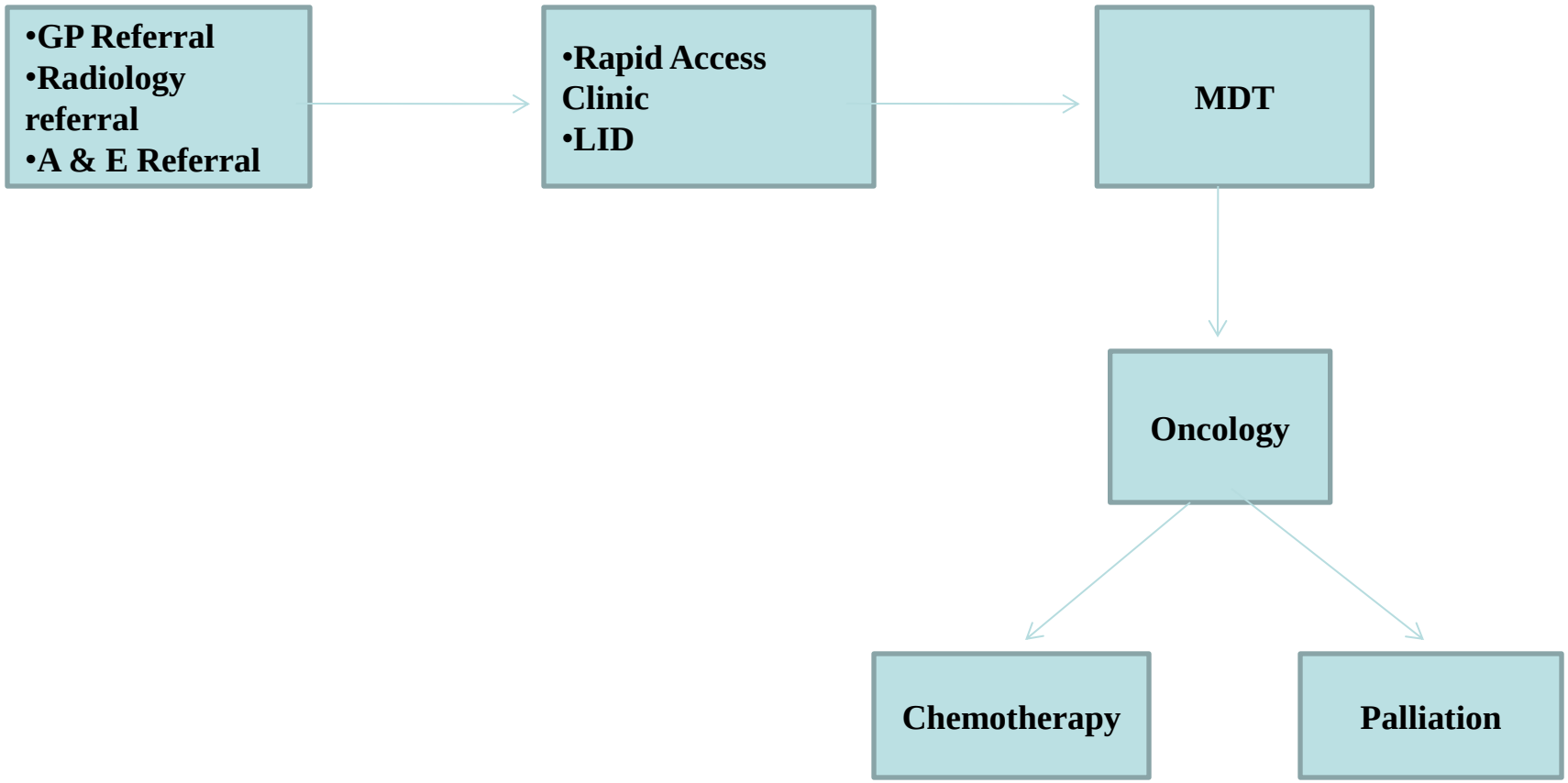
Hyponatremia/hypercalcemia

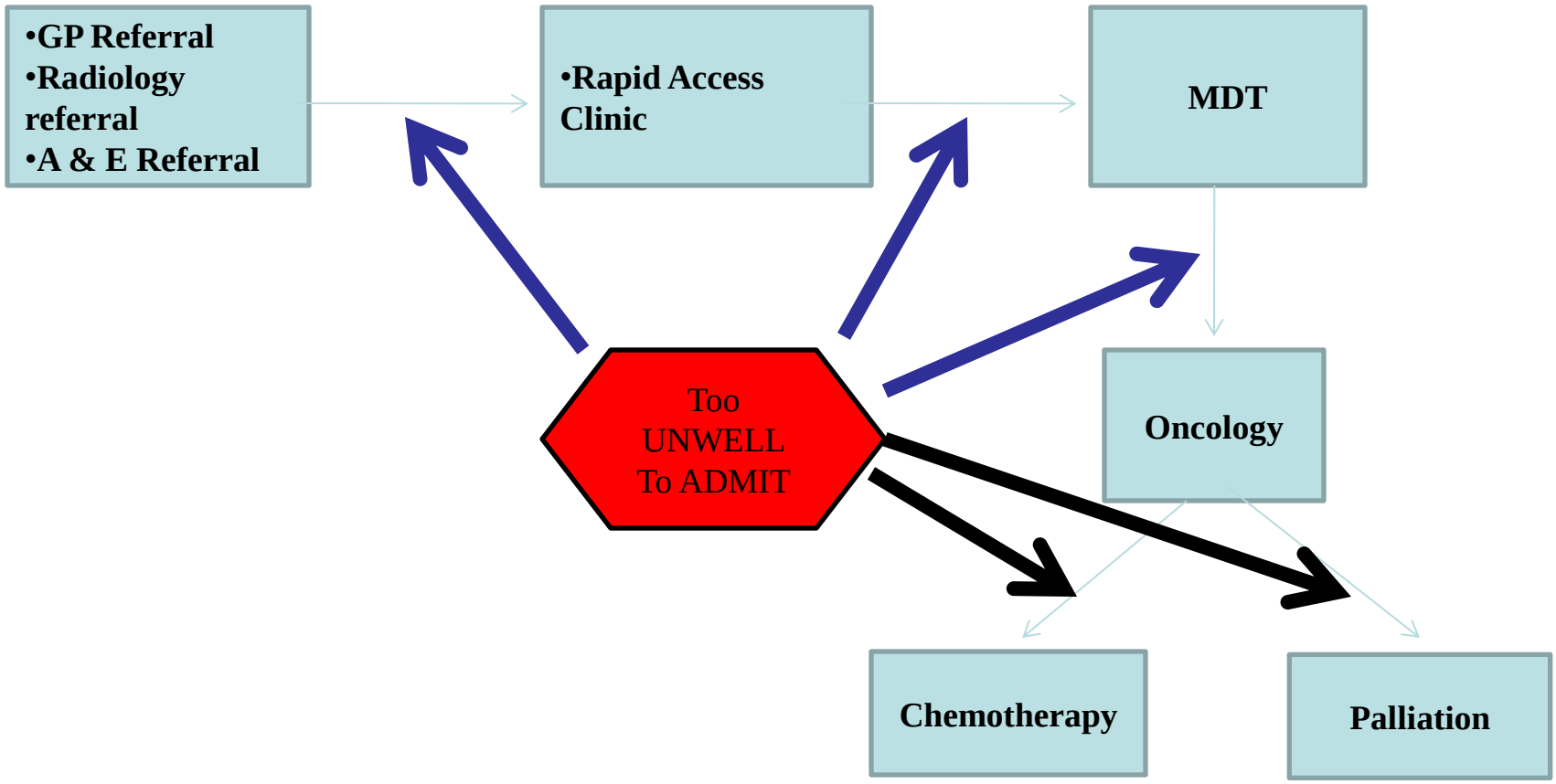
Electrolyte disorders in lung cancer

Therapeutic emergencies in
lung cancer
ELCC 2016
15.4.2016

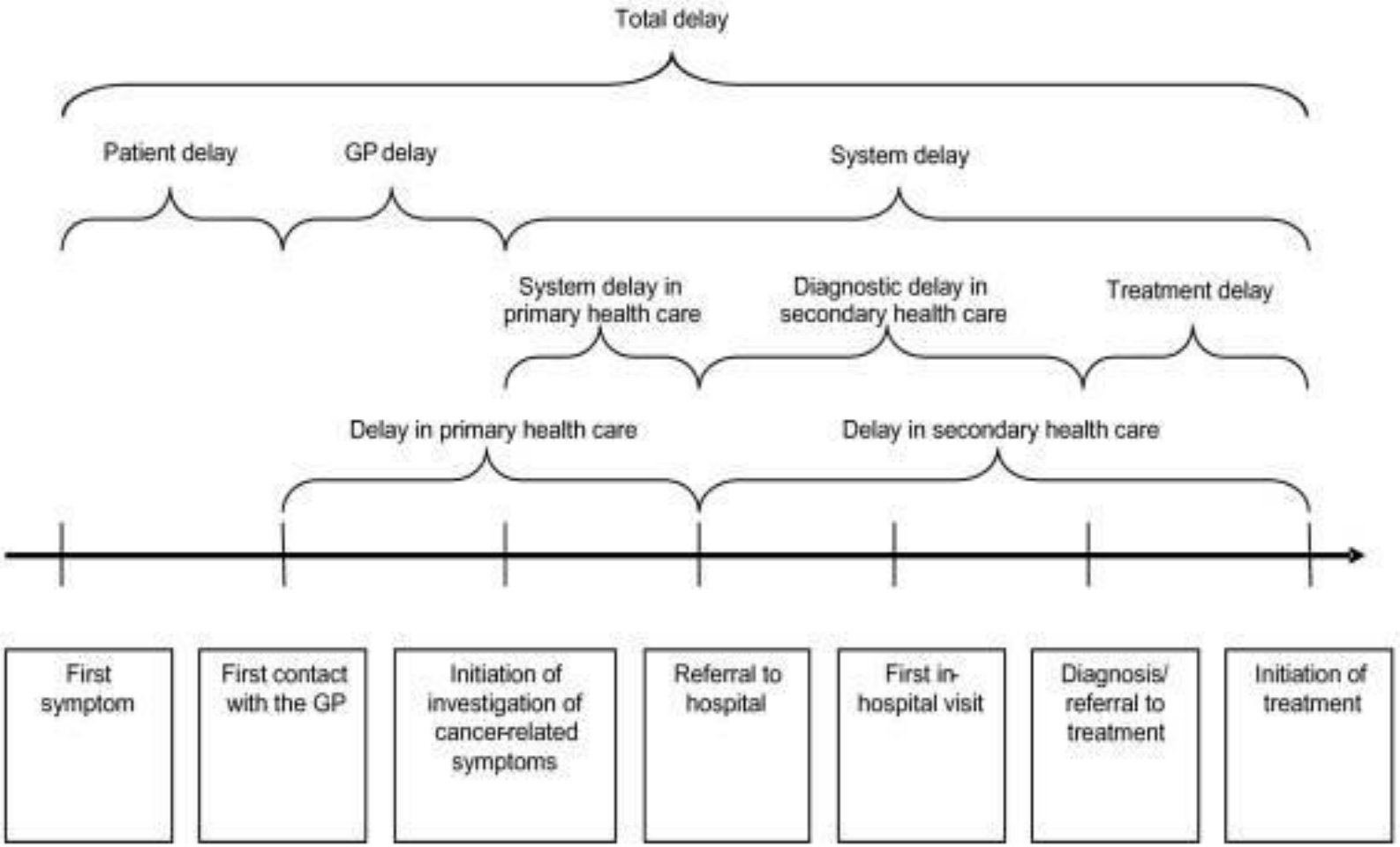
Lung cancer patient pathway



Impact of metabolic disorders



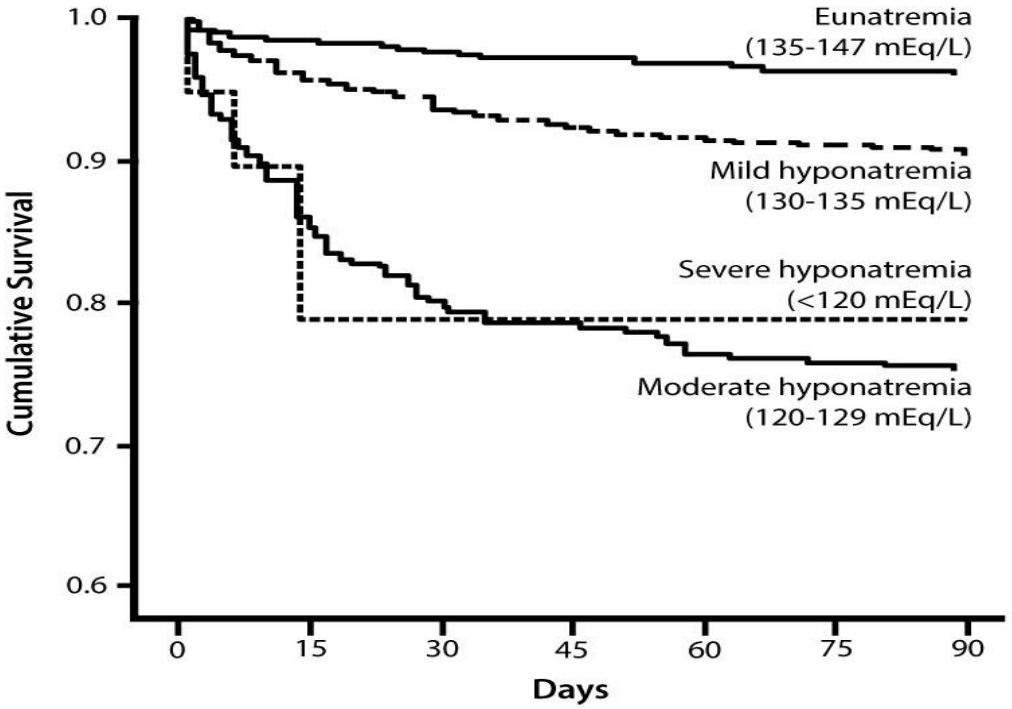
Time intervals from first symptom to treatment of cancer:
a cohort study of 2,212 newly diagnosed cancer patients



BMC Health Serv Res. 2011; 11: 284.

Survival in Patients with Hyponatremia and Cancer

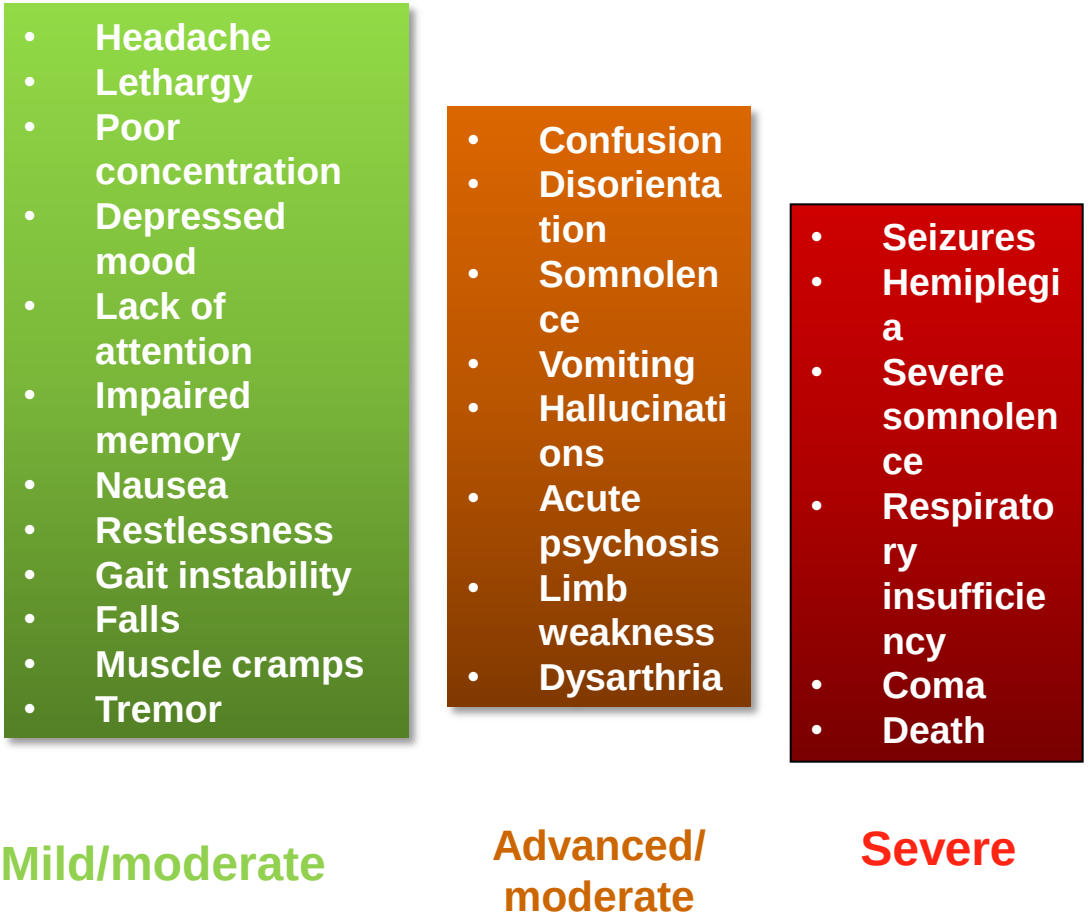
Survival (n=3357) according to the lowest serum sodium during hospitalization



Log rank *P*<0.01

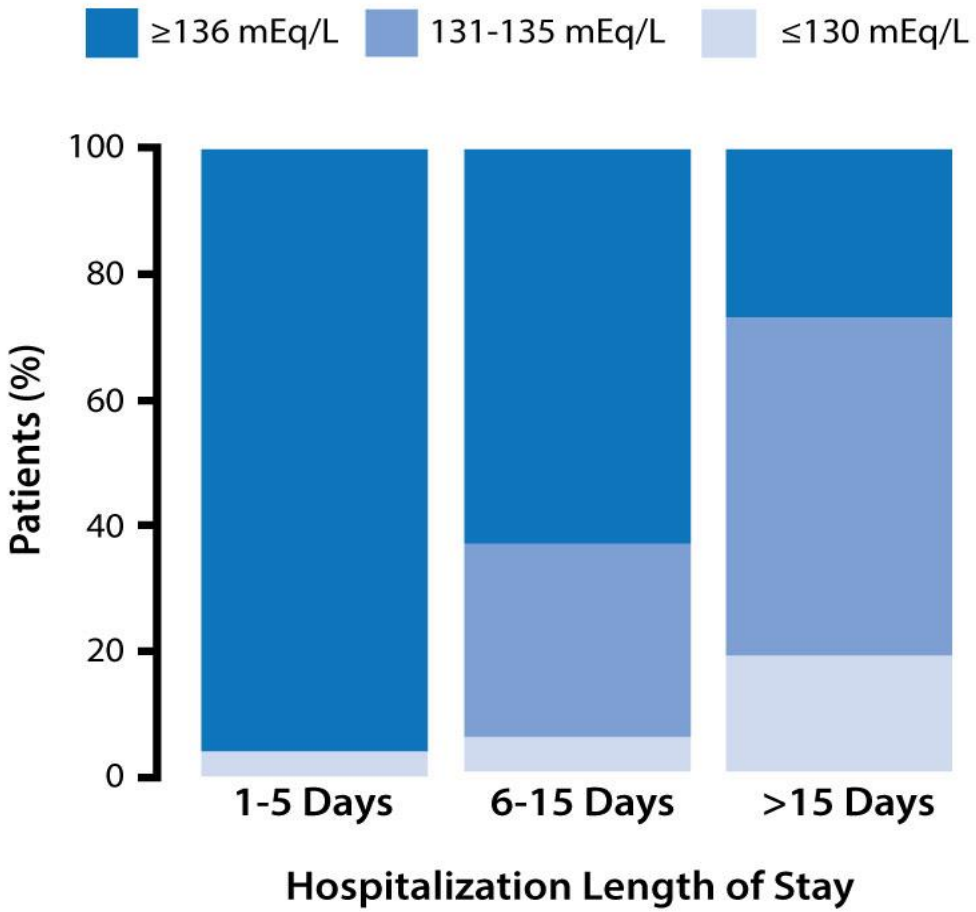
Doshi SM et al. *Am J Kidney Dis.* 2012;59:222-228.

Symptoms of hyponatraemia may reduce patient wellbeing



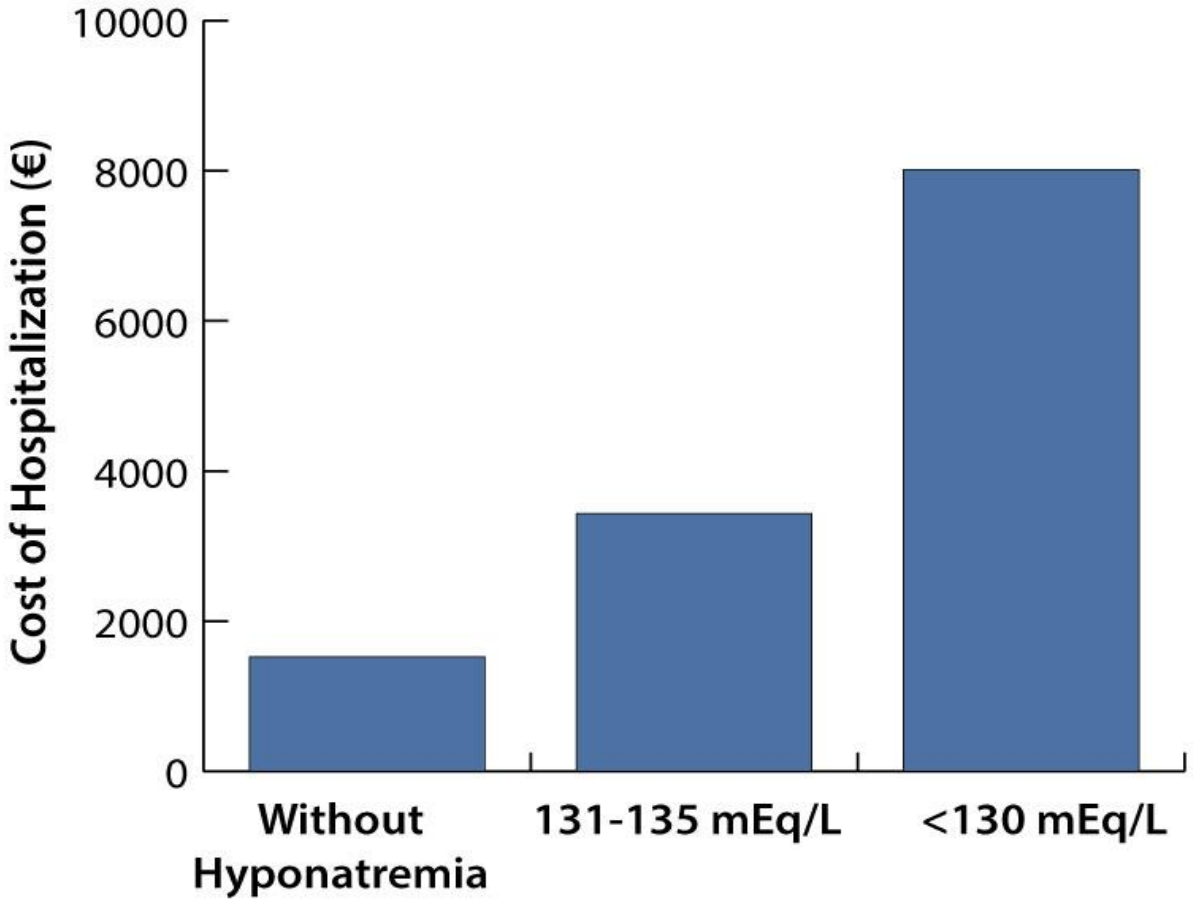
Adapted from Gross P. Ther *Adv Endocrinol Metab.* 2012;3:61-73

Hospital Length of Stay



Berardi R et al. *Support Care Cancer.* 2015;

Cost of Hospitalization



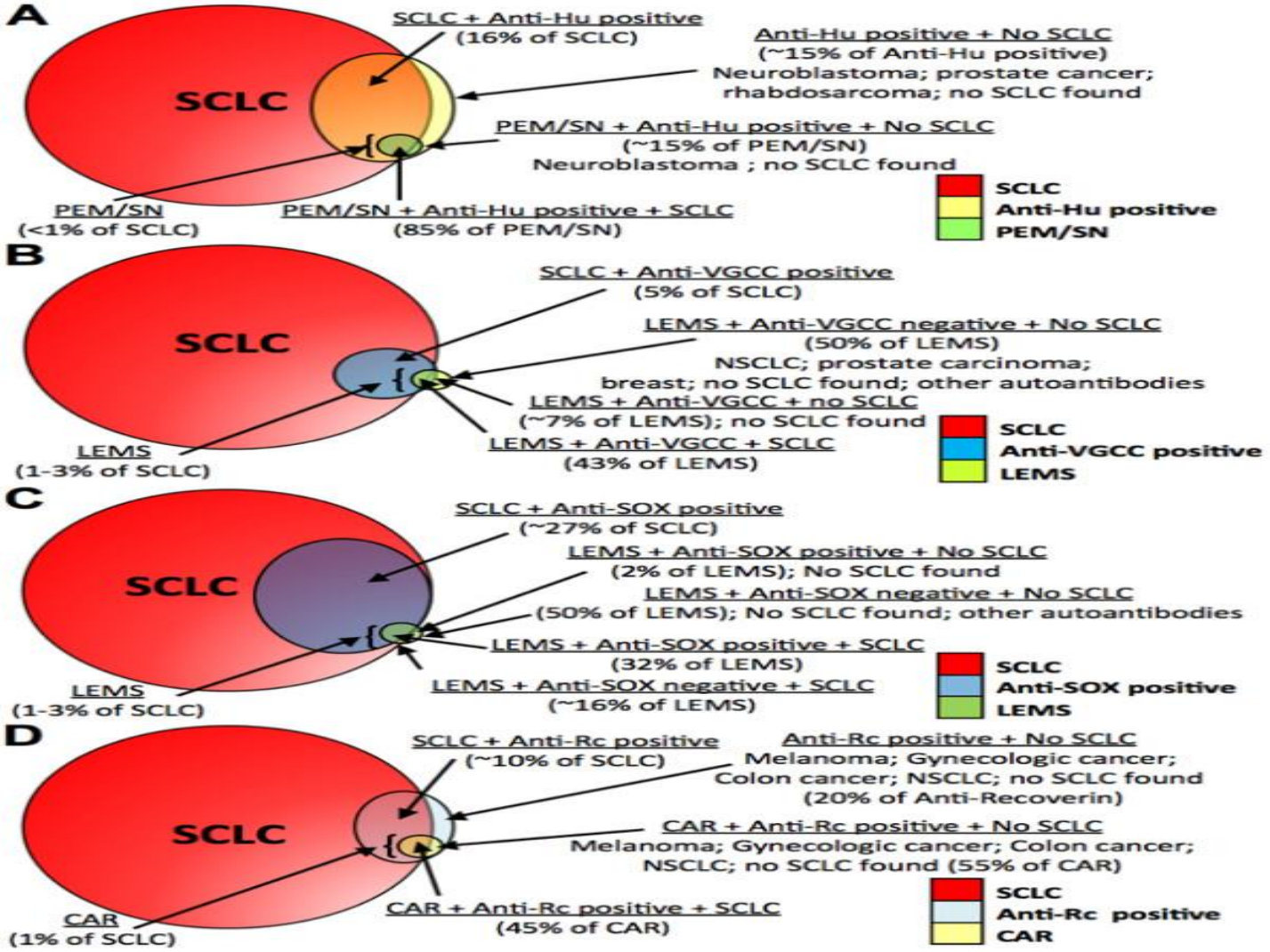
Berardi R et al. *Support Care Cancer.* 2015.

Incidence of HN

- Analysis of 9 clinical trials at 4 hospitals (n=1684)[1]
  - Serum sodium < 136 mEq/L found in **24.6%**
- Retrospective study of patients admitted to M.D. Anderson Cancer center in 2006 (n=3358)[2]
  - Serum sodium < 135 mEq/L found in **47%** of all patients
    - 36% mild (130-134 mEq/L)
    - 10% moderate (120-129 mEq/L)
    - 1% severe (<120 mEq/L)

1. Lassen U et al. *J Clin Oncol.* 1995;13:1215-1220.
2. Doshi SM et al. *Am J Kidney Dis*. 2012;59:222-228.

SCLC and autoantibodies



Medications That May Cause Hyponatremia

- Amiodarone
- Amitriptyline
- Bromocriptine
- Carbamazepine
- Cisplatin
- Chloropropamide
- Cyclophosphamide
- Haloperidol
- Ifosfamide
- Imatinib
- Interferon-alfa
- Interferon-gamma
- Melphalan
- Methotrexate
- Nivolumab
- Pembrzulimab
- Opioids
- Oxcarbamazepine
- Sodium valproate
- SSRIs
- Thiothixine
- Vinblastine
- Vincristine

Grohé C, Berardi R, Burst V. *Crit Rev Oncol Hematol.* 2015;

Survival in Corrected Hyponatremia

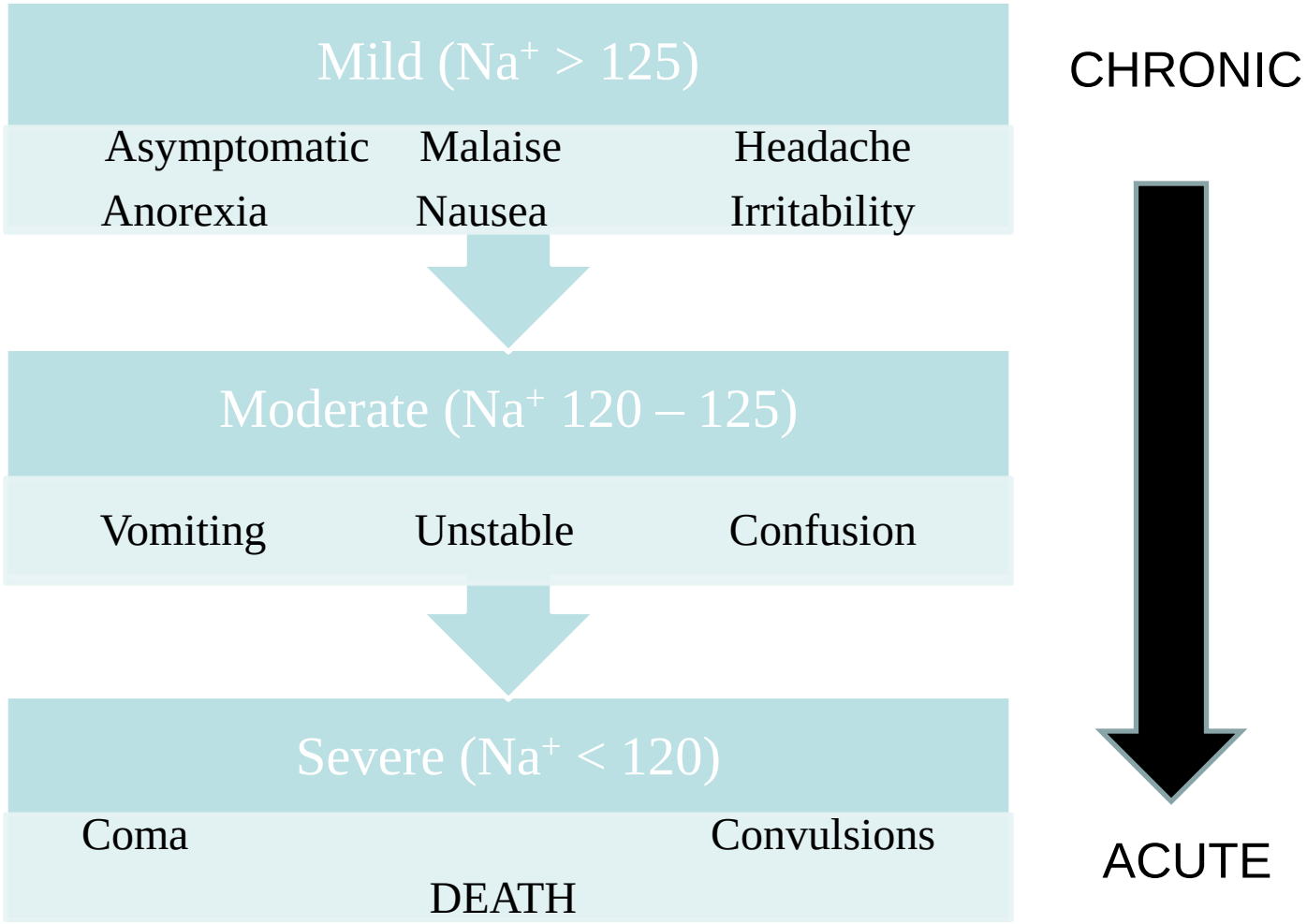
Two-year and median survival for patients with SCLC by hyponatremia status

Status	2-year OS (%)	Median OS (y)
No hyponatremia	30.8 ± 1.3	1.01 ± 0.04
Hyponatremia corrected to ≥138 mEq/L	29.0 ± 8.0	1.11 ± 0.12
Refractory (<138 mEq/L)	13.1 ± 6.9	0.43 ± 0.16

OS=Overall Survival

Grohé C, Berardi R, Burst V. *Crit Rev Oncol Hematol.* 2015.

CLINICAL MANIFESTATIONS



Ellison DH et al. *N Engl J Med*. 2007;356:2064-2072.

Baylis PH. *Int J Biochem Cell Biol*. 2003 Nov;35(11):1495-9.

Appropriate Initial Therapy ?

- Restrict all fluid intake, not just water
- Aim for intake that is 500 mL/day below the 24-hour urine volume
- Do not restrict sodium or protein intake unless indicated

Predictors of the likely failure of fluid restriction

- High urine osmolality (>500 mOsm/kg H_2O)
- Urine Na^+ plus K^+ concentrations > serum Na^+
- 24-hr urine volume <1500 mL/d
- Increase in serum Na^+ <2 mEq/L/day in 24-48 hrs

Verbalis J et al. *J Am Med.* 2013;126:S1-S42.

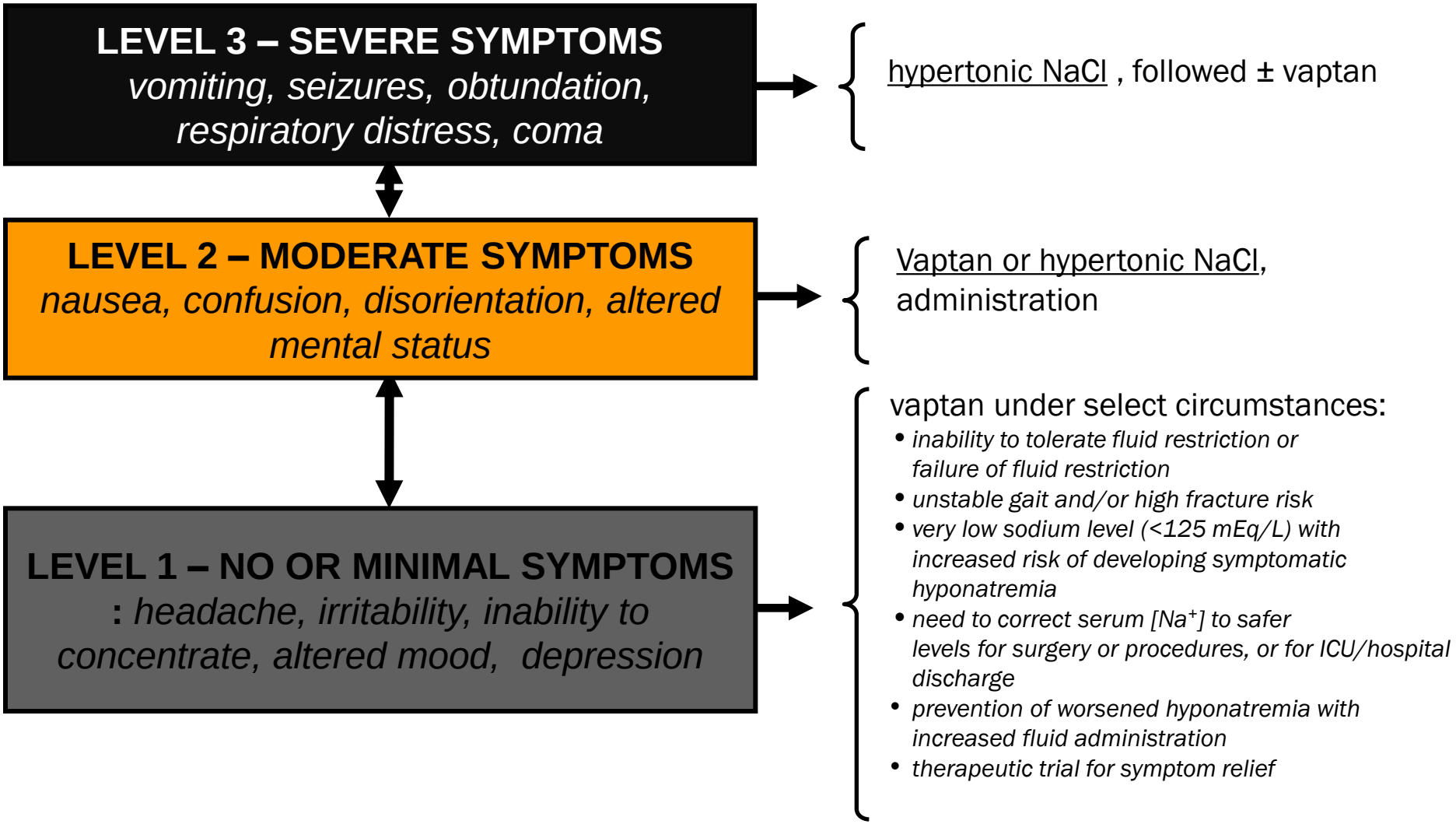
Rationale For Management of Hyponatremia in Patients With Cancer

- Clinical relevance
  - Hyponatremia is associated with a diminished response to treatment
  - Correction and stabilization of sodium levels is necessary to undertake chemotherapy
- Significance of symptoms
- Improved outcomes
  - Hospitalized cancer patients with hyponatremia have higher mortality rates and longer lengths of stay
- Quality of life

Castillo JJ et al. *The Oncologist*. 2012;17:756-765.
Doshi SM et al. *Am J Kid Dis.* 2012;59:222-228.

Hyponatremia treatment algorithm

Euvolemic hyponatremia (SIADH)



Verbalis JG. Journal of Hospital Medicine 2010;5:S18-S26.

Response To Therapy

Initial therapy in patients from US and EU hyponatremia registry

Treatment	N	Baseline Na^+ mEq/L	Median Rate of Change mEq/L/d
None	507	127.0	0.4
Fluid restriction (≤1000 mL)	399	123.0	1.2
Fluid restriction (>1000 mL)	529	126.0	0.7
Normal saline	428	123.0	2.0
Hypertonic saline	72	118.5	3.1
Tolvaptan	131	124.0	3.3

Greenberg A et al. *Kidney International.* 2015;88:167-177.

Hypertonic Saline Correction

- Choose desired correction rate of plasma [Na^+] (eg, 1.0 mEq/L/h)
- Obtain or estimate patient's weight (e.g., 70 kg)
- Multiply weight X desired correction rate and infuse as ml/h of 3% NaCl (eg, 70 kg X 1.0 mEq/L/h = 70 ml/h infusion)

OR:

- 100-200 ml bolus infusion (5-10 min) of 3% NaCl, repeat every 30 min until goal reached
- FOR ALL SALINE CORRECTIONS:
  - Follow serum [Na^+] and urine output every 2-4 hrs during the active correction

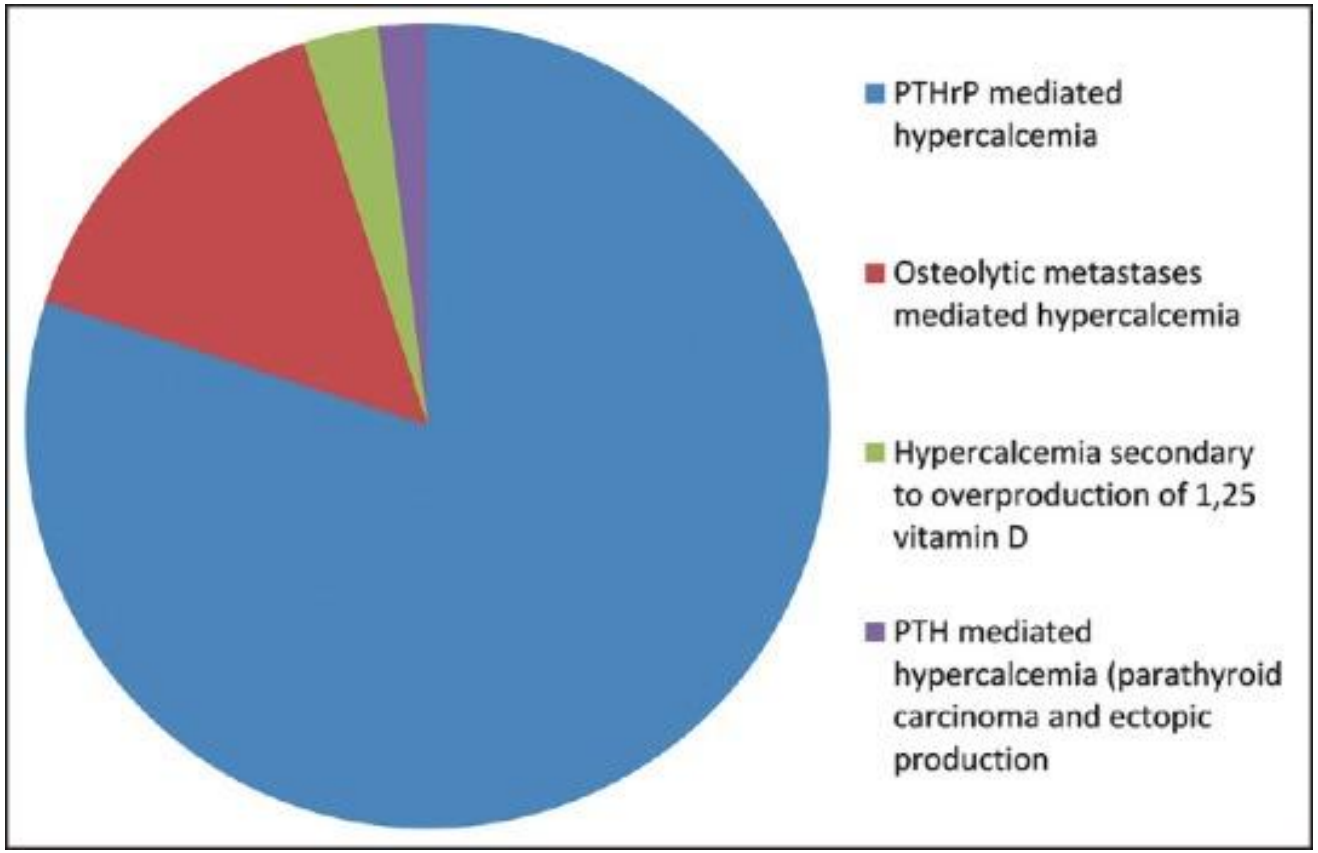
Verbalis J et al. *J Am Med.* 2013;126:S1-S42.

Appropriate Use of Vasopressin Receptor Antagonists

- Patients with SIADH
- Patients who are symptomatic (serum sodium <130 mEq/L)
- Not indicated for patients with depletional hyponatremia or cerebral salt wasting
- Exclude hypovolemic hyponatremia
- Hepatic failure is a relative contraindication

Verbalis J et al. *J Am Med.* 2013;126:S1-S42.

Hypercalcemia of malignancy



N Am J Med Sci. 2015 Nov; 7(11): 483–493.

Prevalence of hypercalcemia of malignancy among cancer patients in the UK

United Kingdom Clinical Practice Research Datalink

- **Hypercalcemic patients (CSC ≥ 10.8 mg/dL) were classified into 4 CSC levels**
- **Among 37,442 cancer patients in 2003-2012 the prevalence of grade 1 HCM increased from 0.13% to 0.45% and the prevalence of HCM overall (grade 1 or higher) increased from 0.20% to 0.67%**
- **Prevalence estimates varied across cancer type and were highest for lung cancer, multiple myeloma and patients with stage IV cancer.**
- **Our findings suggest that HCM in general is not a common condition**

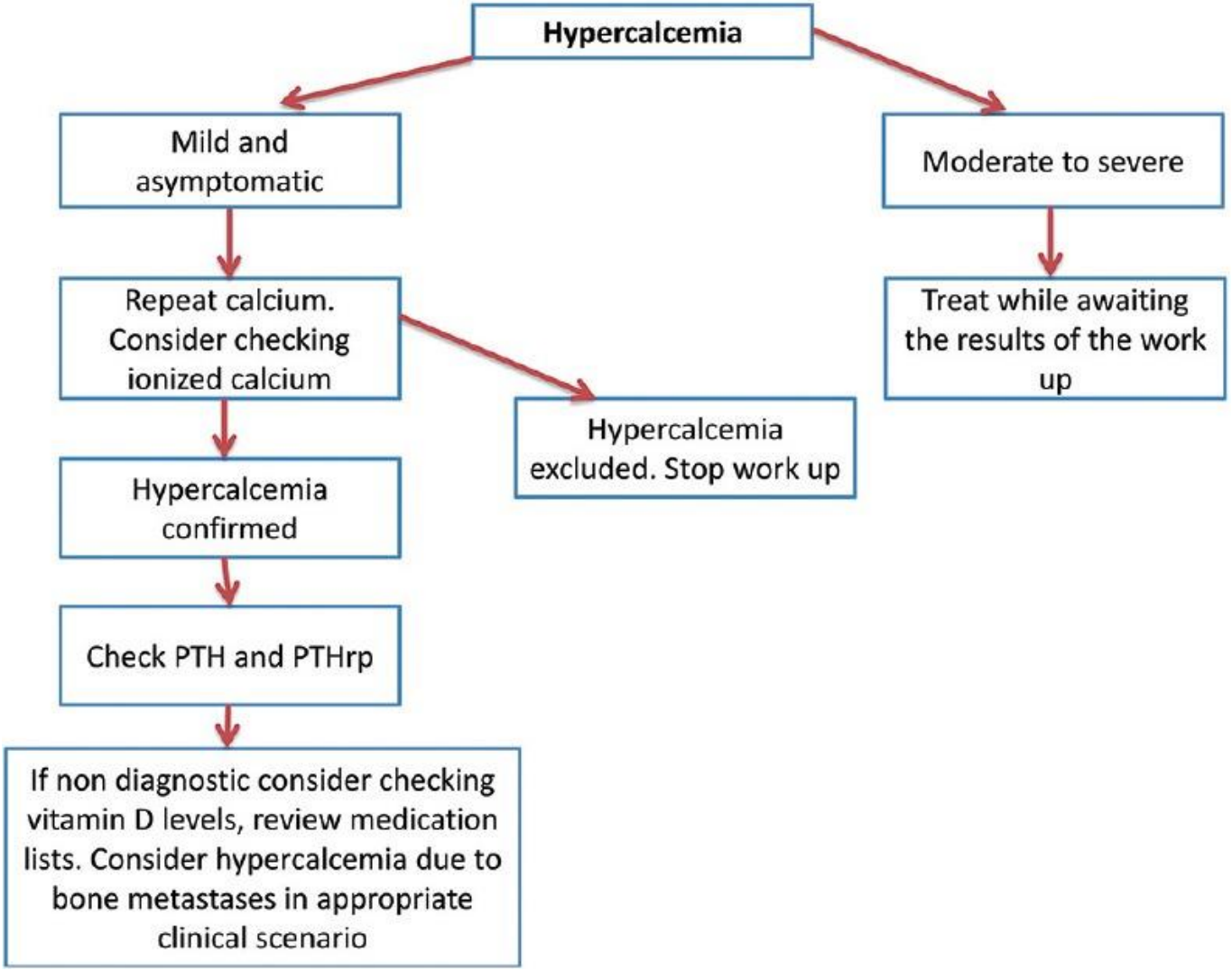
Cancer Epidemiol. 2015 Dec;39(6):901-7.

Hypercalcemia in lung cancer

Table 2: Cox univariate analysis of the prognostic factors for median survival time of the 64 lung cancer patients complicated with malignancy-associated hypercalcemia

Potential factors	Number of cases	Median survival time (days)	*P*
Gender			
Male	43	90	0.026
Female	21	225	
Age (years)			
<60	17	246	0.022
≥60	47	66	
Pathological subtype			
Adenocarcinoma	22	90	0.32
Nonadenocarcinoma	30	132	
Small cell carcinoma	12	52	
Peak value of albumin-corrected calcium (mmol/L)			
<2.9	46	186	<0.001
≥2.9	18	14	
Alkaline phosphatases (U/L)			
≥120	38	182	0.043
<120	26	36	
Creatinine clearance (ml/min)			
≥80	26	186	0.106
<80	38	45	
Bone metastasis			
Yes	29	55	0.122
No	35	182	
Liver metastasis			
Yes	21	47	0.106
No	43	135	
Brain metastasis			
Yes	15	66	0.041
No	49	135	
Adrenal metastasis			
Yes	9	90	0.799
No	55	107	
Number of distant metastasis			
1	18	562	0.003
2	19	58	
≥3	27	42	

Diagnostic workflow



N Am J Med Sci. 2015 Nov; 7(11): 483–493

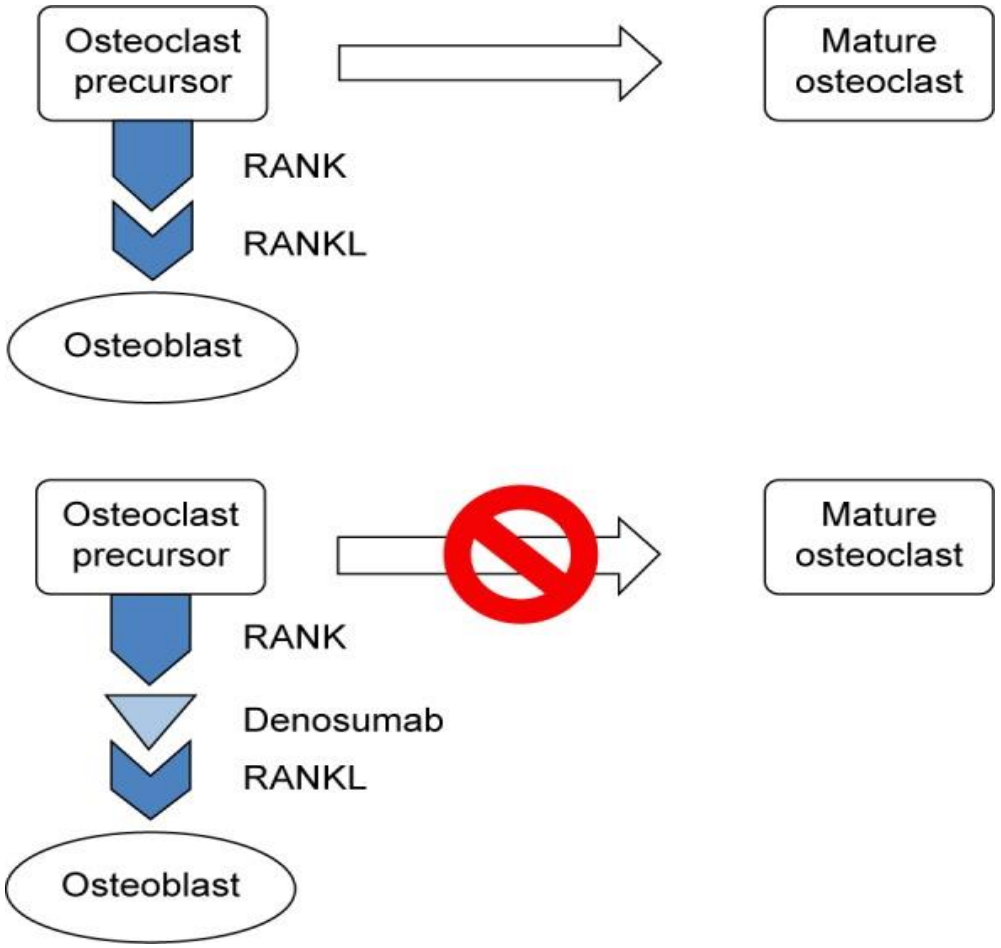
Pharmacologic therapeutic options for the management of hypercalcemia

Agent	Typical dose	Mechanism of action	Modification based on underlying renal and liver disease	Onset of action	Common side effects
Normal saline	200-300 milliners/ hour, lower rate in patients with underlying cardiac and kidney disease	Volume repletion, increased renal calcium clearance	Consider lower rate in patients with underlying renal disease	Within hours of administration	Volume overload, non-anion gap metabolic acidosis
Calcitonin	4-8 international units/kg subcutaneously or intramuscularly	Inhibition of osteoclast activity and increase in renal calcium clearance	No dosage adjustment is needed	Within 4 h of administration. Tachyphylaxis develops after 48 h	Nausea, rhinitis, hypersensitivity reactions
Bisphosphonates	Zoledronic acid 4 mg administered IV over 15 min; pamidronate 60-90 mg administered IV over 2-24 h; ibandronate 2-6 mg administered IV over 1-2 h	Inhibition of osteoclast acitivity, osteoclast apoptosis and improved osteoblast survival	Zoledronic acid: Do not use in patients with creatinine >4.5 mg/dl (consider increasing the infusion duration in patients with kidney disease); no need for hepatic adjustment Pamidronate and ibandronate: Do not use if glomerular filtration rate is <30; no need for hepatic adjustment	Within 2-4 days after administration. Do not repeat administration earlier than 1 week after the previous IV infusion	Flu-like symptoms, bone aches, nephrotic syndrome, acute kidney injury, osteonecrosis of the jaw
Denosumab	120 mg subcutaneously	Impairs osteoclast activity	No need for renal and hepatic adjustment. Consider half dose for patients with renal disease to decrease the risk of hypocalcemia	Within 2-4 days after administration. Do not repeat administration earlier than 1 week after the previous dosing	Bone pain, nausea, diarrhea, shortness of breath, osteonecrosis of the jaw and possibly increase in the risk of infections after long-term use

N Am J Med Sci. 2015 Nov; 7(11): 483–493

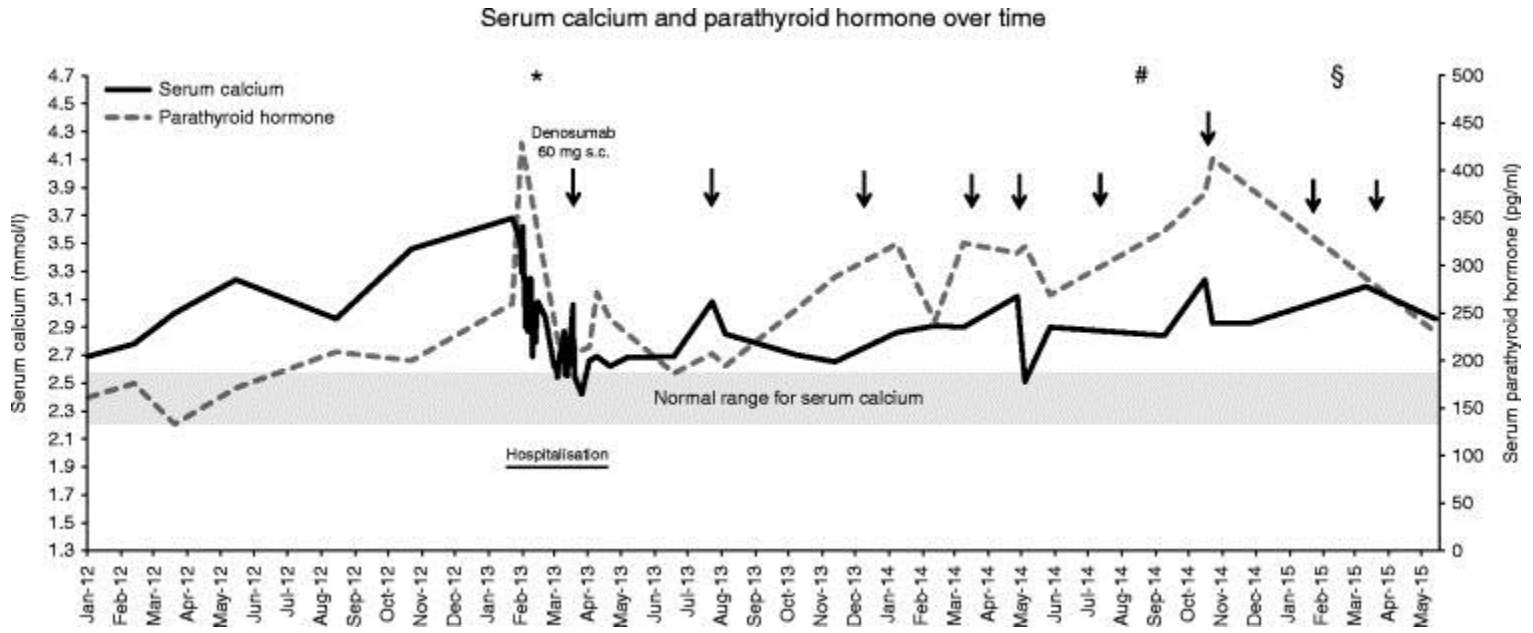
Denosumab mode of action

a monoclonal antibody against the receptor activator of nuclear factor κB ligand, and the calcimimetic cinacalcet



Ther Clin Risk Manag. 2015; 11: 1779–1788.

Denosumab rescue therapy



Endocrinol Diabetes Metab Case Rep. 2015; 2015: 150082.

Conclusions

- Hyponatremia is a common electrolyte disorder in patients with cancer and associated with a more negative prognosis
- The incidence of hyponatremia varies widely among different cancer types with a relatively high prevalence in SCLC
- Hyponatremia is often caused by SIADH in cancer patients; ectopic secretion of ADH may be important
- Hypercalcemia in lung cancer is a potential life threatening complication and is not as frequent as HN
- Persistent hypercalcemia requires parathyroid hormone pathway workup and immediate initiation of therapeutic options