73 M who presents with an intraabdominal mass

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Endorama
January 5, 2017

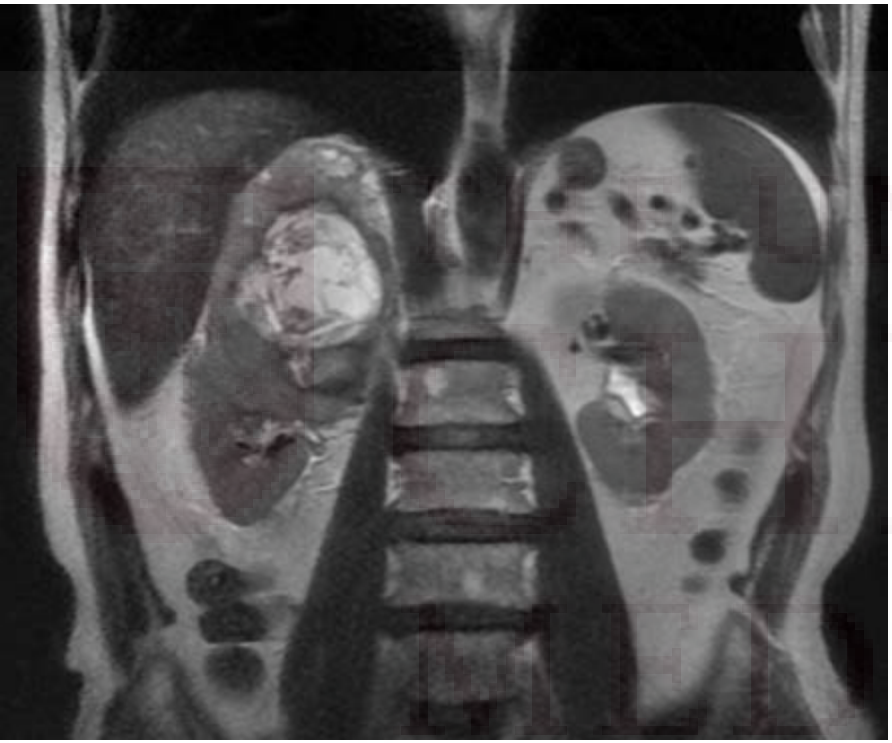
73 M who presents with a large intraabdominal mass

- Patient is admitted from the Emergency Department overnight
- Endocrine consulted the following morning for evaluation of possible pheochromocytoma

HPI:

- Discharged the previous day from a local hospital and advised to present to University of Chicago for advanced options
- Good health until 2 years ago – retired teacher, working as a missionary
- Over the past 2 years, developed recurrent bouts R flank pain, nausea, hematuria. Diagnosed with recurrent prostatitis, treated with antibiotics
- Recent weight loss, worsening control of HTN
- Late June 2016, following 4th bout of prostatis, he underwent renal US with dopplers which revealed a **"large, solid heterogeneous mass… 8.7 x 8.7 cm at the upper pole of the R kidney"**

MRI 7/11



Impression:
Large heterogeneous mass measuring 12 cm in cephalocaudal extent with significant central necrosis. Primary differential considerations would be an adrenal malignancy or a renal malignancy and based on current imaging I would favor a primary right adrenocortical carcinoma...

Review of prior admission from CareEverywhere:

- Patient was admitted to another hospital on 8/1 for a planned surgical resection of the mass
- Attempted pre-operative IR renal angiogram for renal artery ablation aborted due to SBP up to 230s.
- Subsequently underwent exploratory laparotomy however, the mass was found to be encasing the IVC and deemed unresectable, and he was discharged.
- Re-admitted the following day with nausea, vomiting, shortness of breath and diagnosed with post-operative ileus, pancreatitis and aspiration PNA which were treated with bowel rest and antibiotics.
- Labs sent on the day of surgery returned…

Perioperative Labs return:

8/1
Plasma metanephrines **0.53** (0-0.49 nmol/L)
Plasma normetanephrine **>50** (0-0.89 nmol/L)

24h Urine fractionated catecholamines
urine epinephrine **49** (1-5 ug/d)
urine norepinephrine **1906** (11-60 ug/d)
urine dopamine 217 (56-272 ug/d)

8/3
Urine metanephrine **1000** (62-207ug/d)
Urine norepinephrine (?normetanephrine) **28060** (125-510 ug/d)

- Clonidine patch initiated for poorly controlled HTN and patient was advised to present to UCMC for further evaluation

More history

- ROS: pertinent negatives include no headache, only rare palpitations, no diaphoresis
- PMH:
  - HTN – well controlled on oral regimen x 30 years
  - Pre-diabetes
  - HLD
  - Osteoarthritis
- PSH: None prior to laparotomy
- Soc: Retired school teacher (high school math), international missionary work
- FH: Father alive in 90s, Mother dec. 81 yo from CAD. No FH of endocrinopathies (including no MEN2, NF1, VHL) or other malignancies
- PTA meds: Lisinopril 20, HCTZ 25 mg prn, simvastatin and lorazepam prn insomnia, vitamin D3, CoQ, garlic, flaxseed, mg, MVI, red yeast rice extract, fiber

Physical Exam

- Vitals: BP **181/78** Pulse 82 Temp 36.3 °C (97.3 °F), RR 17, SpO2 94% BMI 25.09 kg/m2
- General: No apparent distress. Appears comfortable
- HEENT: NC/AT. No pharyngeal erythema. PERRL, EOMI.
- Neck: No neck tenderness. No thyromegaly or thyroid nodules appreciated.
- Cardiovascular: normal rate, regular rhythm. Peripheral pulses 2+ symmetric, no edema.
- Pulmonary/Chest: clear bilaterally, no increased WOB, rales or wheezes.
- Gastrointestinal: soft, non-tender, non-distended abdomen. No rebound or guarding. **Large Y-shaped surgical wound with staples c/d/i.**
- Musculoskeletal: No deformities, no joint swelling. Normal tone.
- Neurological: AOx3, no focal deficits.
- Lymph: No cervical, supraclavicular LAD.
- Skin: no rash. No apparent bald spots.
- Psychiatric: normal mood, thought content, appropriate.

Labs from admission

8/12

138	102	14	96
4.0	22	0.8	

Ca 9.0

Mg 1.6

Ph 3.0

6.6	3.0
1.3	**0.7c/**0.6u
48	**69**
187	

15.3	**1.2**
26.9	

Lipase **458**

	10.1	
12.3		557
	31.0	

8/13

Plasma metanephrines **pending**

24h Urine free cortisol **pending**

24h Urine metanephrines **pending**

Renin **pending**

Aldosterone **pending**

Strategy for blood pressure management?

- Titrate off the clonidine
  - Central a2 agonist→reduces sympathetic outflow→reduced peripheral resistance/tone
  - Abrupt withdrawal can lead to rebound HTN due to rapid return of (non-tumor) catecholamine release
  - Half-life ~ 20 hours
    - Day 1: 0.3 mg q 24 hours since 8/10
    - Day 2-3: 0.1 mg Q12, initiate alpha blockade
    - Day 4: Discontinue

No literature on use of clonidine for HTN in pheo…

Clonidine suppression test

- Used to aid in interpretation of mildly elevated normetanephrine
- Based on the principle that clonidine inhibits neuronal but ***not*** tumor-derived catecholamines
- Test:
  - Stop all sympatholytic drugs
  - Supine 20'
  - Administer clonidine 300 ug/70kg
  - Assess normetanephrine levels at 3 hours
    - Persistently elevated normetanephrine with <40% suppression is suggestive of a pheo

Drug	Mechanism	Anti-HTN action	Dosing	Notes/Theoretical risks	Cost
Phenoxy-benzamine	Irreversible inhibition of α1 and α2 receptor	24h	BID or TID	• Dose multiple times per day due to R turnover is high • Alpha 2 blockade effects: postural Hypotension and sinus congestion • Post-operative hypotension due to irreversible block	Dibenzyline 10 mg (100): $28797.60 Phenoxy-benzamine HCl 10 mg (100): $12944.52 ($94 for 50 in Canada)
Doxazosin	Competitive inhibition of α1 receptor	>24h	QD – SR	• Can be less effective if large catecholamine release (e.g. large tumor)	$130-140
Terazosin	Competitive inhibition of α1 receptor	24h	QD or BID		$160
Prazosin	Competitive inhibition of α1 receptor	10-24h	BID or TID		$95-230
Phentolamine	*Competitive α1 and α2*	*10-30 min*	*IV*		

Pricing data from Uptodate.com

Is there data for non-selective vs. selectivea1-blockade?

Preoperative selective vs. non-selective α-blockade

- **Retrospective review of consecutive patients undergoing laparoscopic pheochromocytoma resection at 2 centers with diverse protocols**
  - 50 Mayo Clinic patients (non-selective α1blockade 98%)
  - 37 Cleveland Clinic (selectve α1-blockade 65%)
- **Mayo Clinic**
  - phenoxybenzamine, 1-4 weeks before surgery→orthostasis
  - BB (propranolol) added 2-3 days before surgery for HR >80
  - CCB (nicardipine) if needed for normotension
  - For large tumors: metyrosine added 2-3 days before surgery
  - Patients with significant orthostasis (drop in SBP >20 mmHg) admitted for hydration
- **Cleveland Clinic**
  - CCB titrated to target BP
  - Selective α1-blocker added and uptitrated by 2 mg Q3 days to max dose 10 mg
  - BB added for tachycardia or for concomitant CAD
  - Occasionally asymptomatic patients received no preoperative treatment

Weingarten et al. Urology 76:2, 2010, 508.e6–508.e11

Patient demographics

Table 1. Preoperative demographics, comorbidities, and blood pressure

Characteristic	Mayo Clinic (n = 50)	Cleveland Clinic (n = 37)	*P* Value
Sex			.054
Male	19 (38.0)	22 (59.5%)	
Female	31 (62.0)	15 (40.5%)	
Age (y)	53 ± 16	52 ± 13	.884
Body mass index (kg/m^2)	26.5 ± 4.6	29.8 ± 7.1	.009
American Society of Anesthesiologists physical status			.602
II	21 (42.0)	13 (35.1)	
III	28 (56.0)	22 (59.5)	
IV	1 (2.0)	2 (5.4)	
Preoperative comorbidities			
Diabetes mellitus	5 (10.0)	9 (24.3)	.085
Cardiomyopathy (ejection fraction <40%)	0 (0.0)	2 (5.4)	.178
Coronary artery disease	6 (12.0)	4 (11)	1.000
Previous myocardial infarction	3 (6.0)	2 (5.4)	1.000
Previous stroke	4 (8.0)	3 (8.1)	1.000
Chronic obstructive pulmonary disease	1 (2.0)	2 (5.4)	.572
Asthma	3 (6.0)	1 (2.7)	.634
Chronic renal insufficiency*	0 (0.0)	3 (8.1)	.073
Tumor largest dimension (cm)	4.0 ± 1.8	4.4 ± 2.2	
Preoperative BP (mm Hg)			
Systolic BP	139 ± 22	139 ± 22	.950
Mean BP	99 ± 18	93 ± 19	.402
Diastolic BP	83 ± 12	73 ± 17	.058

Data presented as numbers, with percentages in parentheses, or mean ± standard deviation.
* Defined as preoperative creatinine ≥1.8 mg/dL.

Weingarten et al. Urology 76:2, 2010, 508.e6–508.e11

More pressor use at Mayo, less time under anesthesia

Table 3. Intraoperative characteristics; anesthesia duration, invasive monitoring, and intraoperative use of vasoactive drugs

Characteristic	Mayo Clinic (n = 50)	Cleveland Clinic (n = 37)	*P* Value
Anesthetic duration (min)	201 ± 43	306 ± 185	<.001
Monitors			
Arterial line	50 (100.0)	37 (100.0)	.425
Central line	15 (30.0)	22 (59.5)	.008
Pulmonary artery catheter	4 (8.0)	9 (24.3)	.065
Vasoactive drugs			
Nitroprusside	31 (62.0)	25 (67.6)	.592
Nitroglycerin	1 (2.0)	17 (46.0)	<.001
β-Blocker	26 (52.0)	10 (27.0)	.027
α/β-Blocker (labetalol)	12 (24.0)	15 (40.5)	.109
Calcium channel blocker	0 (0.0)	3 (8.1)	.073
Phenylephrine	28 (56.0)	10 (27.0)	.009
Dopamine	1 (2.0)	0 (0.0)	1.00
Epinephrine	2 (4.0)	1 (2.7)	1.00
Norepinephrine	1 (2.0)	1 (2.7)	1.00

Data presented as mean ± standard deviation or numbers, with percentages in parentheses.

Weingarten et al. Urology 76:2, 2010, 508.e6–508.e11

BP lower at Mayo, more fluid given at Cleveland Clinic

Table 4. Intraoperative hemodynamics and administered fluids

Intraoperative Hemodynamics	Mayo Clinic (n = 50)	Cleveland Clinic (n = 37)	*P* Value
Greatest intraoperative BP (mm Hg)			
Systolic BP	187 ± 30	209 ± 44	.011
Mean BP	136 ± 20	151 ± 30	.004
Diastolic BP	109 ± 18	114 ± 26	.294
Systolic BP ≥30% baseline (min)	2 (0–11)	5 (0–22)	.119
Systolic BP ≥200 mm Hg (min)	0 (0–2)	0 (0–7)	.071
Lowest intraoperative BP (mm Hg)			
Systolic BP	73 ± 14	78 ± 15	.159
Mean BP	55 ± 11	56 ± 10	.870
Diastolic BP	46 ± 9	43 ± 9	.191
Systolic BP ≤ 30% baseline, min	28 (6–62)	13 (3–49)	.114
Systolic BP ≤30% baseline (% anesthesia time)	15.7 (3.3–24.9)	5.1 (0.9–16.0)	.026
Greatest heart rate (beats/min)	104 ± 28	105 ± 18	.765
Interval heart rate ≥110 beats/min (min)	0 (0–1)	0 (0–1)	.719
Lowest heart rate (beats/min)	47 ± 10	51 ± 10	.120
Interval heart rate ≤50 beats/min (min)	2 (0–11)	0 (0–7)	.379
Estimated blood loss (mL)	75 (25–150)	100 (82–250)	.010
Intraoperative crystalloid (L)	3.0 (2.0–3.1)	5.0 (3.4–6.4)	<.001
Intraoperative colloid (L)	0 (0–0)	1.00 (0.5–1.0)	<.001

BP = blood pressure.
Data presented as mean ± standard deviation or median, with interquartile ranges in parentheses.

Weingarten et al. Urology 76:2, 2010, 508.e6–508.e11

Selective vs. non-selectivea-blockade – no difference

- Cleveland Clinic patients:
  - Had a greater intraoperative maximal systolic blood pressure: 209 ± 44 mm Hg versus 187 ± 30 mm Hg, P = .011
  - Received a greater amount of IV fluid
    - median 5000 crystalloid/1000 colloid vs. 2977 crystalloid/0 colloid
- Mayo Clinic patients received more phenylephrine (56.0% versus 27.0%, P = .009).
- **No difference** in the postoperative surgical outcomes, length of hospital stay
- **Limitations:** Retrospective review with small numbers, significant inter-institution and patient variability

Weingarten et al. Urology 76:2, 2010, 508.e6–508.e11

Selective vs Non-selective α-blockade

Retrospective review of unilateral laparoscopic adrenalectomy for pheochromocytomas from 2001 to 2015 at a single institution

- N=52, ***similar demographic and tumor characteristics***
  - Selective α-blockade 18 (35%)
    - Terazosin, prazosin, doxazosin
  - Non-selective α-blockade in 34 (65%)
- Outcomes:
  - Intraoperative SBP <80, SBP >200, *both* SBP <80 and >200, HR>120, vasopressor or vasodilator use
  - Post-operative vasopressor in PACU *or* ICU admission
  - Length of admission, complications

Randle et al. Ann Surg Oncol (2017) 24:244–250

Patient Characteristics

TABLE 1 Patient and tumor characteristics

Variable	Selective α-blockade ($n = 18$)	Non-selective α-blockade ($n = 34$)	p value
Age, years [median (IQR)]	55 (26)	53 (23.5)	0.77
Sex [n (%)]			0.24
Male	5 (27.8)	15 (44.1)	
Female	13 (72.2)	19 (55.9)	
Tobacco use [n (%)]	6 (33.3)	10 (29.4)	0.77
Diabetes mellitus [n (%)]	3 (16.7)	7 (20.6)	0.73
Charlson comorbidity index [median (IQR)]	1.5 (3.0)	2.0 (1.5)	0.89
Body mass index [median (IQR)]	26.5 (11.3)	28.3 (7.6)	0.86
Familial [n (%)]	2 (11.1)	6 (17.6)	0.53
Tumor laterality [n (%)]			0.82
Right	8 (44.4)	14 (41.2)	
Left	10 (55.6)	20 (58.8)	
Tumor size, cm [median (IQR)]	3.3 (2.7)	3.5 (2.2)	0.60
Duration of blockade, weeks [median (IQR)]	5 (2)	6 (4)	0.05
Preoperative SBP, mmHg [median (IQR)]	128 (23)	128 (47.5)	0.21
Preoperative pulse [median (IQR)]	78 (9)	80 (15)	0.59
Incidental [n (%)]	9 (50.0)	2 (5.9)	<0.001
Elevated metanephrines [n (%)]	15 (83.3)	28 (82.4)	1.0
Elevated normetanephrines [n (%)]	8 (44.4)	7 (20.6)	0.11
β-Blocker [n (%)]	6 (33.3)	17 (50.0)	0.25
Calcium channel blocker [n (%)]	2 (11.8)	3 (9.7)	0.82
Metyrosine [n (%)]	0 (0)	1 (2.9)	0.35

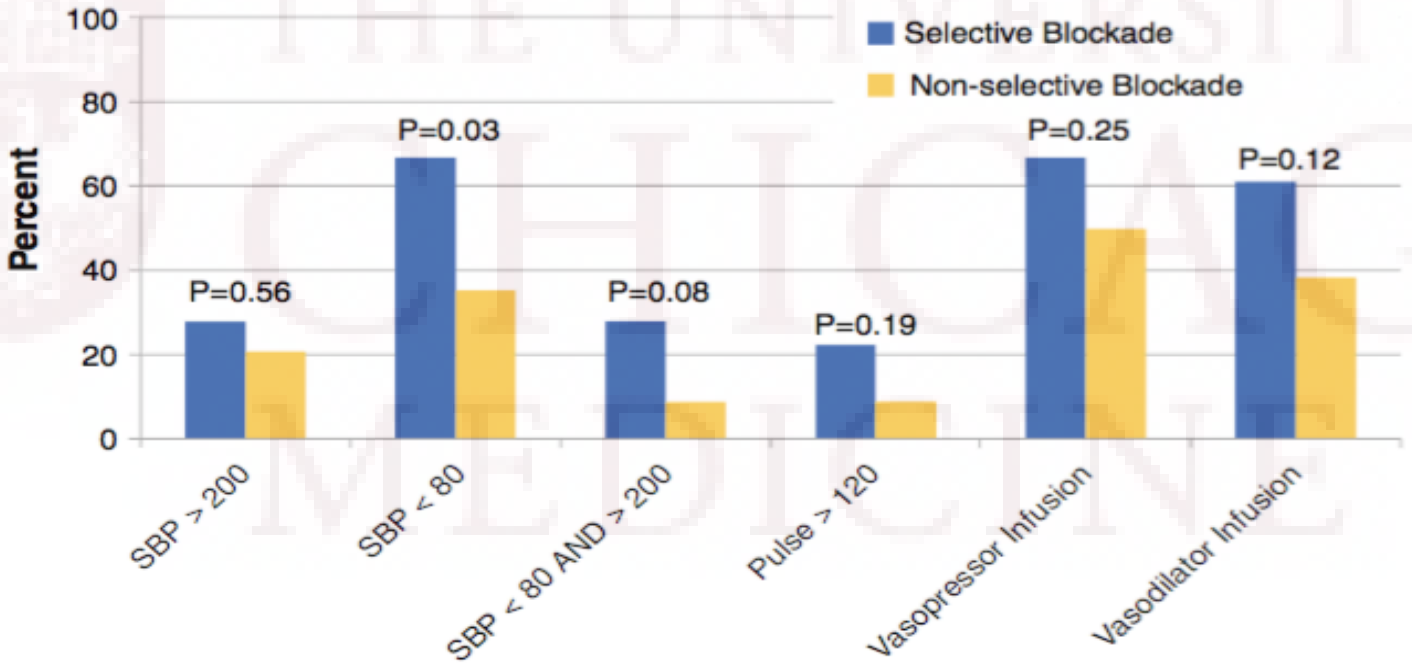
Randle et al. Ann Surg Oncol (2017) 24:244–250

TABLE 2 Intraoperative hemodynamic and support variables

Variable	Selective α-blockade ($n = 18$)	Non-selective α-blockade ($n = 34$)	p value
Central venous access, $n = 51$ [n (%)]	12 (66.7)	19 (55.9)	0.45
Initial SBP, mmHg [median (IQR)]	136.5 (35.5)	130 (23.5)	0.36
Highest SBP, mmHg [median (IQR)]	190 (28.0)	175 (35.5)	0.07
Lowest SBP, mmHg [median (IQR)]	76.5 (11.5)	80 (17.5)	0.07
SBP range (highest–lowest SBP), mmHg [median (IQR)]	114.5 (41)	107 (44.5)	0.03
SBP > 200 mmHg [n (%)]	5 (27.8)	7 (20.6)	0.56
No. of times SBP > 200 mmHg [median (IQR)]	0 (1)	0 (0)	0.54
	Mean 0.75	Mean 0.33	
SBP < 80 mmHg [n (%)]	12 (66.7)	12 (35.3)	0.03
No. of times SBP < 80 mmHg [median (IQR)]	1 (2.0)	0 (2.5)	0.12
	Mean 1.6	Mean 1.3	
Cases with SBP > 200 and < 80 mmHg [n (%)]	5 (27.8)	3 (8.8)	0.08
Pulse > 120 [n (%)]	4 (22.2)	3 (8.8)	0.19
No. of times pulse > 120 [median (IQR)]	0 (0)	0 (0)	0.23
	Mean 0.31	Mean 0.57	
Vasopressor infusion [n (%)]	12 (66.7)	17 (50.0)	0.25
Vasodilator infusion [n (%)]	11 (61.1)	13 (38.2)	0.12
Volume crystalloid, mL [median (IQR)]	2250 (1150)	2750 (1750)	0.06
Volume colloid, mL [median (IQR)]	0 (0)	0 (13)	0.02
	Mean 47	Mean 108	
Estimated blood loss, mL [median (IQR)]	40 (94)	100 (75)	0.08
	Mean 83	Mean 136	
Blood transfusion [n (%)]	0 (0)	2 (5.9)	0.19
Urine output, mL [median (IQR)]	313 (188)	200 (245)	0.14

Randle et al. Ann Surg Oncol (2017) 24:244–250

Intraoperative hemodynamics: **trend** toward favoring non-selective blockade



	Selective Blockade	Non-Selective Blockade	*P*
No. of Markers of Intra-operative Hemodynamic Instability, median (range)	**2.5 (0 - 6)**	**2 (0 - 5)**	**0.09**

Selective vs Non-selective α-blockade

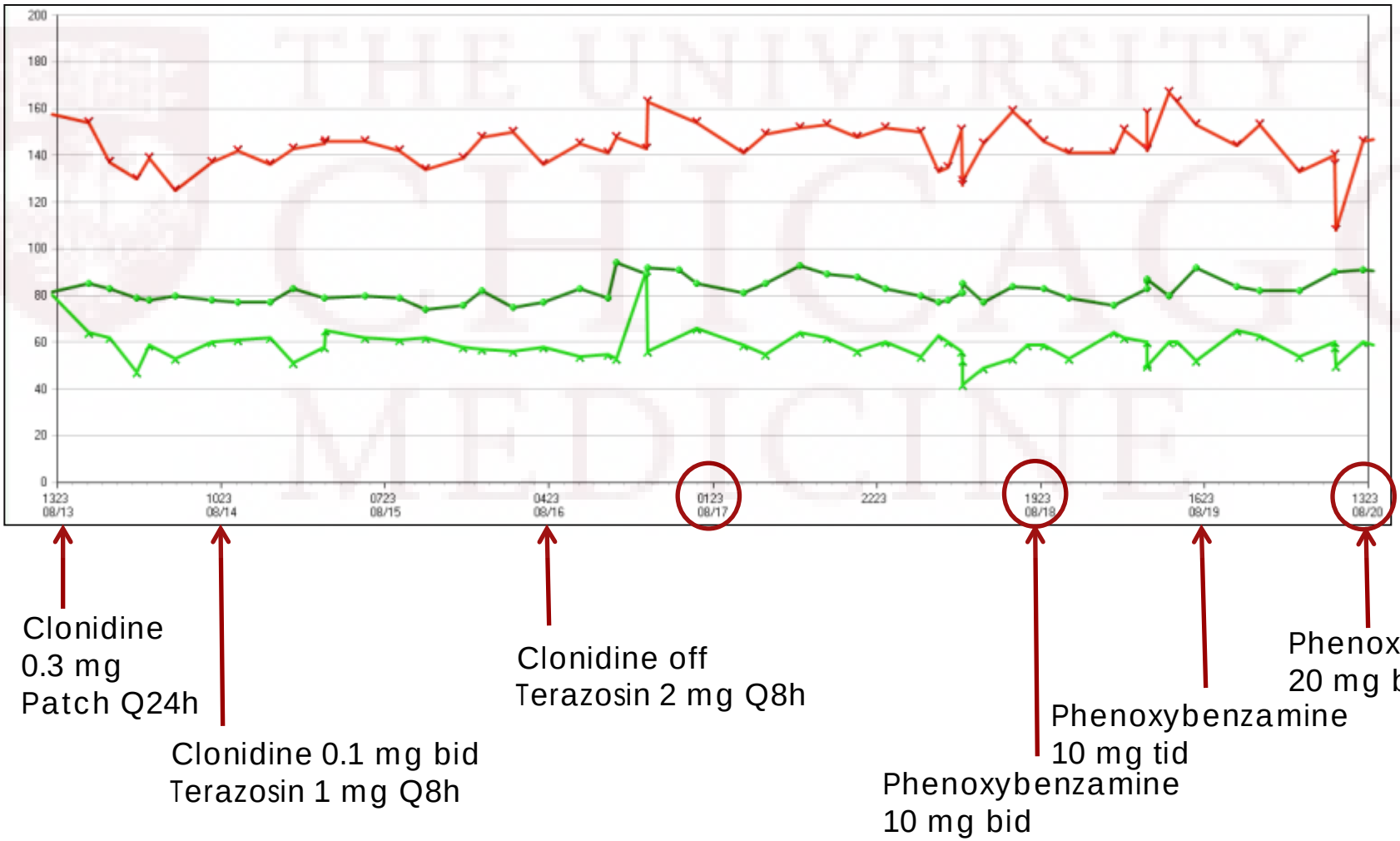
- **Ultimately no significant difference in:**
  - Intraoperative hemodynamics, operative time, blood loss
  - Hospital stay
  - Complication rates
- **Patients who received selective were blockade more likely to have transient intraoperative hypotension and require post-operative support than those who received non-selective blockade.**
- **Limitations:** Retrospective, small sample size. However, the advantages are that patient demographics were more similar in the two groups and the study was performed at a single institution

Randle et al. Ann Surg Oncol (2017) 24:244–250

Patient's vitals:

Advised phenoxybenzamine, however cost prohibitive and no plan for surgery for several weeks. Doxazosin on inpatient formulary but restricted to patients on tube feedings. Terazosin 1 mg Q8 8/13

Patient's vitals:



Does duration of α-blockade matter?

- No difference in intraoperative BP control in patients who were medicated for 1 week compared with those who were medicated for >1 week.

Orchard et al. Surgery. 1993;114:1153-1159.

Labs from admission return:

8/17/2016 2:29 PM - Lab Interface

Component Results

Component	Value	Ref Range & Units	Status
Normetanephrine	**38 (H)**	<0.90 nmol/L	Final
Metanephrine	**1.8 (H)**	<0.50 nmol/L	Final

Comment:

Test(s) performed at: Mayo Clinic Dept of Med and Pathology, 3050 Superior Drive NW, Rochester, MN 55901

24h Urine metanephrines

U Metanephrine	**2537**
U Normetanephrine	**28288**
U Total metanephrine	**308025**

Renin 3.1 (2.3-10.8)
Aldosterone <4.0 (≤ 21 ng/dL)

24h **Urine free cortisol 80** (3.5-45)

What would you like to do?

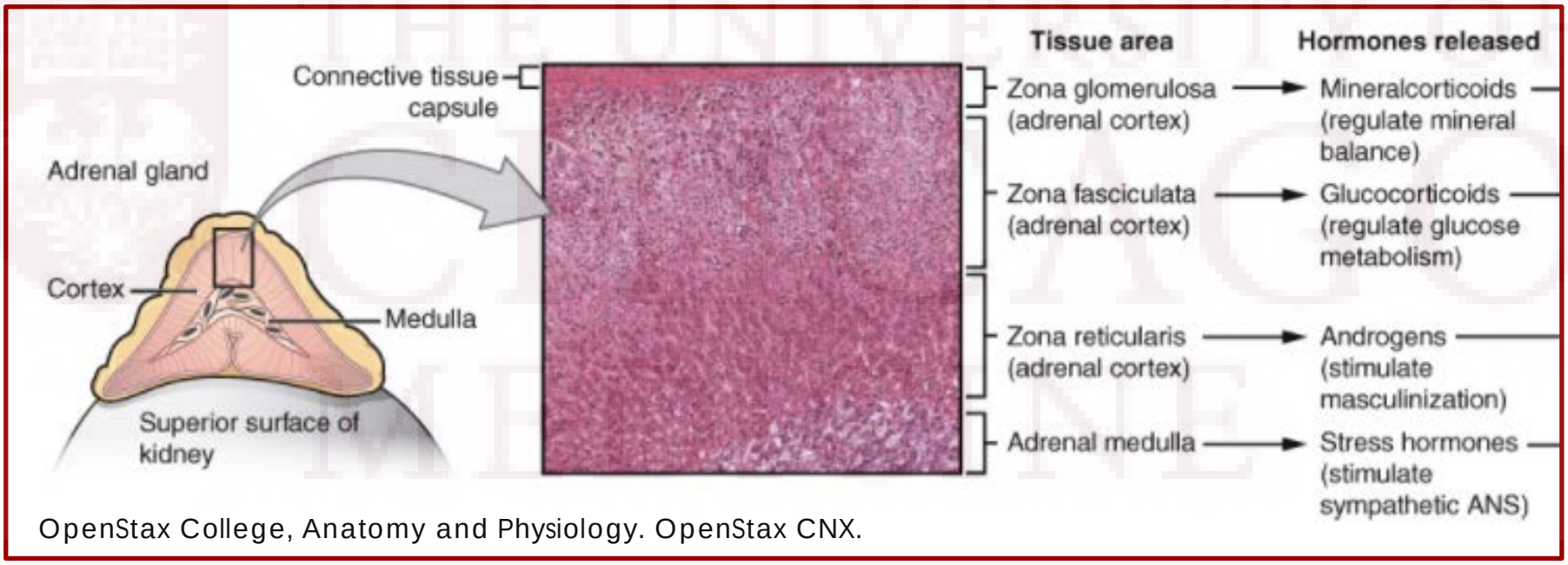
- 9 AM Cortisol 21.6, ACTH 55.4
- 1 mg overnight dex suppression test: 8 AM Cortisol 4.2, ACTH 10.3

How do you interpret this result?

Significant suppression of both ACTH and cortisol suggests against ectopic ACTH.

Consider perioperative glucocorticoids if indicated as chornic excess ACTH and cortisol may suppress endogenous HPA axis.

How often do pheochromocytomas co-secrete other hormones?



OpenStax College, Anatomy and Physiology. OpenStax CNX.

- Mixed lesions are **rare**, particularly mixed corticomedullary tumors (MCMTs)

Michalopoulos et al. Surg Today (2013) 43:1232–1239
Kimura et al. J Clin Endocrinol Metab 94: 746 –747, 2009

Patient update

- Patient discharged on phenoxybenzamine 20 bid
- Advised to monitor orthostatic vitals and maintain a relatively high sodium diet (5000 mg / day)
- Metoprolol 50 XL added for HR control at outpatient follow up visit
- Admission for surgical resection about 6 weeks after discharge

Patient update continued…

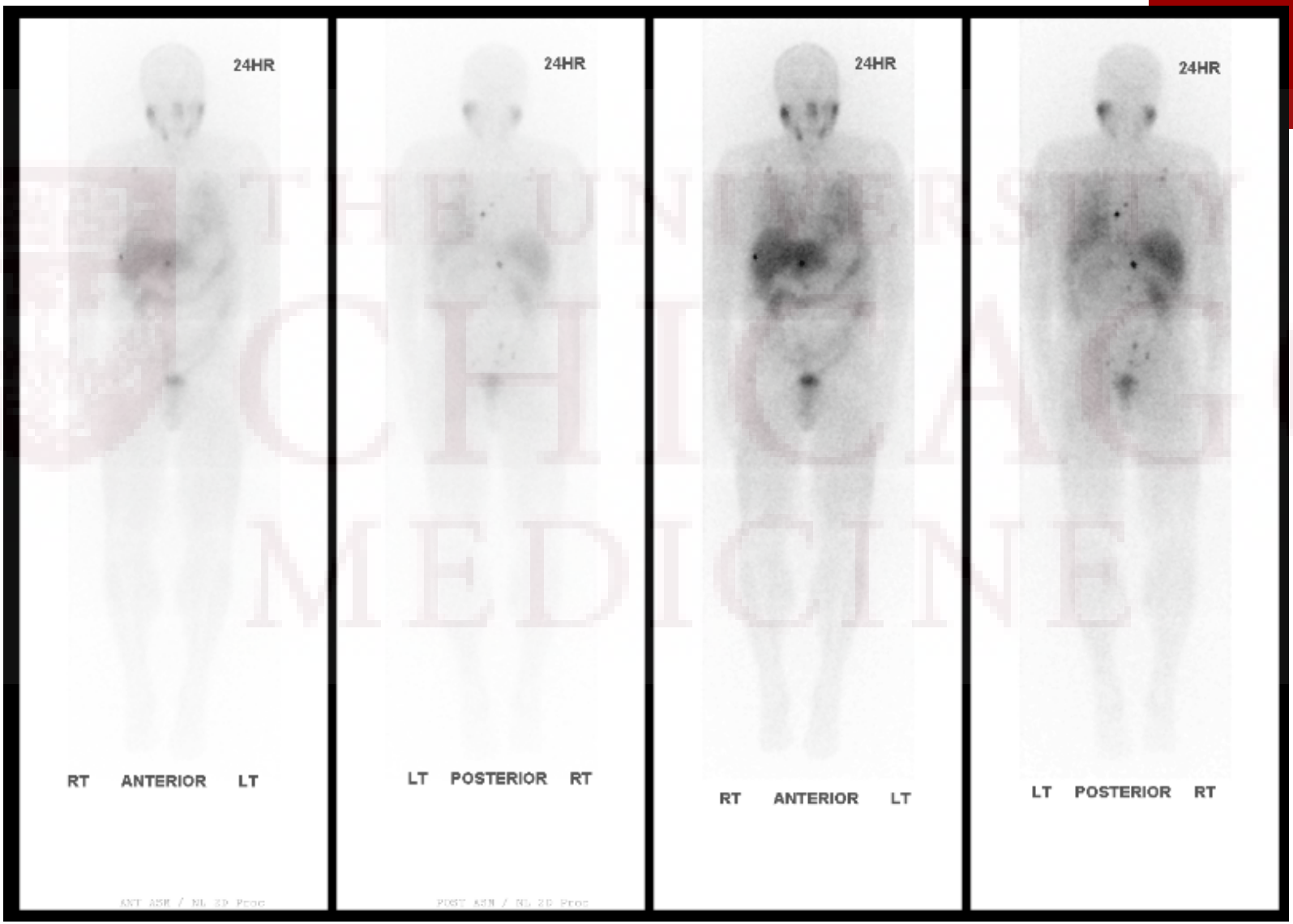
- Complicated surgery
  - R nephrectomy, cholecystectomy, partial hepatectomy, with IVC patch reconstruction and diaphragm repeair
  - 11 L blood loss requiring activation of the Massive Transfusion Protocol with 35 units PRBC and other product
  - Post-operatively did well. Transient hypertension treated with PRN hydralazine and labetalol
- Referred for follow up in Endocrine clinic and for genetic testing of SDHB given metastatic disease

Pathology

FINAL PATHOLOGIC DIAGNOSIS
A. Gallbladder; cholecystectomy:
- Cholelithiasis.
B. Retroperitoneal tumor; excision:
- Malignant pheochromocytoma (5.6 cm) with vascular invasion, involving fibroadipose tissue and extending to the blue inked surface (the vena cava side).
- Metastatic malignant pheochromocytoma in one of two lymph nodes (1/2). (See comment).
C. Retroperitoneal tumor; excision:
- Malignant pheochromocytoma (11.0 cm) with necrosis and vascular invasion, involving renal cortex, perinephric adipose tissue and the wall of the inferior vena cava.
- Tumor extends to the black inked exterior surface of the specimen.
- Liver with necrosis, chronic inflammation, foreign body giant cell reaction and macrovesicular steatosis, no tumor present.
D. Retroperitoneal tumor; excision:
- Malignant pheochromocytoma extending to the blue inked caval side.
E. Liver; biopsy:
- Liver with foreign body giant cell reaction and mild macrovesicular steatosis,

no tumor present. (See comment).

11/30 MIBG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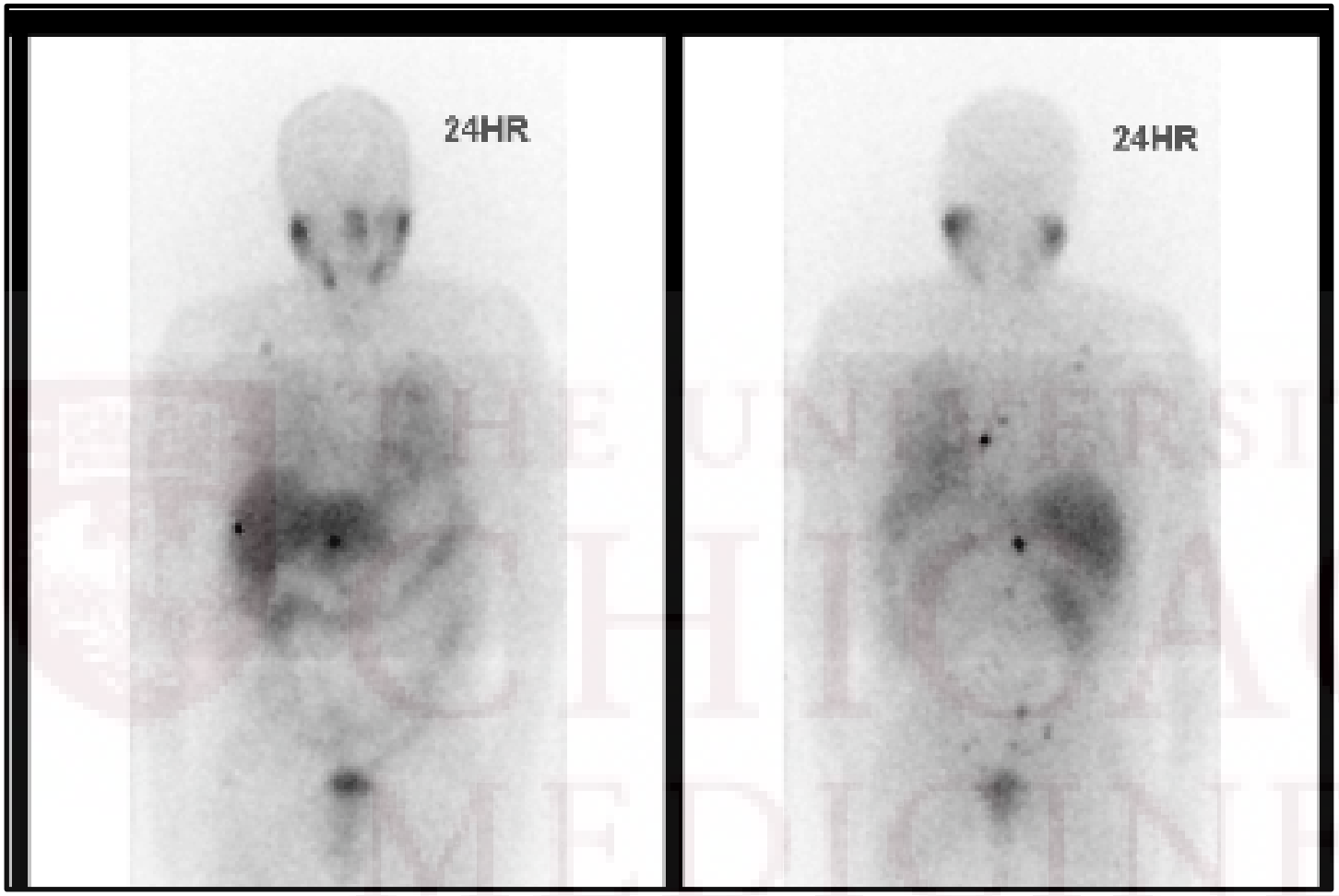

Impression: Metastatic disease to the bones and retroperitoneal lymph nodes.

1. Osseous metastatic disease involving multiple bones
2. Residual metabolically active soft tissue anteromedial to the surgical site for inferior vena caval resection.
3. Metabolically active small aortocaval retroperitoneal lymph nodes.

Management of malignant metastatic pheochromocytoma

- Defined by metastases including nodes and distant sites (WHO)
- Prognosis is variable
- 5 year survival ranges from 34-60% (mean 50%)
- Brain, liver, lung metastases tend to have poorer prognoses than isolated bone mets
- Monitor for and treat symptoms of catecholamine excess

Treatment of malignant metastatic pheochromocytoma

- No curative treatment
- Resection of primary tumor and metastases if possible
- Radiation therapy – palliative
  - Requires close monitoring for RT-induced massive catecholamine release
  - ^{131}I MIBG – ineffective if given after EBRT
  - EBRT
- Embolization
- Ablation (RFA, EtOH, cryo)
- Chemotherapy
  - Cytotoxic (CVD: cyclophosphamide, vincristine and dacarbazine)
  - TKI (Sunitinib – VEGF/PDGF inhibitor)

Patient course

- Current BP regimen:
  - Amlodipine 5 mg daily
  - Metoprolol succinate 25 mg daily
- Pending evaluation in hematology/oncology clinic tomorrow
- Possible referral to University of Michigan for palliative radiation therapy

References

- Lenders et al. PPGL Guidelines. J Clin Endocrinol Metab, June 2014, 99(6):1915–1942
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