Oncological Emergencies

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Oncology Hospitalist

- In my 18h year as an attending at UK.
- Spend most of my clinical time on co-management teams with:
  - hematological malignancies (Acute leukemia, lymphoma, multiple myeloma)
  - solid tumors (Lung cancer, colon cancer, head and neck cancer, brain tumors, sarcoma, pancreatic cancer, neuroendocrine tumors, Breast cancer)

Disclosures

- I have no financial disclosures

Objectives

By the end of this talk the attendee should be able to:

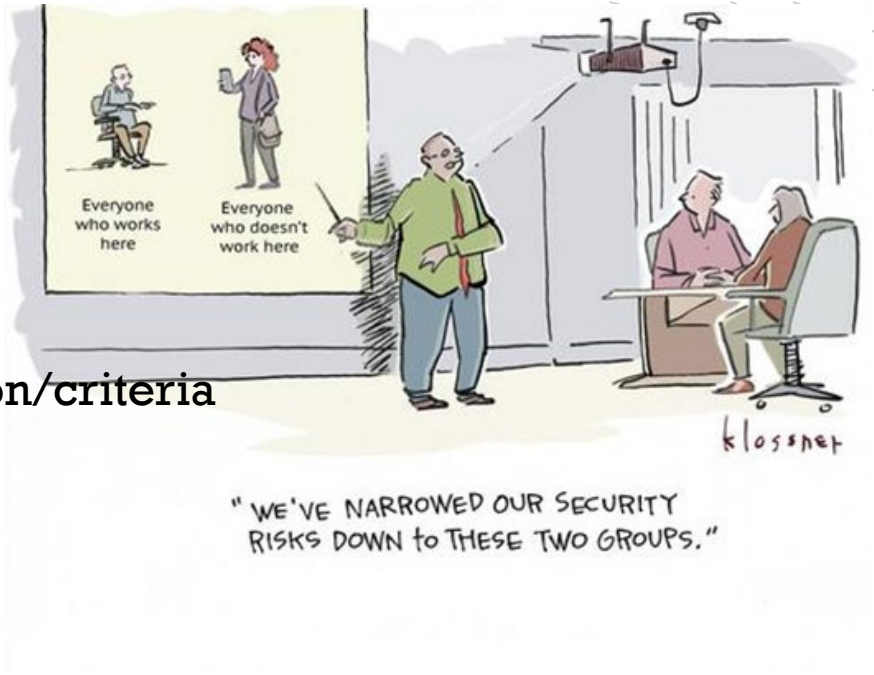
- Recognize common oncological emergencies
- Identify which patients are at risk for each type
- Reiterate the evaluation and management of each type

Topics we will cover today-

- 1.neutropenic fever
- 2.tumor lysis syndrome
- 3.neoplastic spinal cord compression
- 4.SVC syndrome
- 5.new brain tumors with acute cerebral edema
- 6.hypercalcemia of malignancy
- 7. hyperviscosity syndrome/leukostasis

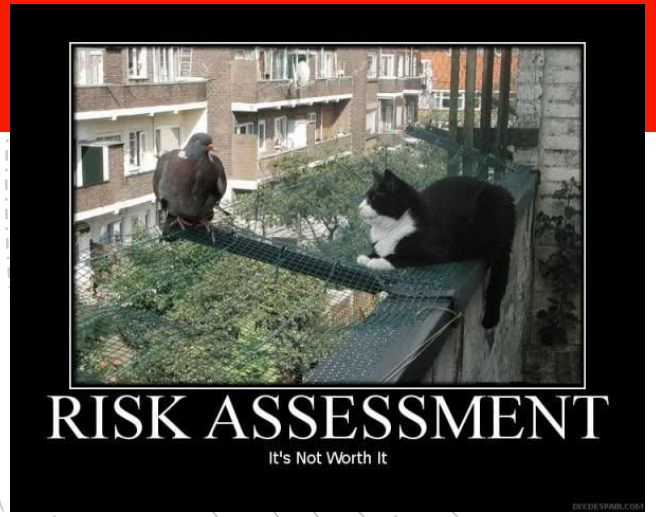
format

1. clinical constellation/criteria
2. risk group

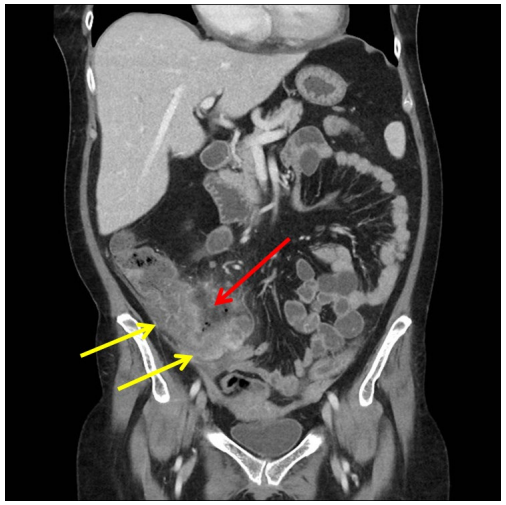


3. Management
4. mortality

Neutropenic fever



- Criteria: ANC <500 and fever >101 or 100.5 for 1h
- Can have SIRS/Sepsis syndrome and even shock or look fairly stable.
- Symptoms if any related to underlying site of infection
- Historically great concern for Pseudomonas infection (prior 90%mort if BSI)
- typhlitis (Greek *'typhlon")*
  - *Clostridium*



RISK:

- Especially common in hematological malignancy pts, sometimes even before treatment.
- Also common in some solid tumor patients on cytotoxic chemotherapy.
- Not particularly common on those managed with immunotherapy alone or radiation alone.

Workup/ Management

- Culture for infection, use HPI and exam to drive.
  - 2 sets Blood cultures (everyone)
  - Other cultures as indicated by history:
    - Urinalysis/ reflex cultures
    - CXR
    - respiratory PCR/Covid testing
    - stool testing
    - LP
    - Evaluate for wounds/cellulitis
    - Consider abdominal imaging for n/v/pain
- Antibiotics within an HOUR.
- Empiric Pseudomonas coverage (cefepime, pip/tazo, meropenem)
- Consider empiric MRSA coverage only if indicated by history (Pna, ssti, line infection or shock)
- Adjust coverage if MDRO history or credible allergy history
- Follow up cultures and check daily cbc with diff. If neutropenia resolves and infectious workup is negative, stop antibiotics.
- Consider GCSF if pt unstable, but with oncology guidance.
  - Little evidence- but possibly decrease LOS, duration of neutropenia but maybe no mortality benefit
  - "at high risk for infection-associated complications or who have factors predictive of a poor outcome."

FREE ACCESS | Guideline Summaries | March 08, 2018

Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update Summary

Authors: Randy A. Taplitz, Erin B. Kennedy, and Christopher R. Flowers | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Oncology Practice • Volume 14, Number 4 • https://doi.org/10.1200/JOP.18.00016

- Patients with febrile neutropenia who are eligible for discharge and outpatient management must also meet the following psychosocial and logistic requirements:◦ Residence ≤ 1 hour or ≤ 30 miles (48 km) from clinic or hospital;
- ◦ Patient's primary care physician or oncologist agrees to outpatient management;
- ◦ Able to comply with logistic requirements, including frequent clinic visits;
- ◦ Family member or caregiver at home 24 hours a day;
- ◦ Access to a telephone and transportation 24 hours a day; and
- ◦ No history of noncompliance with treatment protocols.
- The following additional measures are recommended:
- ◦ Frequent evaluation for at least 3 days in clinic or at home;
- ◦ Daily or frequent telephone contact to verify (by home thermometry) that fever resolves;
- ◦ Monitoring of absolute neutrophil count and platelet count for myeloid reconstitution;
- ◦ Frequent return visits to clinic; and

Outpt vs Inpt

- Unable to tolerate PO meds
- Outpts who do not defervesce
- Cultures show not covered by oral abx

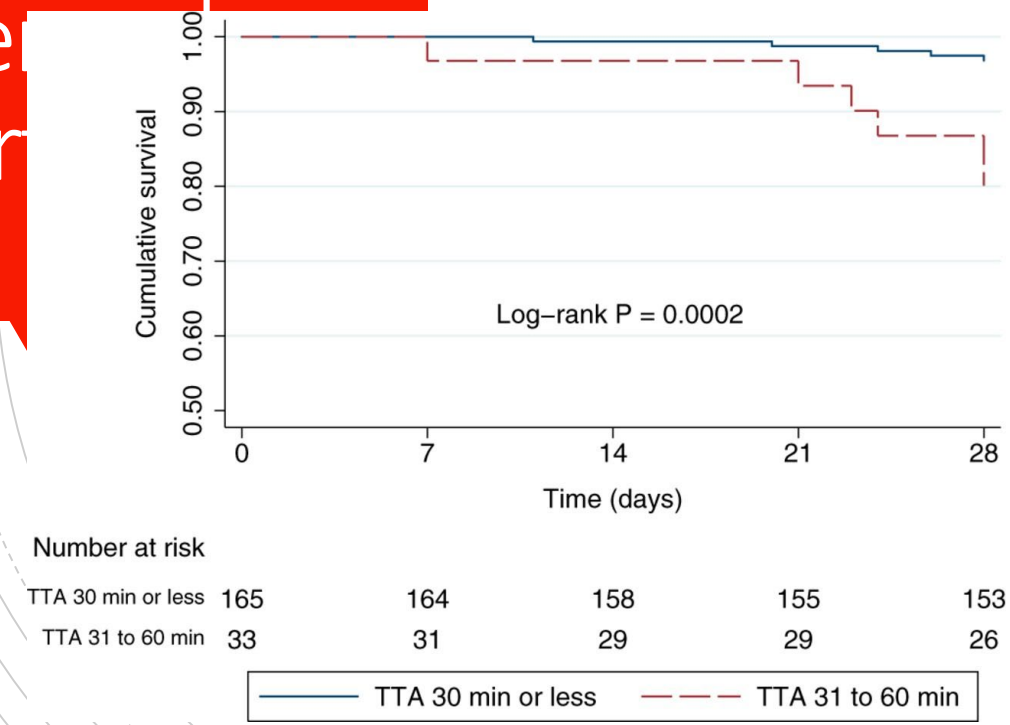
MASCC Score

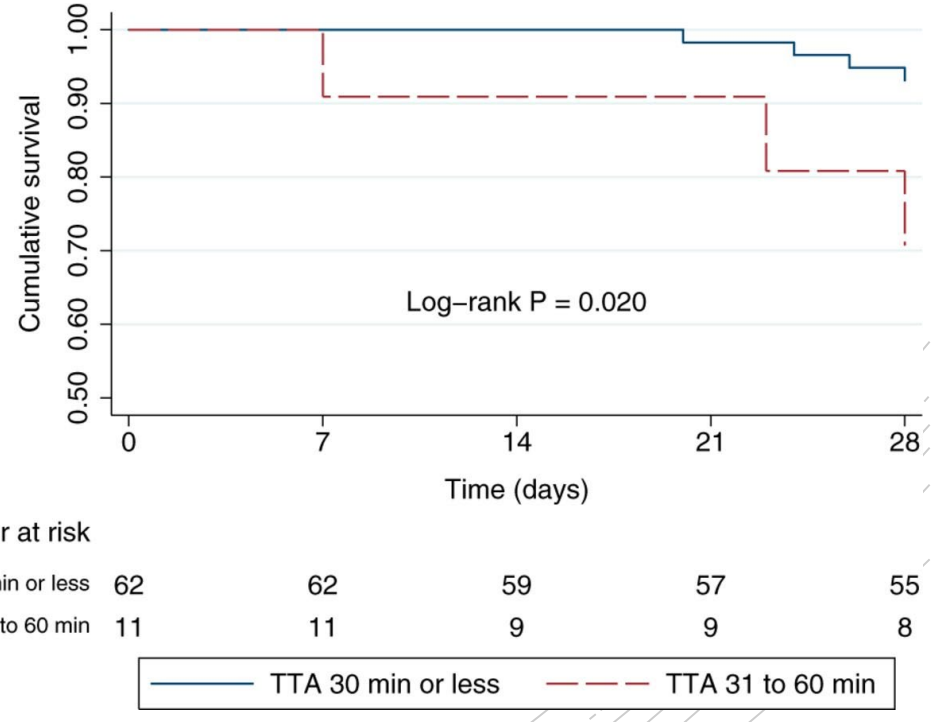
Characteristic	Score
Burden of illness:[1] • No or mild symptoms • Moderate symptoms • Severe symptoms	 5 3 0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient at presentation	3
Age <60 years	2

[1]Only one score for this characteristic (5, 3 or 0 – points are not cumulative).
A score of 21 or more points is predictive of low-risk febrile neutropenia.

Neutropenic fever mor

- Mortality 5.4-15% overall. One study showed inpt is 2.3%, and larger volume hospitals have lower
- Risk of death at 30d shown to be higher with ICU admission, Abnormal LFTs, positive blood cultures
- low hemoglobin/high CRP was even elevated risk at 1y mark.
- Time to antibiotics has been show to effect LOS and mortality





Tumor lysis syndrome

- Defined as 2 or more simultaneously abnormal levels of: Elevated Potassium, Uric acid, Phosphorous and low calcium
- AKI due to uric acid crystalluria, calcium phosphate crystals.
- Can cause kidney failure, arrhythmia, seizures, sudden cardiac death

- Most in hematological malignancies, (ALL>AML>lymphoma> myeloma or chronic leukemias) especially after treatment.
- More likely with high burden of disease (very high blast counts, bulky lymphadenopathy) or very high proliferation
- Can occur in solid tumors but much more rare usually after treatment, and with very advanced cancers
- Can occur spontaneously in both

Cairo-Bishop Criteria

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change From Baseline
Uric acid	≥ 476 µmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

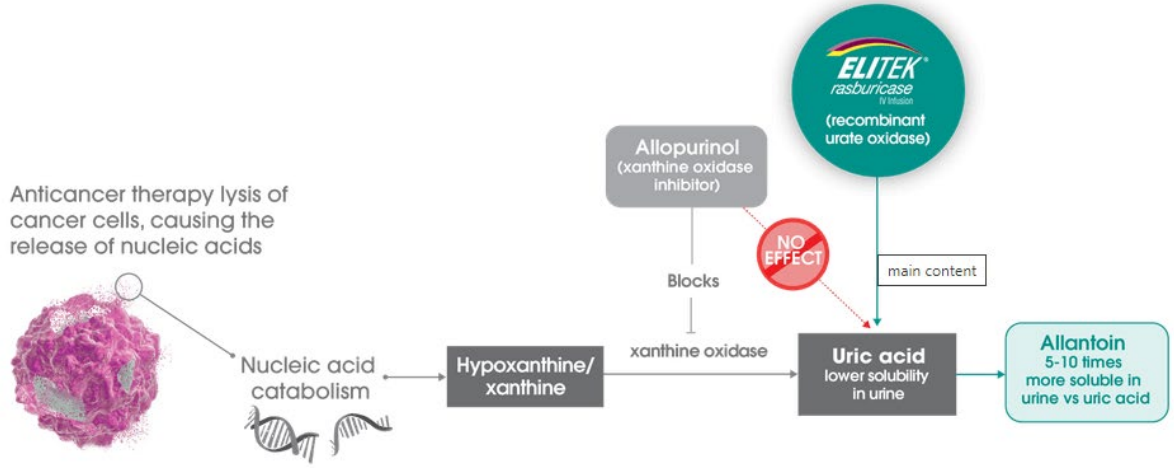
NOTE. Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy.

- Clinical tumor lysis syndrome is LTLS + one of:
  - Creatinine >1.5 ULN
  - Seizure
  - Cardiac arrythmia or sudden cardiac death

TLS- Evaluation and Management

- Frequent labs (q6-8h) - BMP, Phos, Uric acid (first 72h into treatment)
- IVF Normal Saline (no longer favor alkalinization)
- Allopurinol prophylactically
- Exercise Caution with elyte replacement
- Consider cytoreduction (hydrea, leukapheresis)
- If uric acid > consider rasburicase (*ice subsequent blood draws for uric acid)
- May even suspend treatment until controlled.

Mechanism of action: ELITEK vs allopurinol[1,2]



Tumor lysis syndrome - Mortality

- Mortality varies in studies. Most recent study post rasburicase era 21% in hospital mortality.
- TLS from AML or solid tumor was higher mortality.
- Females have higher mortality

Complication	Odds ratio for mortality	*p* value	Coefficient for increased length of stay	*p* value
Acute respiratory failure	3.42	<.01	1.61	.03
Sepsis	2.73	<.01	6.24	<.01
Acute renal failure	2.66	<.01	−0.95	.04
Dialysis	NS	NS	2.88	<.01
Mechanical ventilation	2.68	<.01	2.44	.02
Cardiopulmonary arrest	10.98	<.01	−3.72	.04
Hyperkalemia	1.51	<.01	−4.12	<.01
Hypocalcemia	0.59	<.01	2.98	<.01
Cerebral hemorrhage	2.00	.01	7.55	<.01
Gastrointestinal hemorrhage	1.43	.02	5.32	<.01

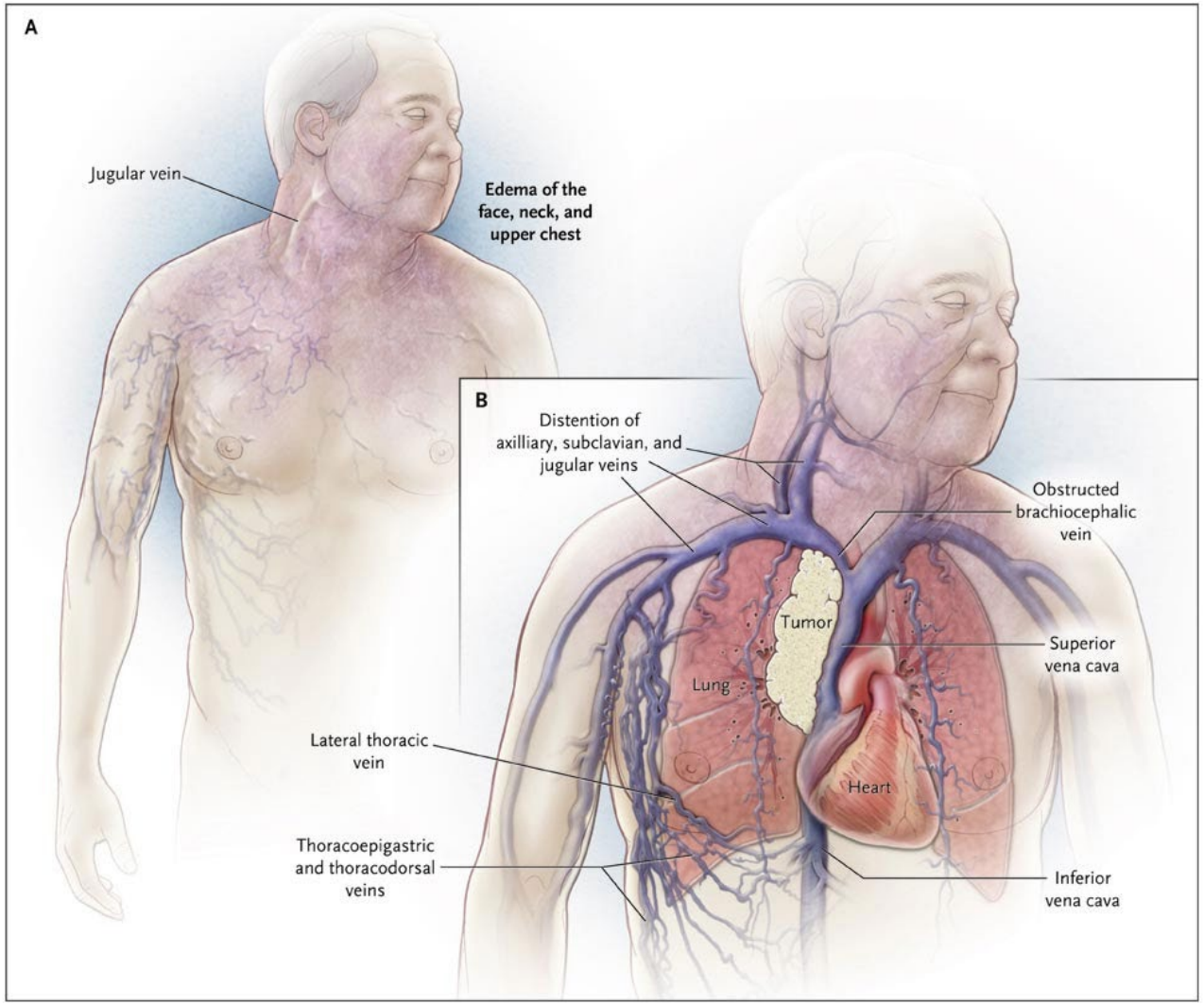
Seizure omitted due to nonsignificance ($p > .10$)
Abbreviation: NS, nonsignificant.

SVC syndrome -symptoms

Symptoms:

- headache, especially when leaning forward
- Facial swelling and or upper extremity swelling or redness, can be only temporary with positioning
- Dizziness/syncopal
- Vision changes
- Voice changes

SVC symptoms – clinical exam



SVC syndrome -risk groups

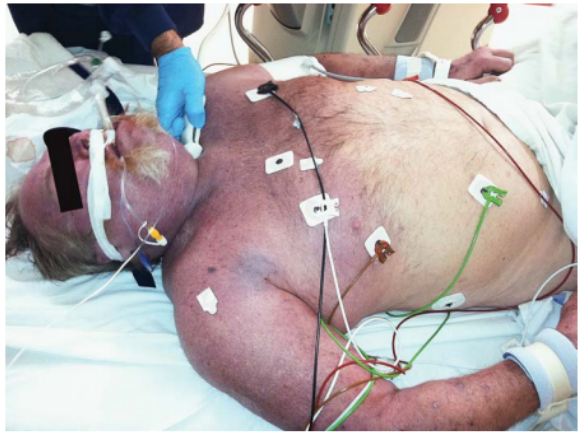
- Thoracic tumors- NSCLC, SCLC, NHL, thymoma, Germ cell tumors
- Lymphadenopathy
- Clots- especially related to devices
- Post radiation fibrosis
- Fibrosing mediastinitis (postinfectious)

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Lindsey R. Baden, M.D., *Editor*

Superior Vena Cava Syndrome



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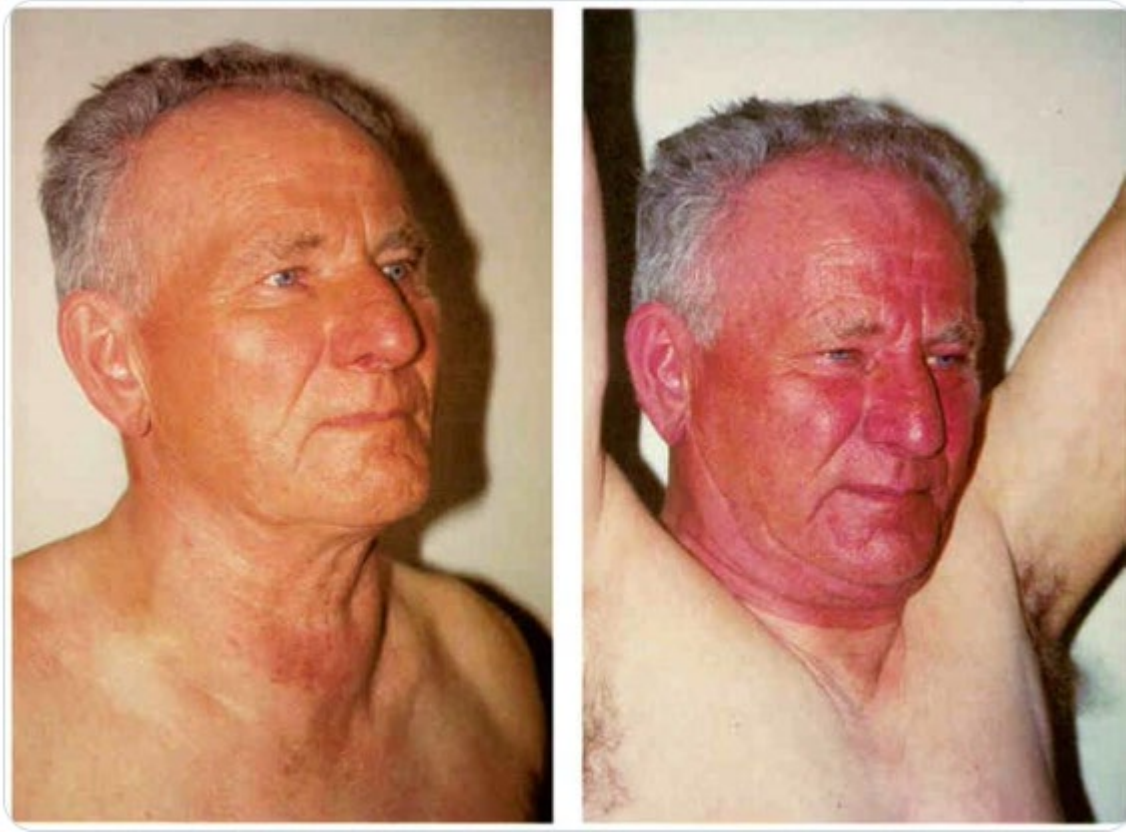
A 59-YEAR-OLD MAN WITH HYPERTENSION AND CROHN'S DISEASE THAT was complicated by fistulas was found unconscious at home. He was being treated with infliximab administered through a central venous access device, which had been placed for long-term intermittent treatment. The patient had been treated unsuccessfully with sulfasalazine, glucocorticoids, and immunomodulatory therapies, including methotrexate, azathioprine, and mercaptopurine. He was intubated and brought to the emergency department. Vital signs were stable, and the physical examination was notable for cyanosis of the head, neck, upper torso, and arms. Venography showed occlusion of the superior vena cava, a finding

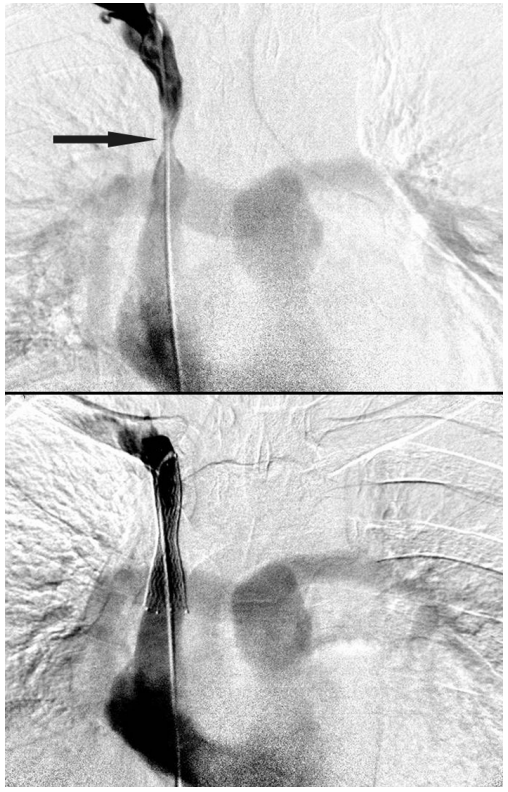
SVC syndrome - evaluation



- Consider maneuvers to elicit (pemberton's, place recumbent)
- CT scan urgently of chest/neck
- Biopsy of lesions via bronch vs. Interventional radiology
- https://www.grepmed.com/images/13189/pembertons-clinical-sign-physicalexam-video

SVC syndrome- management

- Positioning is very important. UPRIGHT.
- Management/ Mortality depends on the etiology
  - SCLC or lymphoma- urgent chemo
  - NSCLC – urgent radiation therapy
  - Clot- remove device/catheter directed thrombosis



Role of stenting:
"Patients with symptomatic superior vena cava obstruction who have malignant disease and a short to medium life expectancy, either at the initial presentation or after failed chemotherapy or radiotherapy
OR Patients with symptomatic superior vena cava obstruction secondary to benign disease"

Metastatic Spinal Cord Compression

- Often presents with back pain, maybe present for prolonged period before. Can be localized or radicular.
- Progressive limb weakness, bowel or bladder dysfunction, LE or pelvic sensory loss
- More common in solid tumors. In adults: Breast, prostate, Lung, NHL, Melanoma and RCC

Metastatic Spinal Cord Compression - first steps

- Dexamathasone 10mg IV stat followed by 4mg q6h, but can be po.
- STAT MRI CTL spine w/wo contrast.
- Neurosurgery consultation asap.
- Oncology consult to delineate future treatment options and expected prognosis to help neurosurgery to decide if the patient is a surgical candidate bc the recovery from surgery is usually measured in months.
- Tokuhashi/Tomita/ SORG scores

Characteristic	Score
General condition	
Poor (PS 10% to 40%)	0
Moderate (PS 50% to 70%)	1
Good (PS 80% to 100%)	2
Number of extraspinal metastatic foci	
≥3	0
1-2	1
0	2
Number of metastases in vertebral body	
≥3	0
2	1
1	2
Metastases to other internal organs	
Unresectable	0
Resectable	1
Absent	2
Primary site of malignancy	
Lung, osteosarcoma, stomach, bladder, esophagus, or pancreas	0
Liver, gallbladder, unidentified	1
Others	3
Kidney, uterus	4
Thyroid, breast, prostate, carcinoid	5
Palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
Non (Frankel E)	2
Total Score	**Months**
0-8	>6
9-11	≥6
12-15	≥12

Scoring system				Prognostic score	Tretment goal	Surgical strategy
Point	Prognostic factors					
	Primary tumor	Visceral mets.[a]	Bone mets.[b]			
1	Slow growth (breast, thyroid, etc.)		Solitary or isolated	2 3	Long-term local control	Wide or marginal excision
				4 5	Middle-term local control	Marginal or intralesional excision
2	Moderate growth (kidney, uterus, etc.)	Treatable	Multiple	6 7	Short-term local control	Palliative surgery
4	Rapid growth (lung, stomach, etc.)	Un-treatable		8 9 10	Terminal care	Supportive care

Surgery outcomes

Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial

Roy A Patchell, Phillip A Tibbs, William F Regine, Richard Payne, Stephen Saris, Richard J Kryscio, Mohammed Mohiuddin, Byron Young

Summary

Background The standard treatment for spinal cord compression caused by metastatic cancer is corticosteroids and radiotherapy. The role of surgery has not been established. We assessed the efficacy of direct decompressive surgery.

Methods In this randomised, multi-institutional, non-blinded trial, we randomly assigned patients with spinal cord compression caused by metastatic cancer to either surgery followed by radiotherapy (n=50) or radiotherapy alone (n=51). Radiotherapy for both treatment groups was given in ten 3 Gy fractions. The primary endpoint was the ability to walk. Secondary endpoints were urinary continence, muscle strength and functional status, the need for corticosteroids and opioid analgesics, and survival time. All analyses were by intention to treat.

Findings After an interim analysis the study was stopped because the criterion of a predetermined early stopping rule was met. Thus, 123 patients were assessed for eligibility before the study closed and 101 were randomised. Significantly more patients in the surgery group (42/50, 84%) than in the radiotherapy group (29/51, 57%) were able to walk after treatment (odds ratio 6·2 [95% CI 2·0–19·8] p=0·001). Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days *vs* 13 days, p=0·003). 32 patients entered the study unable to walk; significantly more patients in the surgery group regained the ability to walk than patients in the radiation group (10/16 [62%] *vs* 3/16 [19%], p=0·01). The need for corticosteroids and opioid analgesics was significantly reduced in the surgical group.

Interpretation Direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.

Lancet 2005; 366: 643–48
Published online July 21, 2005
DOI:10.1016/S0140-6736(05)66954-1

See Comment page 609

Department of Surgery (Neurosurgery) (R A Patchell MD, P A Tibbs MD, B Young MD), **Department of Neurology** (R A Patchell), **Department of Statistics** (R J Kryscio PhD), **and Department of Radiation Medicine** (M Mohiuddin MD), **University of Kentucky Medical Center, Lexington, KY, USA; Department of Radiation Oncology, University of Maryland Medical School, Baltimore, MD, USA** (W F Regine MD); **Duke Institute on Care at the End of Life, Duke University Medical Center, Durham, NC, USA** (R Payne MD);

Cochrane database systematic review 2008 concluded that surgery most beneficial in ambulatory pts with poor radiation sensitivity tumors, and nonambulant if a single area of compression, paraplegia <48h and survival more than 3m.

Subsequent metaanalysis in 2023 show no benefit of surgery if no neuro deficits, suggests vertebrectomy diminishing in value.

Metastatic spinal cord compression -next steps

- Consider urgent radiation medicine consult if no plan for surgery.
- Define goals of care- there is a palliative benefit of short course radiation even if the patient wants comfort measures/hospice
- Don't assume radiation isn't possible even if they have had in the past.
- Think about urinary retention and constipation early.
- PT OT and rehab.

Relative radiosensitivity of neoplasms for the purposes of ESCC decision-making*

Radiosensitive tumors	Radioresistant tumors
▪ Lymphoma ▪ Myeloma ▪ Small cell lung cancer ▪ Germ cell tumors ▪ Prostate cancer ▪ Breast cancer	▪ Melanoma ▪ Renal cell carcinoma ▪ Non-small cell lung cancer ▪ Gastrointestinal cancers ▪ Sarcoma

ESCC: epidural spinal cord compression; NOMS: Neoplasm, Oncologic, Mechanical, Systemic; cEBRT: conventional external beam radiation therapy.

* For the purposes of ESCC decision-making as part of the NOMS framework, tumors are classified as "relatively radiosensitive" and "relatively radioresistant" based on their predicted responsiveness to cEBRT in the dose ranges that are within spinal cord tolerance.

Acute Brain tumors with Acute Cerebral Edema

- May be the presenting issue of the cancer or present in a patient with known cancer
- Headache, especially early AM or nocturnal. Worse when bending over
- Refractory N/V without other explanation
- Seizures (about 1:5)
- AMS
- Focal neurological deficits

- primary brain tumors :GBM/astrocytoma or primary CNS lymphoma
- SCLC, Melanoma, Breast, Germ cell tumors

Acute Brain tumors with Acute Cerebral edema

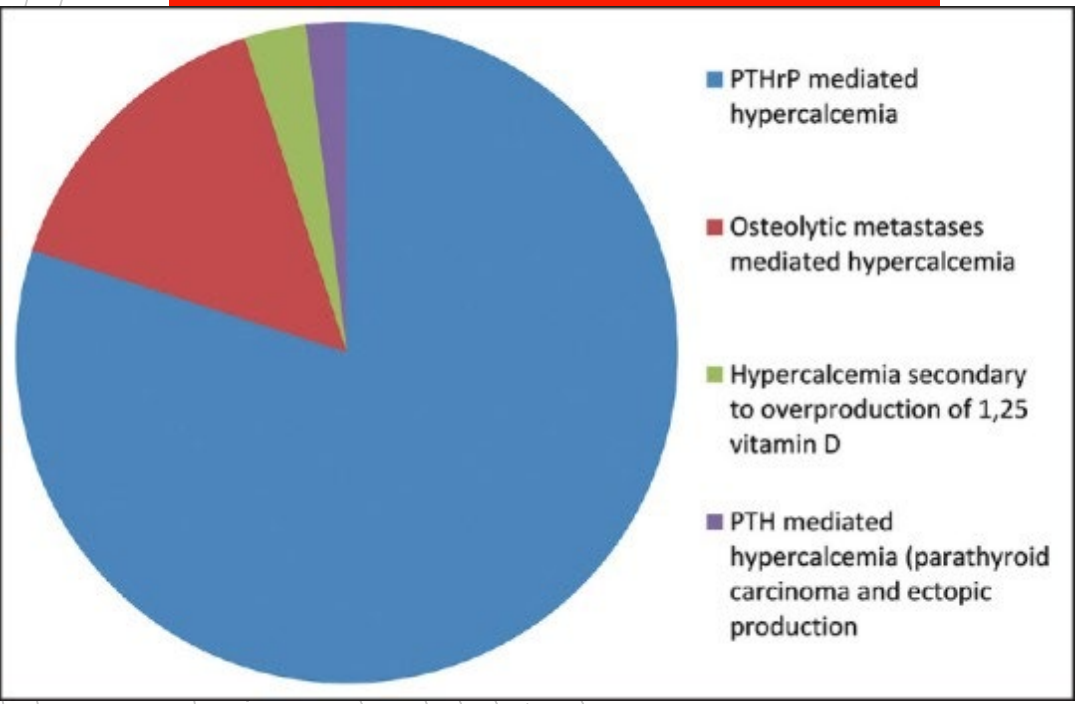
- Often found on head ct, need MRI to confirm.
  - Grey-white border for metastatic lesions
  - Consider contrasted Chest/Abd/Pelvis CTs concurrently to see if primary vs metastatic and/or restage

- Consider anticonvulsants if presented with seizures, otherwise not worth the risk generally
- If edema consider steroids, dexamethasone preferred 4mg q6h. Taper over a few weeks and consider GI PPx while on board
- Neurosurgery consult to consider surgical options

Acute Brain tumors with Cerebral Edema -surgical considerations

- Who benefits from surgery
  - Fewer number of mets- shifting target
  - Tumors >3cm Favorable location (cerebral, not occipital or speech areas, nor brainstem/basal ganglia)
  - Tumors <3cm in posterior fossa
  - Less chemosensitive etiologies

- Postoperative MRI for radiation planning
- After surgery, 10-14d healing prior to radiation or most chemotherapy
  - hormonal therapies or targeted therapies likely ok.
  - Stereotactic radiosurgery vs Sterotactic External Beam Radiotherapy



- Known malignancy and Calcium >12.
- More concerning over 14.
- confused to stuporous, anorexia to n/v/constipation, pancreatitis, arrhthymias, HTN, AKI, Nephrogenic DI
- Corrected Ca= 0.8(4-pt albumin) +total calcium

Risk:

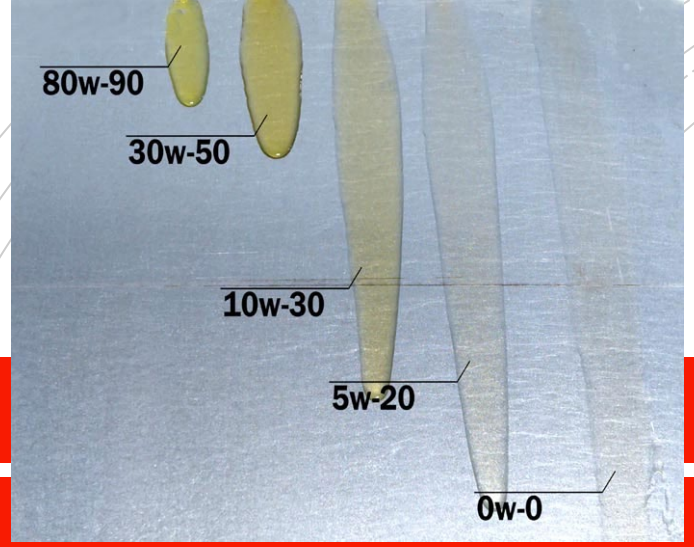
3 unique mechanisms, each with diff higher risk neoplasms

- Squamous cell carcinoma (lung, head/neck, bladder) secreting PTHrP (80%)
- Osteolytic Bone metastases (breast, myeloma)
- Lymphoma secreting 1, 25Vit D

Hypercalcemia of Malignancy

Management:

- IVF 200mL/hr (most of these pts are dry bc hypercalcemia has a mild diuretic effect)
- If pt tends to be volume overloaded (CKD/HF hx) consider loop diuretic in addition to the fluid.
- Measure PTH, PTHrp, Vit D levels
- Consider bisphosphonate vs denosumab IV if >14
  - Pamidronate (60-90mg IV)
  - Zolendronic acid (4mg IV)
  - Denosumab 120mg SQ weekly
  - If symptomatic, add calcitonin IM/SQ. This works faster (~4h) than bisphosphonate (2d), but beware of tachyphylaxis.



Hyperviscosity syndrome/ Leukostasis

$$\text{Volume Flowrate} = f = \frac{P_1 - P_2}{R} = \frac{\pi(\text{Pressure diference})(\text{radius})^4}{8(\text{viscosity})(\text{length})}$$

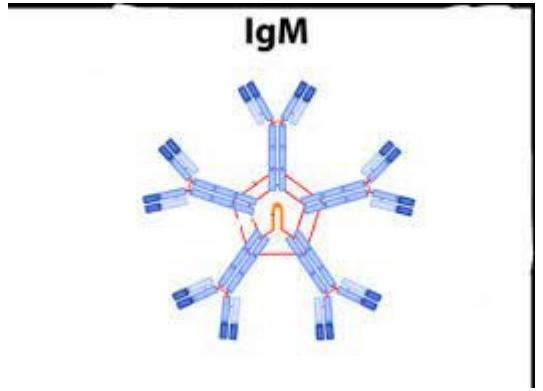
$$\text{Resistance to Flow} \quad R = \frac{8nL}{\pi r^4}$$

Viscosity is opposition to flow.

Hyperviscosity syndrome

Clinically : small vessels effected (Poiseuille's law)

- Mucosal bleeding (epistaxis)
- visual disturbance/papilledema,
- coma/cerebral hemorrhage/seizures,
- Heart failure



- Monoclonal
  - Most are hematological malignancies!
    - Waldenstrom's (10-30% cases have HVS)
    - Multiple myeloma
  - cryoglobinemia
- Polyclonal
  - Rheumatoid arthritis
  - Uncontrolled HIV
  - Sjogren's

Hyperviscosity syndrome/ Leukostasis

- Check serum viscosity if symptoms or M-spike >4g or 6
- Therapeutic apheresis if symptomatic
- urgent chemo if not.
- Beware transfusion during these issues! Especially if rouleaux formation

Leukostasis

- Similar concept only cells instead of paraproteins
- Clinically:
  - Respiratory- ALI- alveolar pattern on CXR or PE picture
    - Pseudohypoxemia- leukocyte larceny. pulse ox>>> ABG
  - Neurological – AMS, seizures, focal deficits
  - AKI
  - Less related to size- home to specific areas. Adhesion molecules?

- More common with AML (monocytic) or CLL blast crisis
  - cells "sticky"- inflammatory cytokines upregulate selectin cell surface proteins so adhere to endothelial cells
  - Myeloid blasts are bigger.
  - Can be seen in ALL or CLL but usually with much higher counts
- More common if WBC >100
- Cytoreduction
  - Pheresis
  - Hydroxyurea
  - Steroids maybe
  - ATRA in APML over pheresis

Pheresis side effects to watch for

- Citrate toxicity- hypocalcemia, paresthesias,
- Capillary leak syndrome- esp w IgM bc of sudden oncotic pressure change. Cardiovascular collapse

references

- Randy A. Taplitz et al.Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update Summary. *JOP* **14**, 250-255(2018).DOI:10.1200/JOP.18.00016
- https://www.elitekpro.com/en/
- Mirrakhimov AE, Voore P, Khan M, Ali AM. Tumor lysis syndrome: A clinical review. World J Crit Care Med. 2015 May 4;4(2):130-8. doi: 10.5492/wjccm.v4.i2.130. PMID: 25938028; PMCID: PMC441156
- Bertrand Coiffier et al.,Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review. *JCO* **26**, 2767-2778(2008).DOI:10.1200/JCO.2007.15.0177
- Spinal Cord Crompression Management in Cancer Patients, MD Anderson. https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-spinal-cord-compression-web-algorithm.pdf
- Kim, J., Lee, SH., Park, SJ. *et al.* Analysis of the predictive role and new proposal for surgical strategies based on the modified Tomita and Tokuhashi scoring systems for spinal metastasis. *World J Surg Onc* **12**, 245 (2014). https://doi.org/10.1186/1477-7819-12-245
- https://www.researchgate.net/figure/The-Revised-Tokuhashi-Score_tbl2_322860154
- Morie A. Gertz; Acute hyperviscosity: syndromes and management. *Blood* 2018; 132 (13): 1379–1385. doi: https://doi.org/10.1182/blood-2018-06-846816
- Macaron W, Sargsyan Z, Short NJ. Hyperleukocytosis and leukostasis in acute and chronic leukemias. Leuk Lymphoma. 2022 Aug;63(8):1780-1791. doi: 10.1080/10428194.2022.2056178. Epub 2022 Mar 31. PMID: 35357988.
- Klatersky et al.The Multinational Association for Supportive Care in Cancer Risk Index: A Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer Patients.Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 2000, 18 (16): 3038-51
- Hatamabadi H, Arhami Dolatabadi A, Akhavan A, Safari S. Clinical Characteristics and Associated Factors of Mortality in Febrile Neutropenia Patients; a Cross Sectional Study. Arch Acad Emerg Med. 2019 Jul 27;7(1):39. PMID: 31555769; PMCID: PMC6732199.
- Damien Urban et al.,Mortality Among Neutropenic Cancer Patients Within the United States: The Association With Hospital Volume. *JCO Oncol Pract* **17**, e582-e592(2021).DOI:10.1200/OP.20.00115
- Perron, T., Emara, M. & Ahmed, S. Time to antibiotics and outcomes in cancer patients with febrile neutropenia. *BMC Health Serv Res* **14**, 162 (2014). https://doi.org/10.1186/1472-6963-14-162
- Rosa RG, Goldani LZ. 2014. Cohort Study of the Impact of Time to Antibiotic Administration on Mortality in Patients with Febrile Neutropenia. Antimicrob Agents Chemother 58:.https://doi.org/10.1128/aac.02561-14
- Durani U, Shah ND, Go RS. In-Hospital Outcomes of Tumor Lysis Syndrome: A Population-Based Study Using the National Inpatient Sample. Oncologist. 2017 Dec;22(12):1506-1509. doi: 10.1634/theoncologist.2017-0147. Epub 2017 Sep 13. PMID: 28904174; PMCID: PMC5728022.
- Calvin Ghimire, Nischit Baral, Simi M Mathew, Tejaswi Vinjam, Sajan Acharya, Krishna Prasad Bashyal, Sandip Karki, Ujwala Koduru, Joshua Christy, Arvind Kunadi; Outcomes of Tumor Lysis Syndrome in Hospitalized Patients: A Retrospective Cohort Study from National Inpatient Sample 2016-2019. *Blood* 2022; 140 (Supplement 1): 11741. doi: https://doi.org/10.1182/blood-2022-170073
- Sacchetti A, Grynn J, Pope A, Vasso S. Leukocyte larceny: spurious hypoxemia confirmed with pulse oximetry. J Emerg Med. 1990 Sep-Oct;8(5):567-9. doi: 10.1016/0736-4679(90)90451-z. PMID: 2254603.

- Lynn D. Wilson, M.D., M.P.H., Frank C. Detterbeck, M.D., and Joachim Yahalom, M.D**Superior Vena Cava Syndrome with Malignant Causes May 3, 2007 N Engl J Med 2007;356:1862-1869**

  VOL. 356 NO. 18DOI: 10.1056/NEJMcp067190
- Clarissa Wallace, Kerry Siminoski. The Pemberton Sign. Ann Intern Med.1996;125:568-569. doi:10.7326/0003-4819-125-7-199610010-00006
- Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005 Aug 20-26;366(9486):643-8. doi: 10.1016/S0140-6736(05)66954-1. PMID: 16112300.
- George R, Jeba J, Ramkumar G, Chacko AG, Leng M, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006716. doi: 10.1002/14651858.CD006716.pub2. Update in: Cochrane Database Syst Rev. 2015;9:CD006716. PMID: 18843728.
- Van den Brande R, Thijs D, Bilsky M, Peeters M, Billiet C, Van de Kelft E. Treatment of ambulatory patients with metastatic epidural spinal cord compression: a systematic review and meta-analysis. J Neurosurg Spine. 2023 Oct 27;40(2):175-184. doi: 10.3171/2023.8.SPINE23541. PMID: 37890190.
- Sinicrope FA. Typhlitis. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12821/
- Paprocka P, Durnaś B, Mańkowska A, Król G, Wollny T, Bucki R. *Pseudomonas aeruginosa* Infections in Cancer Patients. *Pathogens*. 2022; 11(6):679. https://doi.org/10.3390/pathogens11060679
- Bennett CL, Djulbegovic B, Norris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med. 2013 Mar 21;368(12):1131-9. doi: 10.1056/NEJMct1210890. Erratum in: N Engl J Med. 2013 Jul 18;369(3):293. Dosage error in article text. PMID: 23514290; PMCID: PMC3947590.
- Huang, Grace. Should G-CSFs be used with Antibiotics to Treat Established Neutropenic Fever?UCLA health proceedings. Vol 22 (2018)
- Otavio A.C. Clark et al., Colony-Stimulating Factors for Chemotherapy-Induced Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials. *JCO* **23**, 4198-4214(2005).DOI:10.1200/JCO.2005.05.645
- Watkinson AF, Yeow TN, Fraser C. Endovascular stenting to treat obstruction of the superior vena cava. BMJ. 2008 Jun 21;336(7658):1434-7. doi: 10.1136/bmj.39562.512789.80. PMID: 18566082; PMCID: PMC2432169.
- Bewersdorf JP, Zeidan AM. Hyperleukocytosis and Leukostasis in Acute Myeloid Leukemia: Can a Better Understanding of the Underlying Molecular Pathophysiology Lead to Novel Treatments? Cells. 2020 Oct 17;9(10):2310. doi: 10.3390/cells9102310. PMID: 33080779; PMCID: PMC7603052.
- Ali, A. M., Mirrakhimov, A. E., Abboud, C. N., and Cashen, A. F. (2016) Leukostasis in adult acute hyperleukocytic leukemia: a clinician's digest. *Hematol Oncol*, 34: 69–78. doi: 10.1002/hon.2292.