematuria**
- **Disminución débito urinario.**
- **Sincope, insuficiencia cardiaca Convulsiones, arritmias**

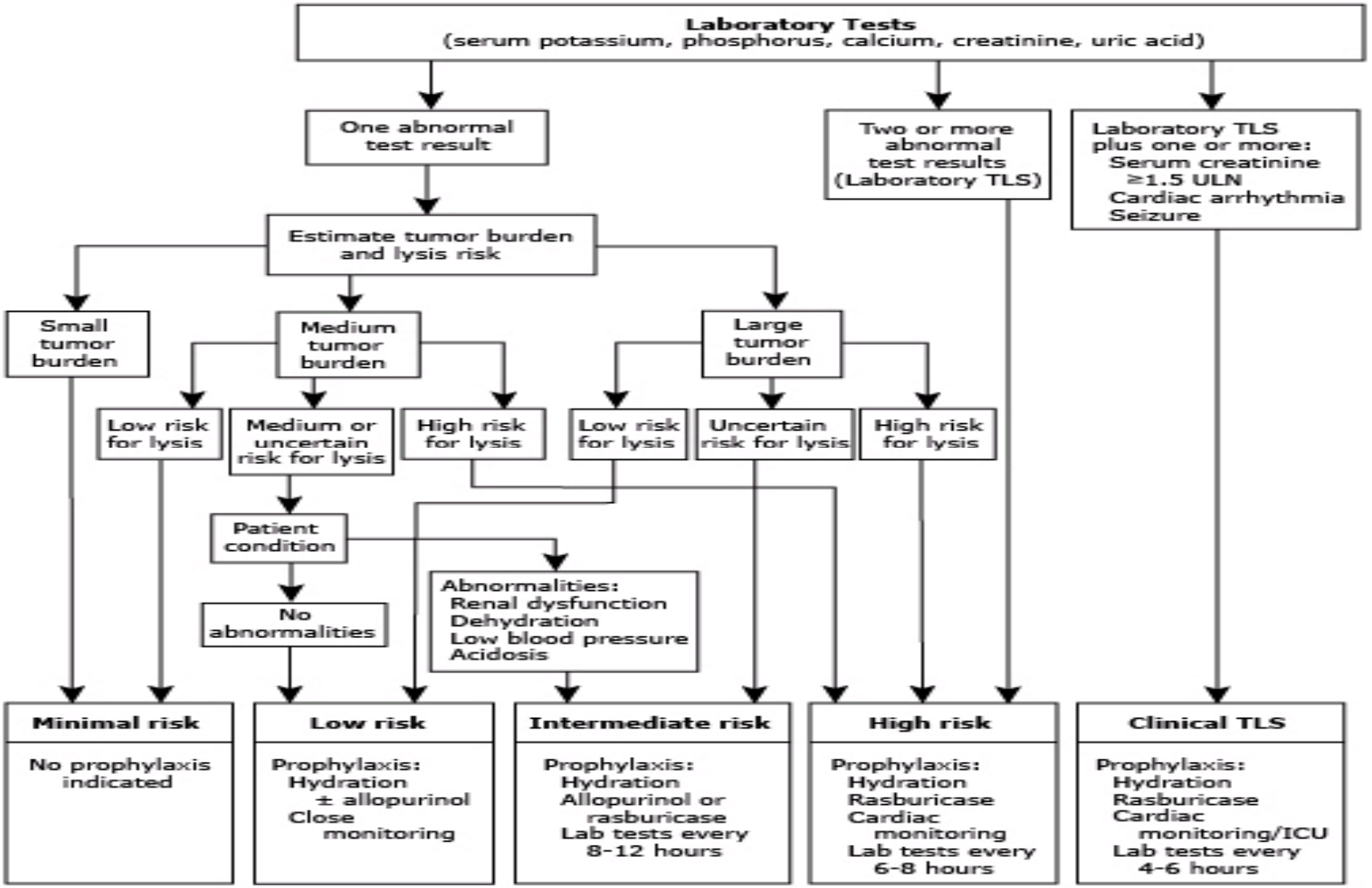
Tratamiento

ALTO INDICE DE SOSPECHA ANTICIPARSE PREVENIR

- **Hipovolemia: S fisiológico o glucosado 3L/m2**
- **Hiperuricemia: Alopurinol 2-3 días antes /2-3 v/d**
- **(300-800MG)**
- **Hiperkalemia: s. glucosado + insulina cristalina, g. de calcio, Kayexalate, hemodiálisis**
- **Hipocalcemia**
- **Alcalinización? En acidosis metabólica? Controversial**
- **Rasburicasa (enzima ác.. Úrico---alantoína)**

- **DIURESIS 2 ML/KG/H**

Algorithmic approach to risk assessment of tumor lysis syndrome



ULN = Upper limit of normal

Modified from Howard SC, Jones DP, Pui CH. The Tumor Lysis Syndrome. N Engl J Med 2011; 364:1844.

TABLE 4. Treatment of Metabolic Abnormalities Associated With Tumor Lysis Syndrome*

Problem	Intervention	Dosages	Comments
Renal insufficiency and hypovolemia	Intravenous fluids	Normal saline, 3 L/m^2 daily (200 mL/kg daily)	Use with caution if history of CHF
	Dialysis		Patients with oliguric renal failure not responding to IV fluids or patients with CHF
Hyperuricemia	Allopurinol	100 mg/m^2 per dose orally every 8 h (10 mg/kg/day divided in 3 doses) or 200–400 mg/m^2 per day IV in divided doses every 8–12 h; commonly used dosages include 600 mg initially followed by 300 mg/d	Reduce dose in renal failure; multiple drug interactions (6-mercaptopurine and azathioprine); IV allopurinol should be used only in patients unable to take oral medications
	Rasburicase	0.05–0.2 mg/kg IV	Contraindicated in G6PD deficiency; transfer blood samples on ice to the laboratory; risk of sensitization and allergic reactions; expensive
Hyperphosphatemia (phosphate level >6.5 mg/mL [>2.1 mmol/L])	Minimize phosphate intake		Low phosphorus diet; phosphorus-free IV fluids
	Phosphate binders (aluminum hydroxide)	50–150 mg/kg daily orally	May interfere with drug absorption

Hyperkalemia	Insulin (regular)	10 units IV	
	Dextrose (50%)	50–100 mL IV	
	Calcium gluconate (10%)	10–20 mL (100–200 mg) IV	Do not give with bicarbonate; use if arrhythmias or ECG changes; can repeat as needed
	Sodium bicarbonate	45 mEq IV (1 ampule of 7.5% $NaHCO_3$)	Use if acidosis; can repeat in 30 min
	Sodium polystyrene sulfonate (Kayexalate)	15–30 g every 6 h orally (can be used rectally)	Can be given with sorbitol
	Albuterol	Inhaled 2.5 mg	For severe hyperkalemia
	Dialysis		Severe hyperkalemia not responsive to other measures; renal failure; volume overload
Hypocalcemia	Calcium gluconate (10%)	5–20 mL (50–200 mg) IV	Only if symptomatic; repeat as necessary; use with caution in patients with severe hyperphosphatemia

* CHF = congestive heart failure; ECG = echocardiogram; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously.

VENA CAVA SUPERIOR: fisiopatología

Ocurre cuando la V. Cava superior es ocluida o comprimida, restringiendo el retorno sanguíneo al corazón (pulmón derecho trombosis nodos linfáticos

Fisiopatología: ocurre por la pared delgada y fácilmente compresible, se produce daño del drenaje venoso de extremidades, cabeza y cuello, si es gradual se desarrollan vasos colaterales.

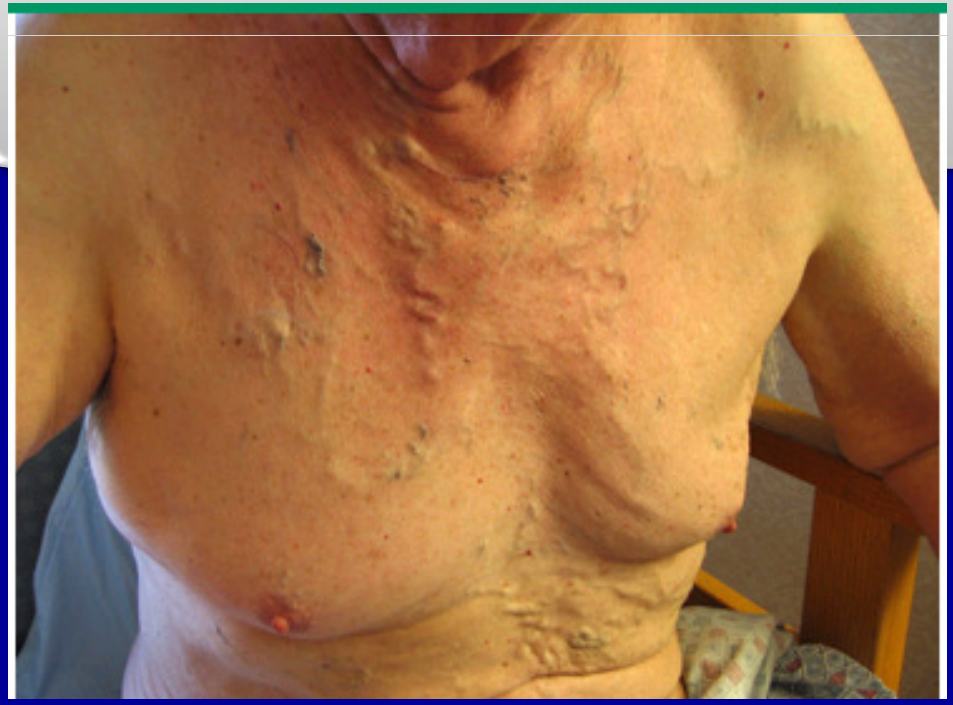
VENA CAVA SUPERIOR

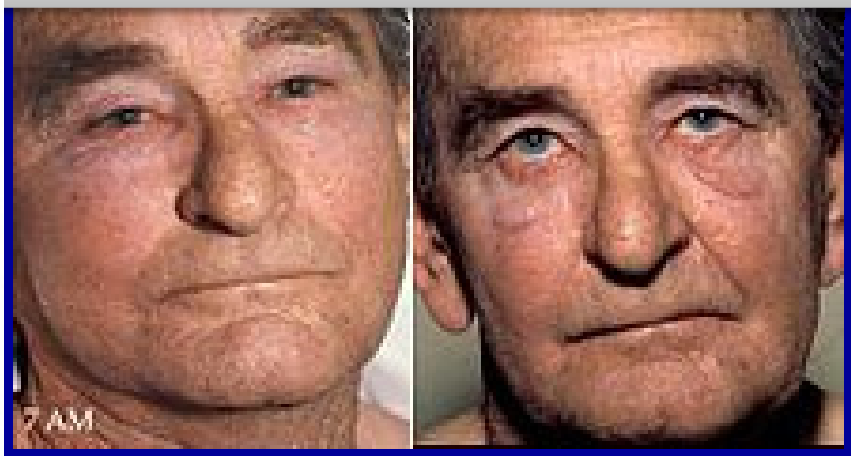
52 a 81 % de los sindrome de cava superior
cáncer pulmón SCLC
Linfomas 2-9% LNH (primarios de mediastino)
cáncer mama
cáncer de células germinales

Clínica: disnea 66%, edema facial 82%, en esclavina, tos, disfagia disfonía ingurgitación venosa,plétora facial y edema de extremidades superiores inferiores (68%).Ortopnea. Cefalea, confusión, mareosa, coma. Cianosis. Quemosis edema periorbitario

Estridor laríngeo

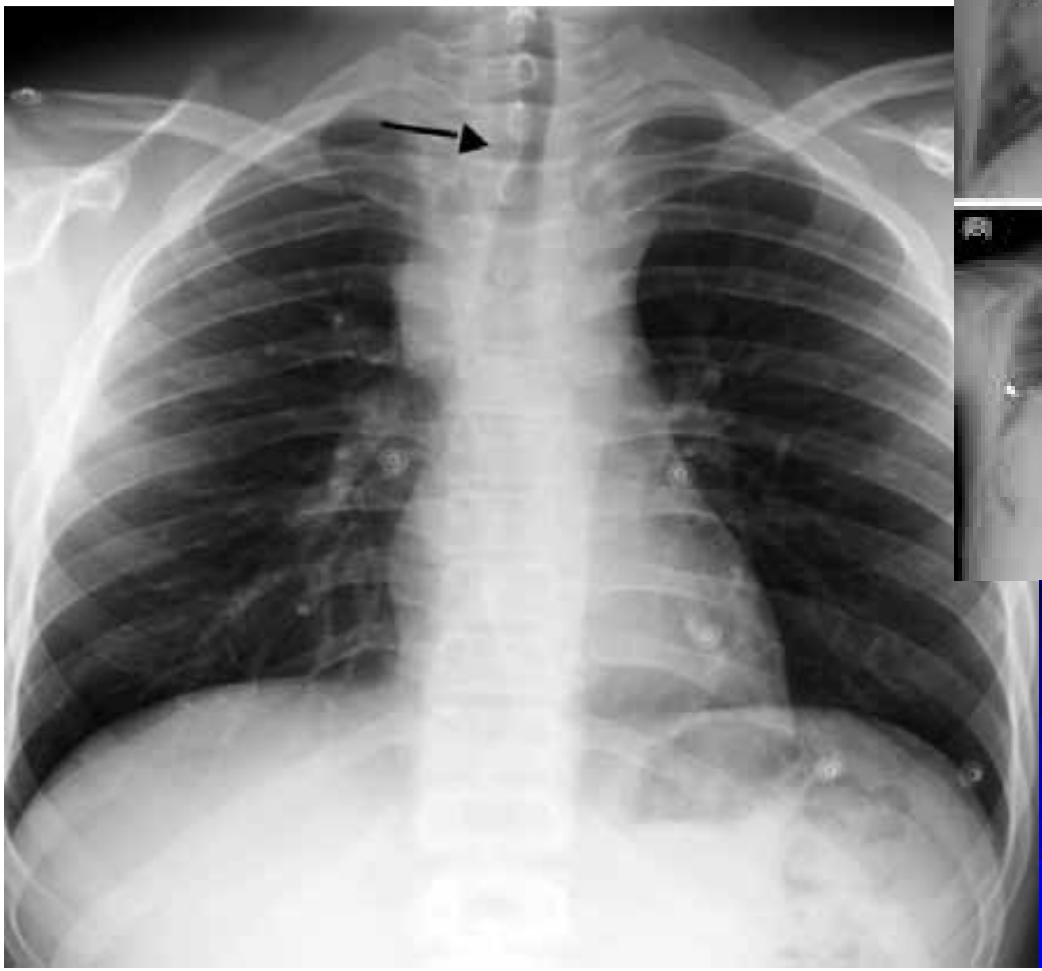
Tratamiento : RDT, QMT, dexametasona 8-16 mg

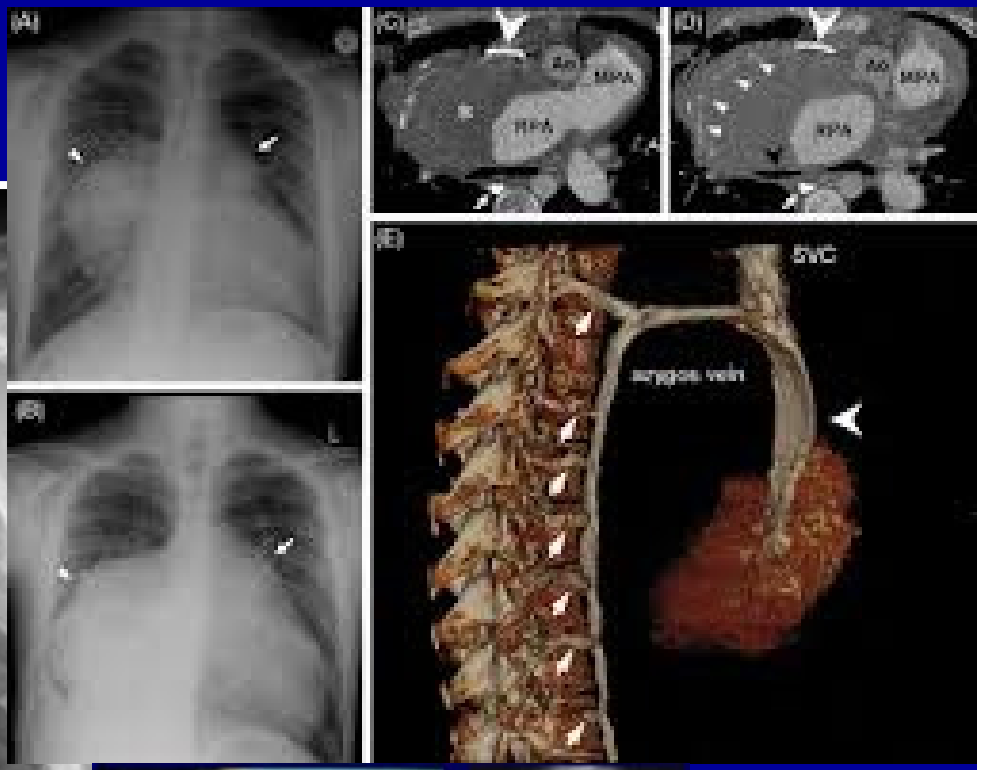


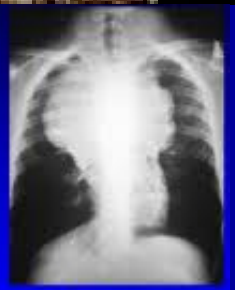


Diagnóstico

- Tomografía axial computada con contraste ev
- Resonancia magnética
- Rx tórax



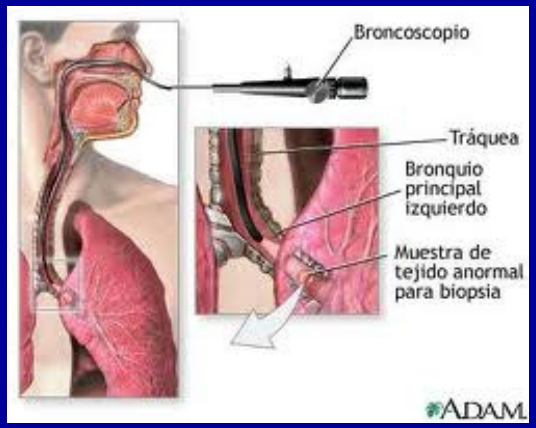




Superior Vena Cava Syndrome

- Diagnóstico:

Fibrobroncoscopía
Mediastinoscopía



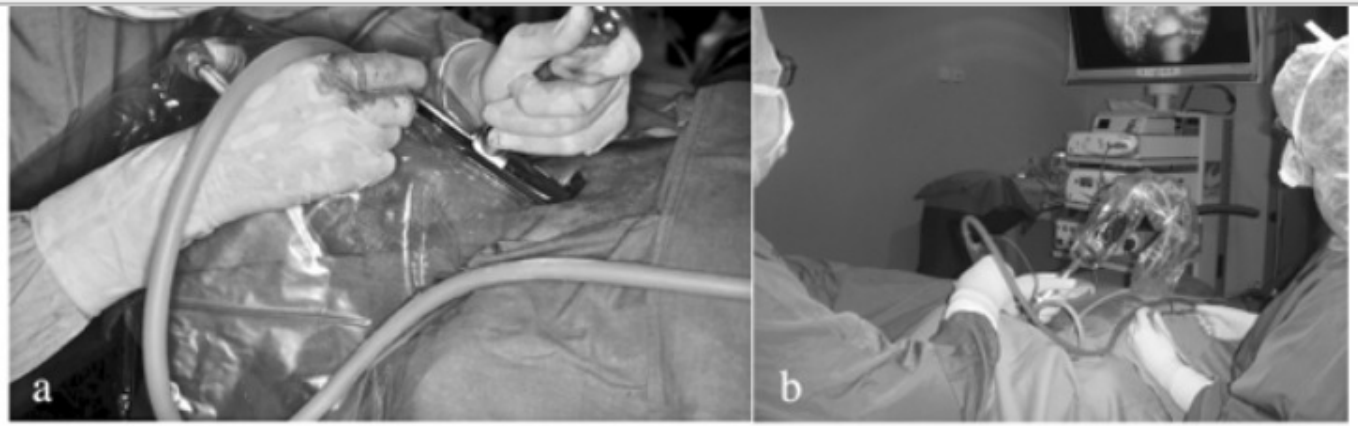


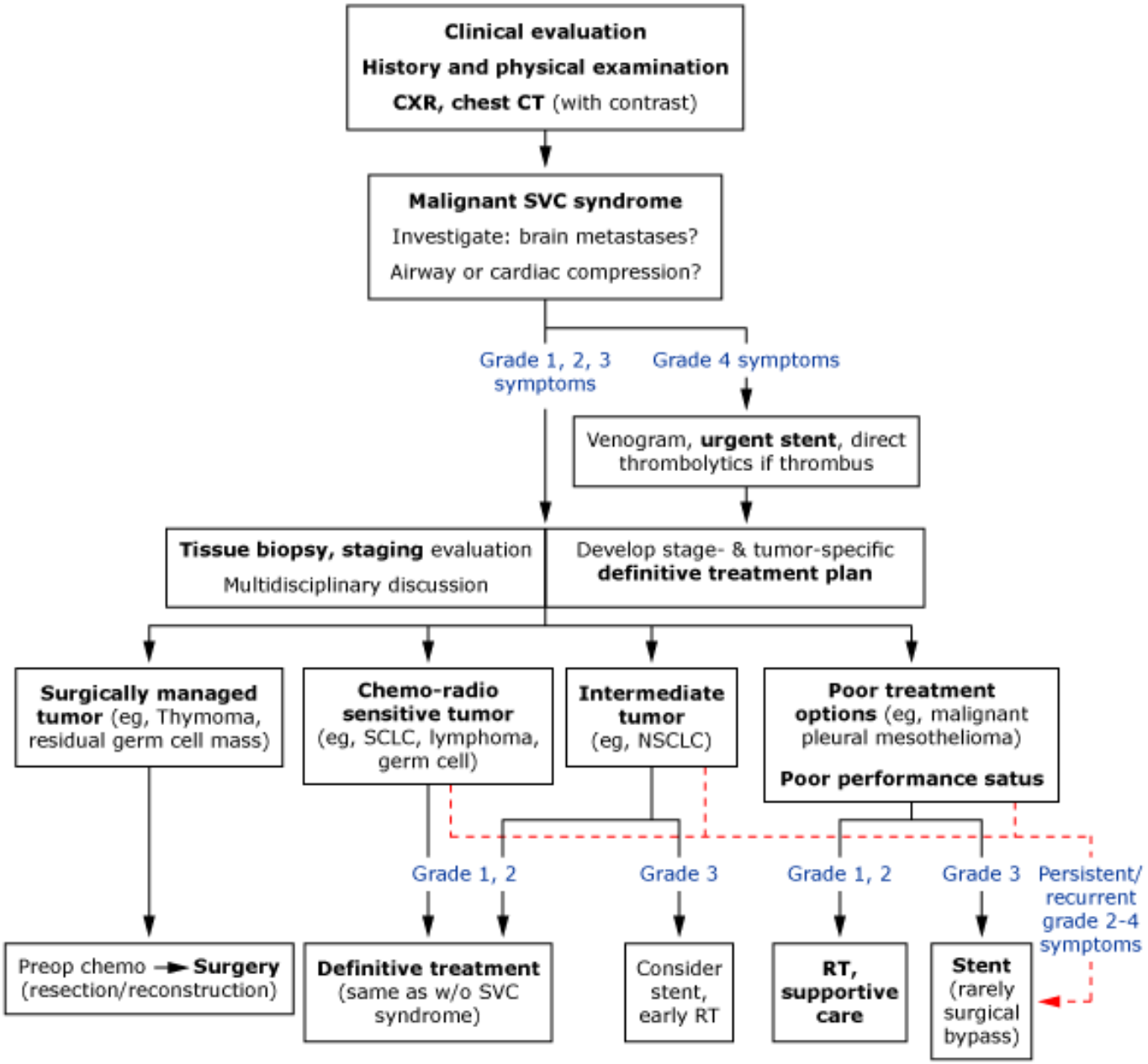
FIGURA 1

Mediastinoscopia. a) Mediastinoscopia cervical convencional. El cirujano explora y diseca el espacio peritraqueal con la ayuda de la cánula de disección-aspiración-coagulación mirando directamente a través del mediastinoscopio. Sólo el cirujano ve lo que está haciendo, b) Videomediastinoscopia. El cirujano realiza la misma maniobra mirando al monitor de televisión y todo el personal del quirófano puede observarlo que está haciendo.

Tratamiento

- soporte
- radioterapia
- quimioterapia
- Stents
- Corticoides?? Dexametasona 8-16 mg/d

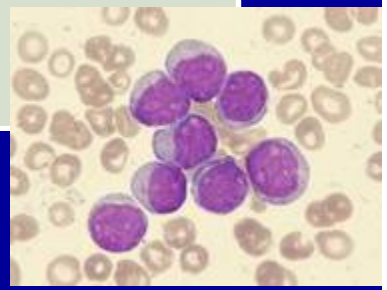
Treatment algorithm of superior vena cava syndrome



HIPERLEUCOCITOSIS: GB 50-100.000/mm3

LEUCOSTASIA: hiperleucocitosis (>100.000/mm3) sintomática con disminución de perfusión tisular (LMC o LMA en crisis blástica, LLC >400.000) se ve compromiso neurológico o respiratorio

hiperviscocidad, células más rígidas



si	no
• Hydrea 1- 2 g c/6-12 hrs • Hidratación • Quimioterapia ev inducción • Prevención de SLT • leucoaferesis	• Transfusiones GR • diuréticos

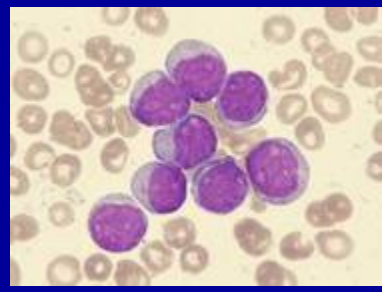
LEUCOSTASIA:

- **falla respiratoria**
- **HIC**
- **Muerte precoz**

Mortalidad puede llegar a 40%

Incidencia:

- **LMA 5-13%**
- **LLA 10-30%**



FR:

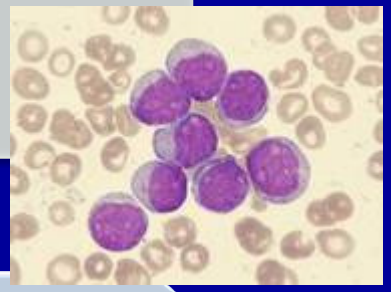
- **edad : menor edad**
- **LLA 11q23, 9;22**
- **LMA M3 M4 M5**

- **Aumento de viscosidad empastamiento de los blastos en la microvasculatura**

Por expresión de moléculas de adhesión
Interacción blastos-célula endotelial lleva a disrupción de la pared vascular y a agregación de granulocitos inducida por complemento

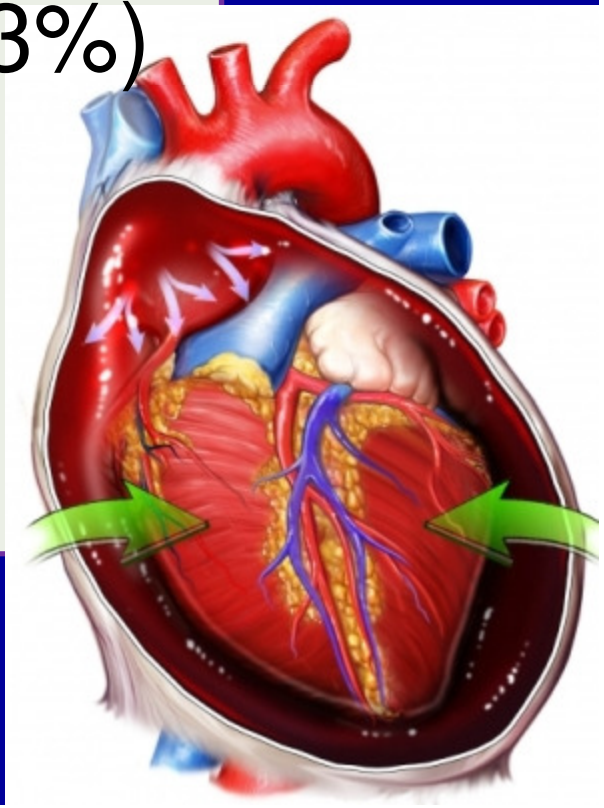
Diagnóstico :hemograma
Tratamiento :citoreducción

Respiratoria	• **disnea hipoxia infiltrado intersticial difuso**
SNC	• **alteraciones visuales cefalea vértigo inestabilidad en la marcha confusión somnolencia**
Otras	• **ECG: sobrecarga derecha, isquemia** • **Isquemia de extremidad infarto intestinal**



COMPROMISO PERICÁRDICO MALIGNO

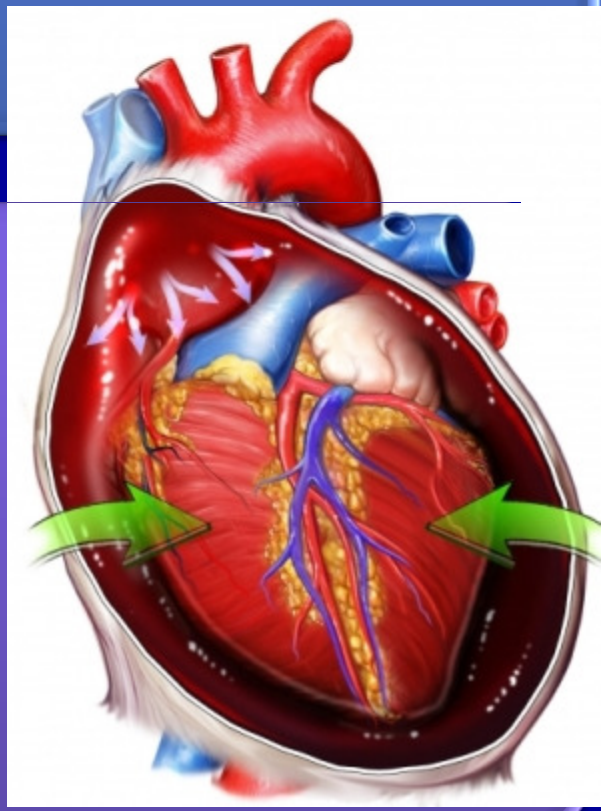
- Pericarditis (4-7%)
- Derrame pericárdico (13-23%)
- Taponamiento cardíaco
- Constricción pericárdica



Frecuente en pacientes con neoplasia avanzada

Muchos son asintomáticos

Cáncer: pulmón, mama, linfoma mediastínico, esófago, melanoma, leucemia (mesotelioma de pericardio raro)



Fisiopatología: ocurre por metástasis al pericardio, invasión directa

Pueden ser de inicio lento o rápido y llegar a producir compresión de las cámaras cardíacas (derechas)

- **Clínica:**

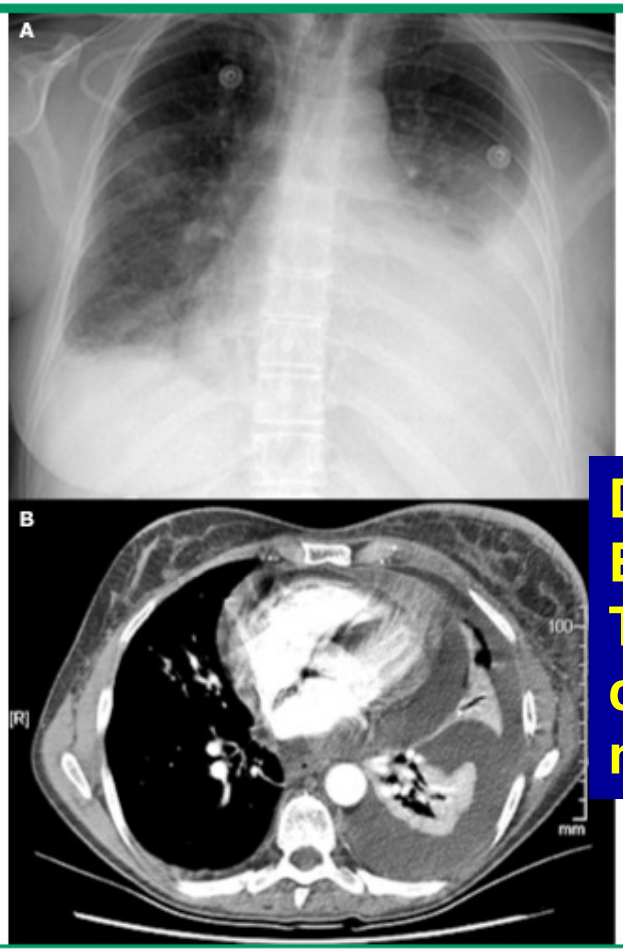
- ***Disnea(93%),***
- ***dolor torácico* 63%**
- **tos, 30-43%**
- **disfagia, singulto, fiebre, disfonía**

- **Taquicardia, tonos cardiacos apagados, yugulares aumentadas, hepatomegalia,**
- **edema facial y de extremidades superiores**

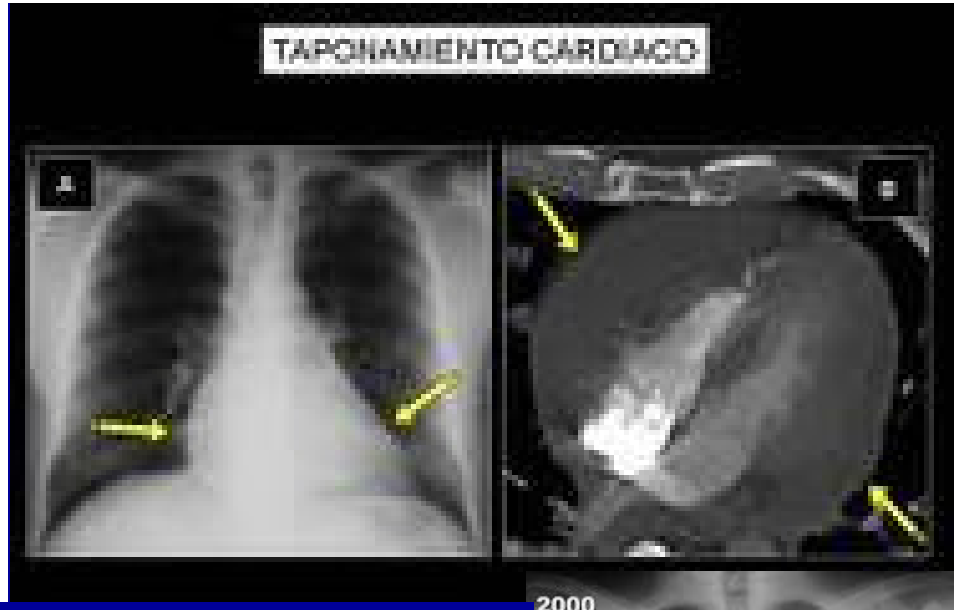
Tríada de Beck: hipotensión, ingurgitación yugular y malestar precordial

- **Pulso paradojal**

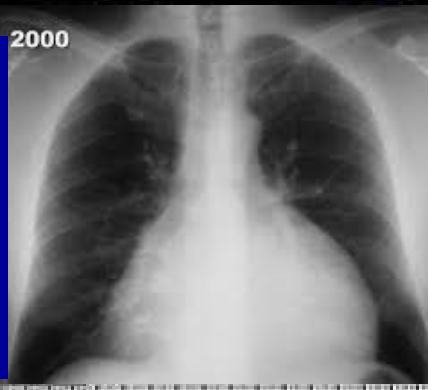
Malignant pericardial and pleural effusions from metastatic breast cancer

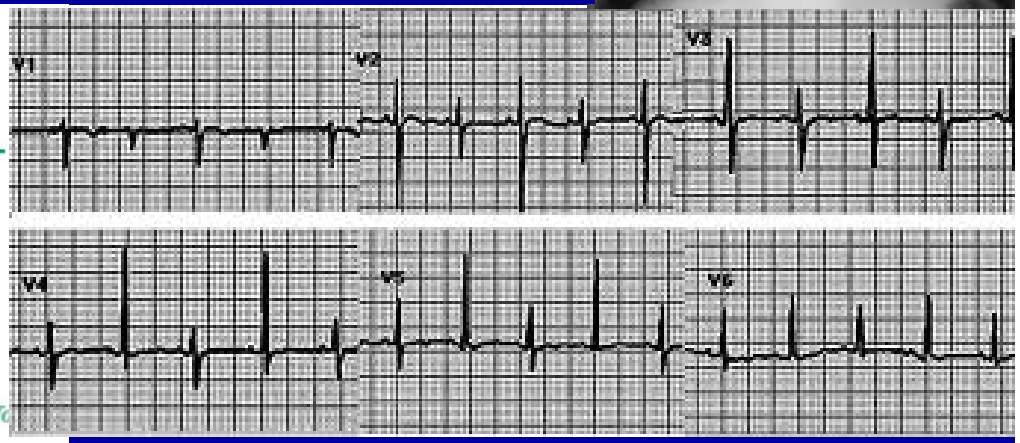


A) Chest radiograph in a patient with concomitant malignant pericardial and malignant pleural effusions from metastatic breast cancer. B) CT scan of the chest in a patient with concomitant malignant pericardial and malignant pleural effusions from metastatic breast cancer.
Courtesy of DeCamp, MM and Gangadharan, SP.



Diagnóstico:
ECG, Rx tórax , ecocardio, Tomografía axial computada, Resonancia nuclear magnética





Taponamiento cardíaco

Tratamiento: evacuación
Monitorización UPC, tratamiento sistémico

pronóstico

Pericardiocentesis
guiada por eco, drenaje
Ventana pericárdica

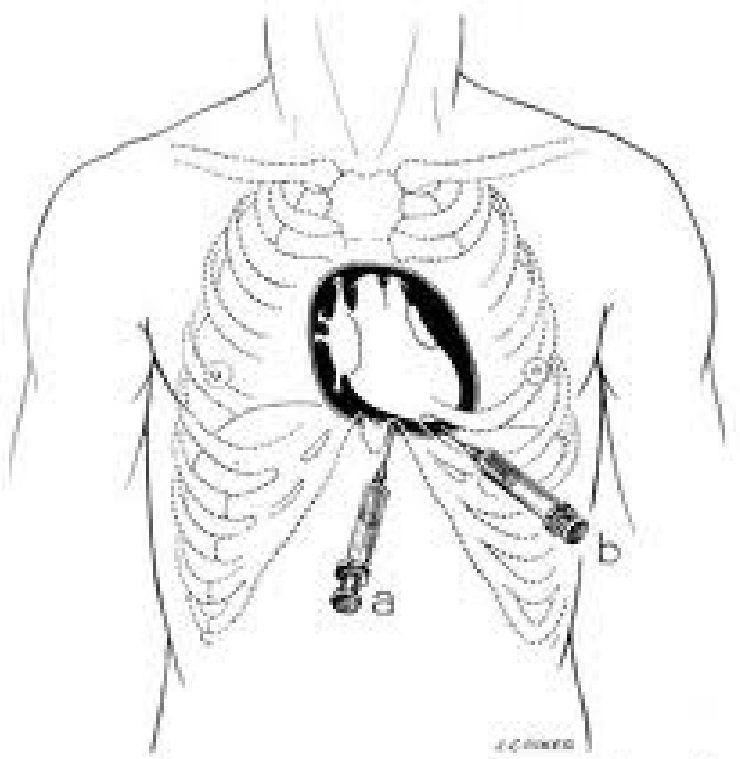


FIGURE 20.—Management of cardiac tamponade by aspiration: Substernal transdiaphragmatic aspiration (a), and left lateral aspiration (b).

S. COMPRESIÓN MEDULAR

Es una verdadera emergencia oncológica. En el 5-20% de los casos es la primera manifestación

El diagnóstico precoz es fundamental por el riesgo vital que le acompaña

Entre 2,5 -6% de los pacientes con cáncer lo presentan durante su evolución.

Cáncer mama, pulmón, próstata, mieloma múltiple acumulan 2/3 de los casos (LNH, cáncer renal)

El pronóstico es variable, si existe plejia o disautonomía trastornos esfinterianos, o han transcurrido más de 24 hrs es pobre

S. COMPRESIÓN MEDULAR

clínica

- **dorsalgia (90-95%) ↑noche, decúbito, radicular**
- **Debilidad muscular(60-85%)**
- **T. sensibilidad, hiperreflexia, espasticidad**
- **Disfunción vesical o intestinal**
- **Ataxia**
- **Agudo en caso de fractura patológica en vertebra metastásica**
- **S cauda equina**

Diagnóstico

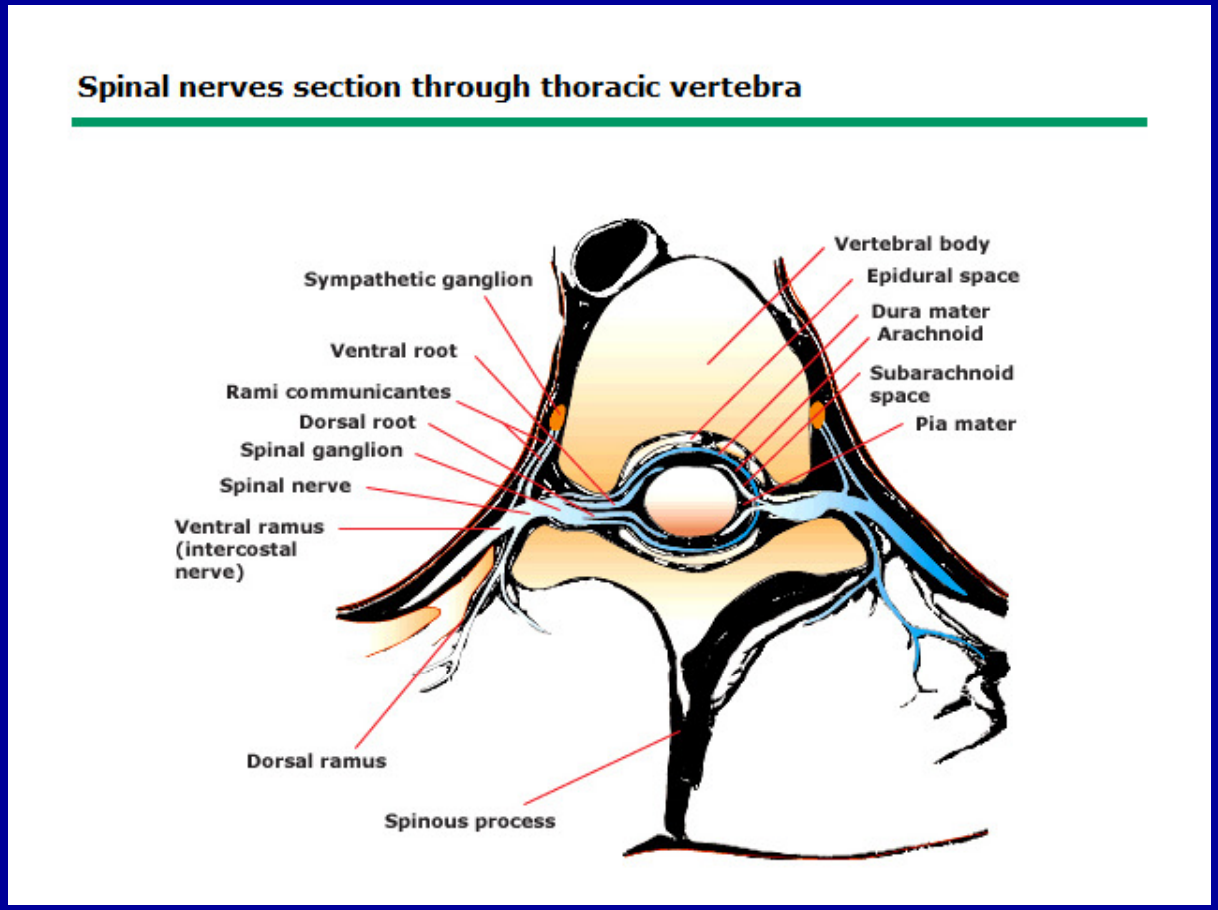
- Resonancia nuclear magnética
- Tomografía axial computada, mielo TAC con contraste
-

S. COMPRESIÓN MEDULAR: Fisiopatología:

- **Metástasis en cuerpos vertebrales erosionan hueso y comprimen la medula espinal**
- **Nivel *torácico* (60%), lumbar (30%) cervical (10%)**

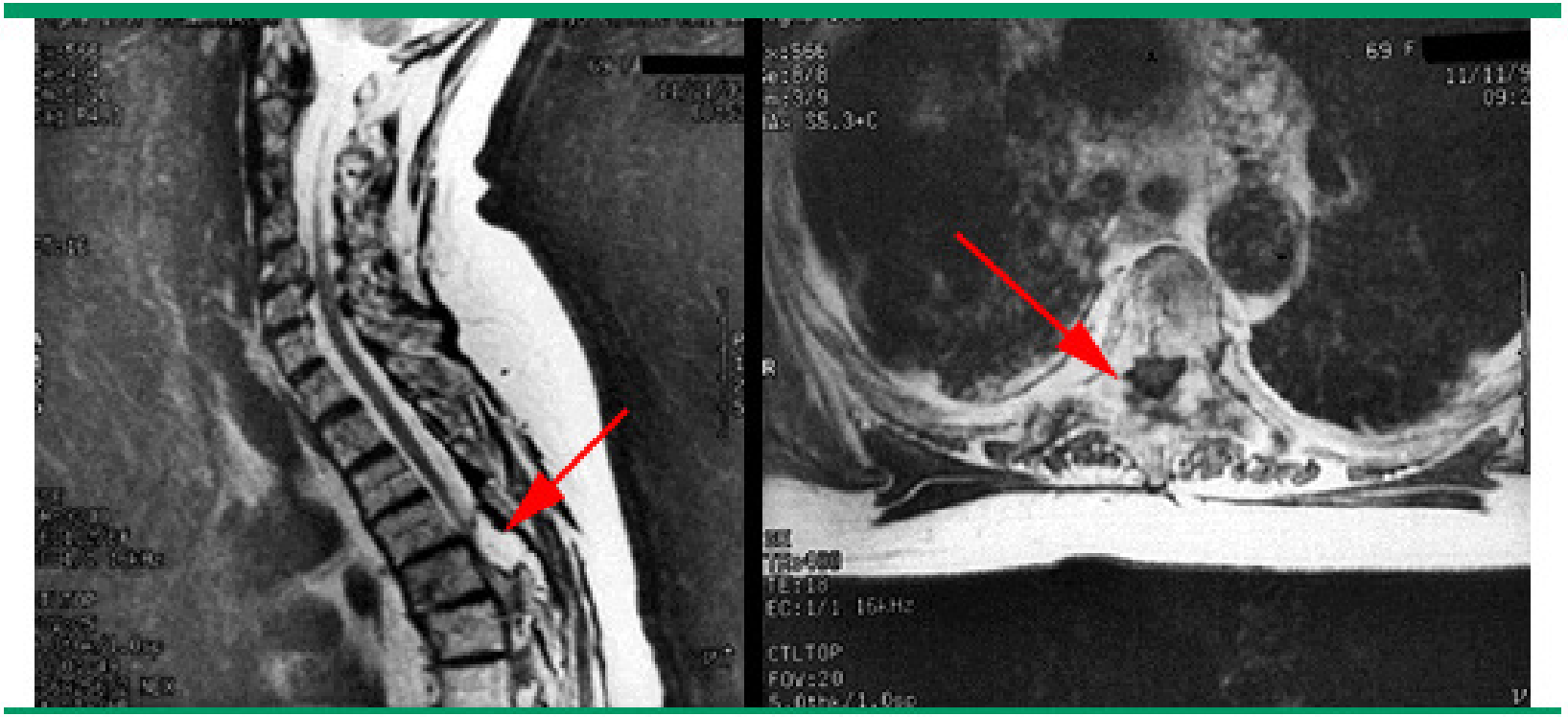
- **Compresión de elementos neurales interrumpiendo flujo axonal o vascular (infarto)**

- **Citoquinas y mediadores de inflamación (VEGF) aumentan el edema medular vasogénico, aumenta presión tisular afecta flujo y agrava la isquemia**



- **Mecánico compresión epidural**
- **Metástasis medula y meninges**
- **Propagación de espacios paravertebrales a través de los agujeros de conjunción**

Epidural spinal cord compression



Sagittal (left panel) and axial (right panel) gadolinium-enhanced spinal MR scan of a 69-year-old women with a remote history of breast cancer, interscapular back pain for one month, and a normal neurologic examination. The scans demonstrate a large epidural lesion compressing the spinal cord (arrows).

Courtesy of David Schiff, MD.

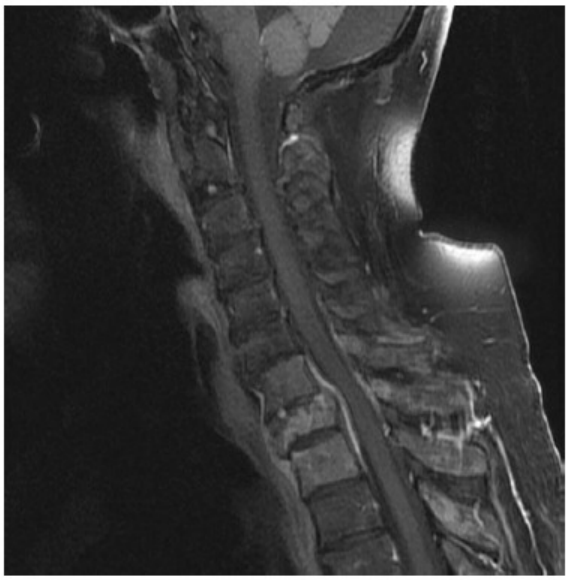


FIGURE 4. Magnetic Resonance Imaging of Spinal Cord Compression.

- Controlar dolor
- evitar complicaciones
- prevenir déficit neurológico

Pronóstico:

- Severidad
- Localización
- Duración de compresión

Tratamiento:

- Corticoides: Dexametasona 10-16 (96 mg) mg ev bolo, 4-6mg c/ 4hrs hasta completar RDT
- Radioterapia
- Cirugía
- Quimioterapia sistémica

CONCLUSIONES:

1) S Ud. .“no piensa” en el diagnóstico posible no va a diagnosticar el problema.

2) Ante la sospecha de emergencia oncológica la evaluación deber ser sin dilación (clínica, imagen, laboratorio)

3) La aplicación del tratamiento debe ser lo más precoz posible

4) Opinión de especialistas , coordinación de equipos multidisciplinarios