53 yo man with metastatic adrenal cortical carcinoma

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Endorama

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History of Present Illness

- 53 yo man with metastatic adrenal cortical carcinoma had presented to GU Medical Oncology Clinic for cycle 12 of temsirolimus.
  - Found to have worsening cough, scant hemoptysis, and pleuritic chest pain.
  - Admitted from clinic.
  - Endocrine is consulted for steroid management.

History of Past Illness

- Presented in Sept. 2007 with R flank pain.
- Found to have 11 cm R adrenal mass on CT scan.
- MRI revealed large heterogeneous mass – 10.0x10.3x11.0 cm.
  - T1: hyperintense central areas c/w hemorrhage.
  - T2: hyperintense central hemorrhagic areas, hypointense peripheral and solid nodular areas.

Imaging Phenotype

Feature	AC adenoma	AC carcinoma	Pheo	Metastasis
Size	usu. ≤3 cm	usu. >4 cm	usu. >3cm	freq. <3 cm
Shape	Round, smooth margins	Irregular, unclear margins	Round, usu. clear margins	Oval to irreg, unclear margins
Texture	Homo.	Hetero	Hetero	Hetero
CT w/o	<10 HU	usu. >25 HU	usu. >25	usu. >25
CT w/contrast	not vascular	usu. vascular	usu. vascular	usu. vascular
CT washout	>50%	<50%	<50%	<50%
MRI (T2, liver)	Isointense	Hyperintense	Markedly hyperintense	Hyperintense
Presence of necrosis, hemorrhage	Rare	Common	Hemorrhage, cysts	Occ. hemorrhage, cysts

Surgical Course

- Underwent en bloc R adrenalectomy and nephrectomy.
- Had partial IVC resection due to difficulty with dissection.
  - On visual inspection, no evidence of tumor invasion into the vena cava.

Pathology Report

- Adrenal cortical carcinoma, 13.6 x 11.5 x 7.5 cm, 670 grams
  - Encapsulated
  - No vascular invasion into pericapsular fat
  - Well-demarcated from adjacent kidney
  - Extensive areas of necrosis
  - Tumors cells show mostly eosinophilic cytoplasm in diffuse sheets
  - Mitotic activity from 3 to 5 per 10HPF
- Kidney with chronic interstitial inflammation
- IVC margin: portions of smooth muscle, no tumor seen

Course

- Nov. 2007-Nov. 2008: adjuvant treatment with mitotane
- March 2009: found to have recurrence with multiple pulmonary metastases
- Aug. 2009: restarted mitotane (palliative intent)
- Oct. 2011: developed hemoptysis, underwent bronchoscopy with endobronchial tumor ablation/debulking
- Dec. 2011-May 2012: Underwent 6 cycles of carboplatin, doxorubicin, and etoposide with mitotane
- May 2012: CT scan reveals mild progression of pulmonary metastases
- June 2012: Transferred care here. Mitotane discontinued and started on oral sirolimus. Did not tolerate due to fatigue, lightheadedness, flushing, and nausea.
- Aug 2012-Dec. 2012: Weekly IV temsirolimus

Medical History

- Past Medical History:
  - Coronary artery disease, s/p PCI
  - Diabetes mellitus type 2
  - Hypertension
  - Dyslipidemia

Medications:

- Hydrocortisone 10 mg BID
- Fludrocortisone 0.1 mg daily
- Januvia 100 mg daily
- Metformin 500 mg BID
- Metoprolol 50 mg BID
- Simvastatin 20 mg daily
- Morphine 15 mg prn
- Multivitamin

Medical History

- Social History:
  - Originally from Morocco
  - Previously worked as truck driver, currently on disability
  - Lives with his 2 children, ages 6 and 10
  - Previously smoked 1ppd x 20 years, quit in 3/2012
  - No ETOH use.
- Family History:
  - No cancer
  - No diabetes mellitus
- ROS:
  - + SOB, cough, hemoptysis, pleuritic chest pain
  - No fevers, chills
  - No lightheadedness
  - No nausea, vomiting, anorexia

Physical Exam

- BP 119/62 | Pulse 65 | Temp(Src) 35.5 °C (95.9 °F) (Tympanic) | Resp 20 | Ht 167.6 cm (5' 6") | Wt 66.225 kg (146 lb) | BMI 23.56 kg/m2 | SpO2 96%
- Constitutional: Patient appears thin, in no acute distress.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. Systolic murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. Decreased breath sounds at right lung base.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended.
- Musculoskeletal/extremities: No peripheral edema.
- Neurological: Alert and oriented to person, place, and date.
- Skin: Skin is warm and dry. No acanthosis nigrans noted.
- Psychiatric: Depressed affect.

Labs

138	102	10	112
3.7	24	0.7	

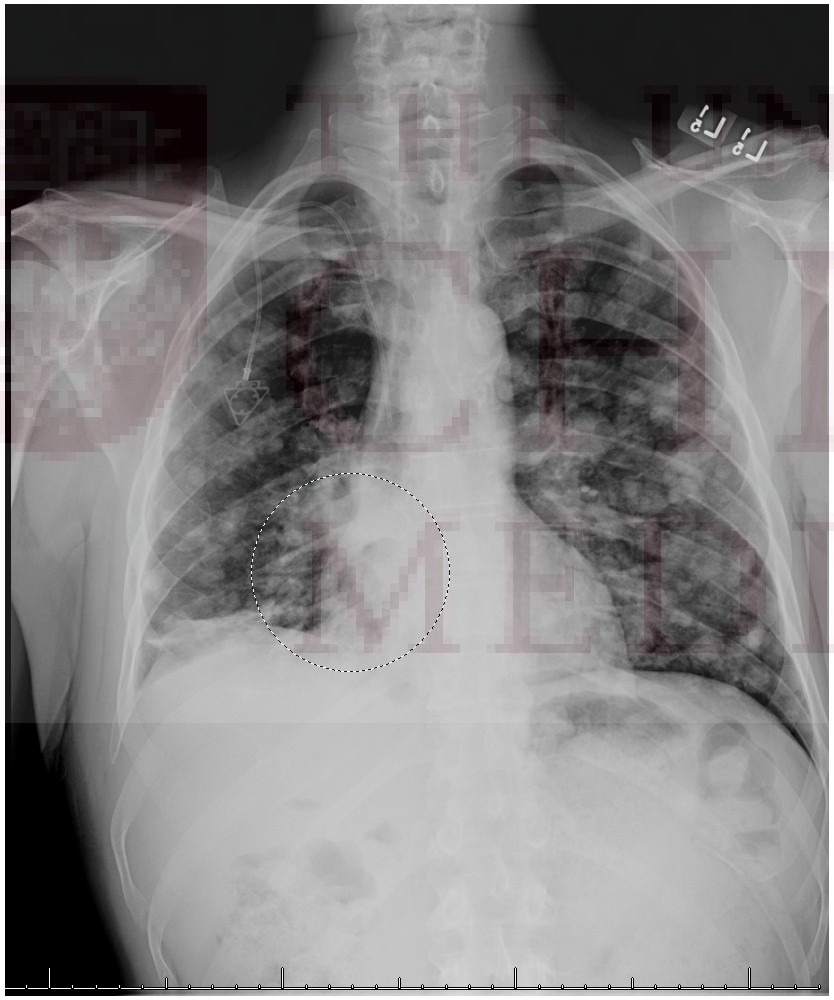
Ca 9.1

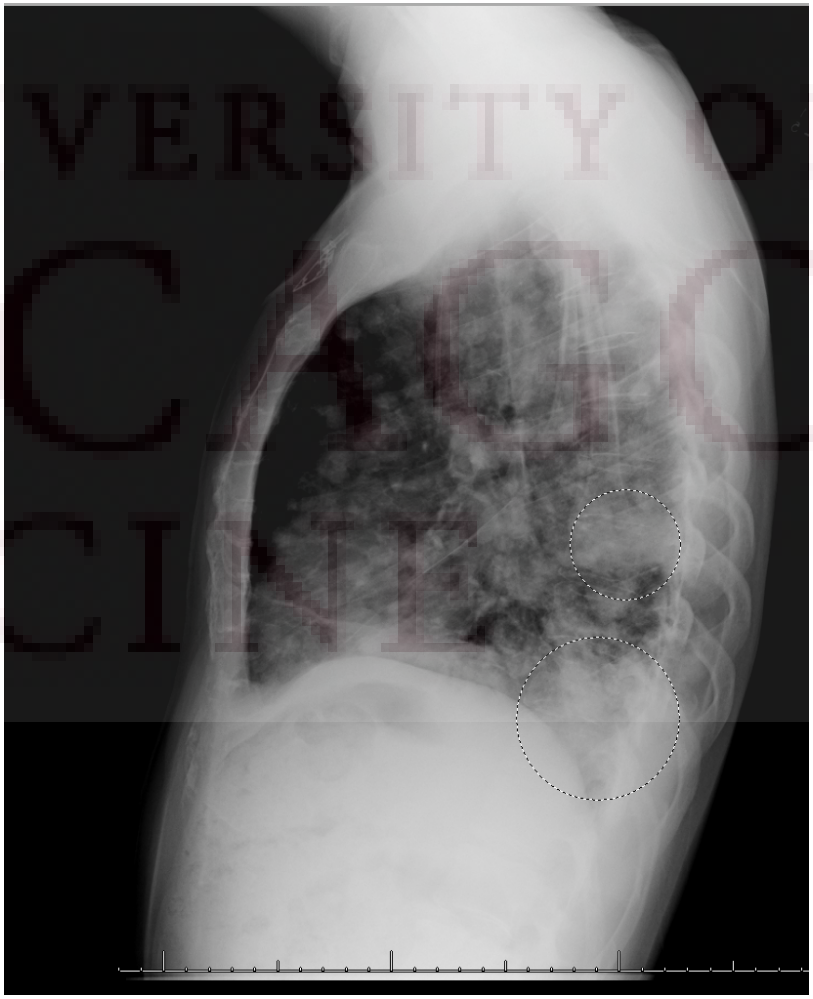
	10.8	
7.7		297
	33.4	

Alb 3.7, TB 0.2, alk phos 65, AST 26, ALT 34

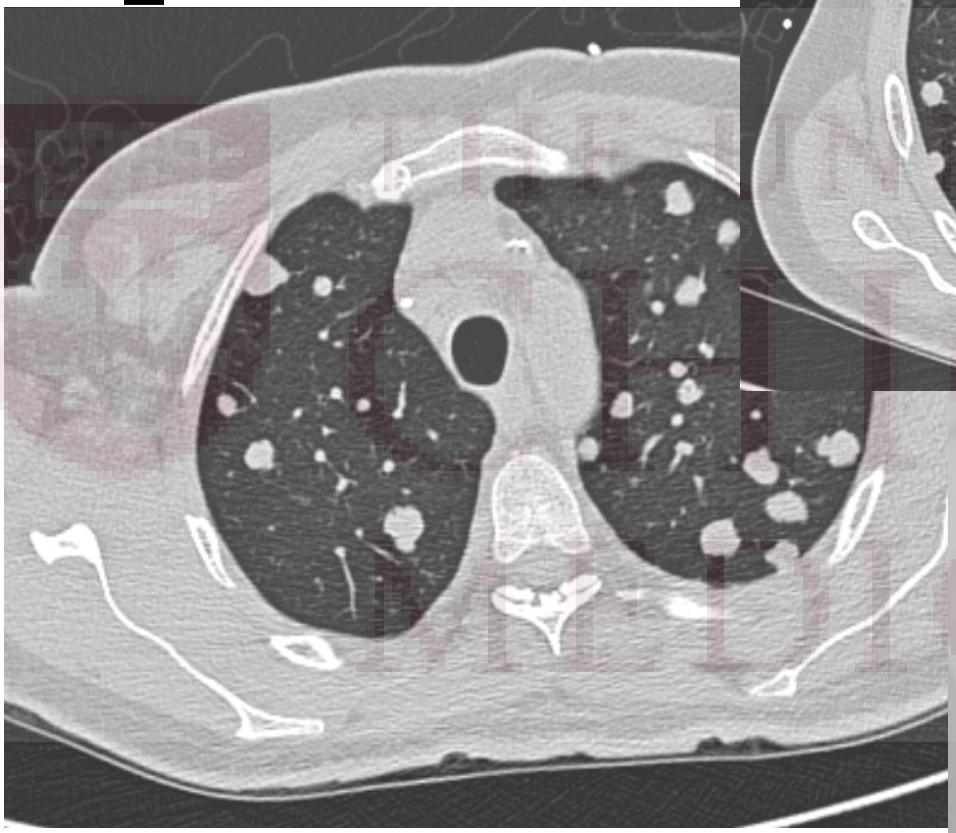
- Urine legionella neg.
- Urine S. pneumoniae neg.

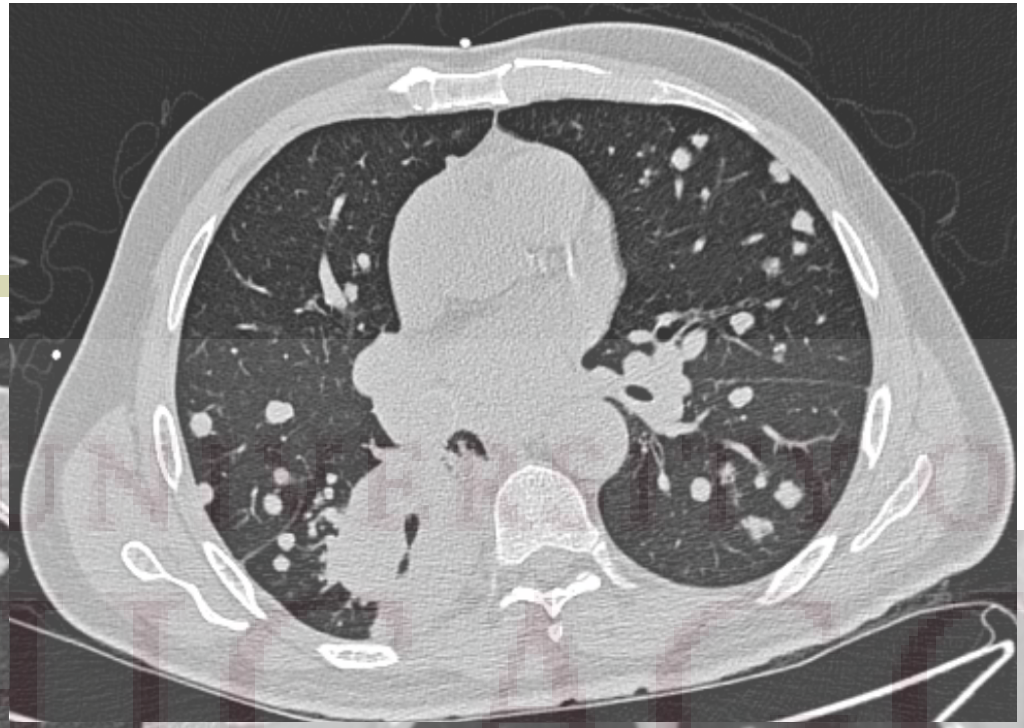
CXR

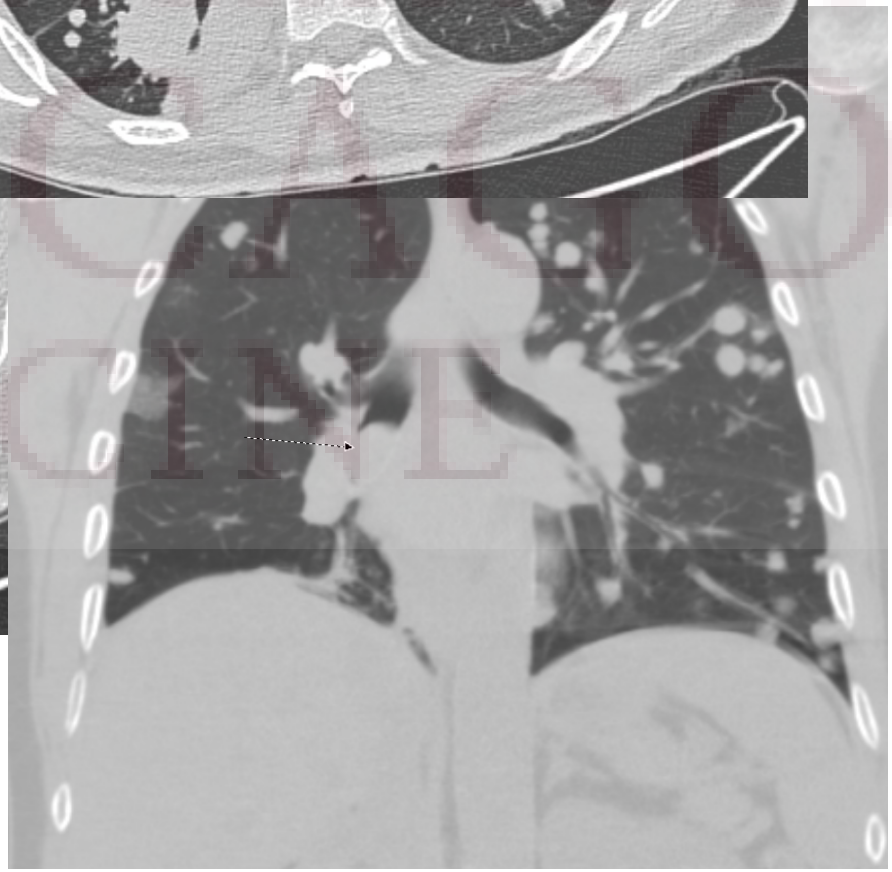




CT chest







Assessment & Plan

- 53 year old man with adrenocortical carcinoma metastatic to the lungs who presented with 2 weeks of shortness of breath, pleuritic chest pain, found to have likely a postobstructive pneumonia.
  - Adrenal insufficiency:
    - Increase hydrocortisone dose to 40 mg QAM and 20 mg QPM for the pneumonia.
    - Increase to 50 mg IV q8 on day of bronchoscopy for tumor debulking.
    - Taper as clinically fit.
    - Continue fludrocortisone.

My Questions:

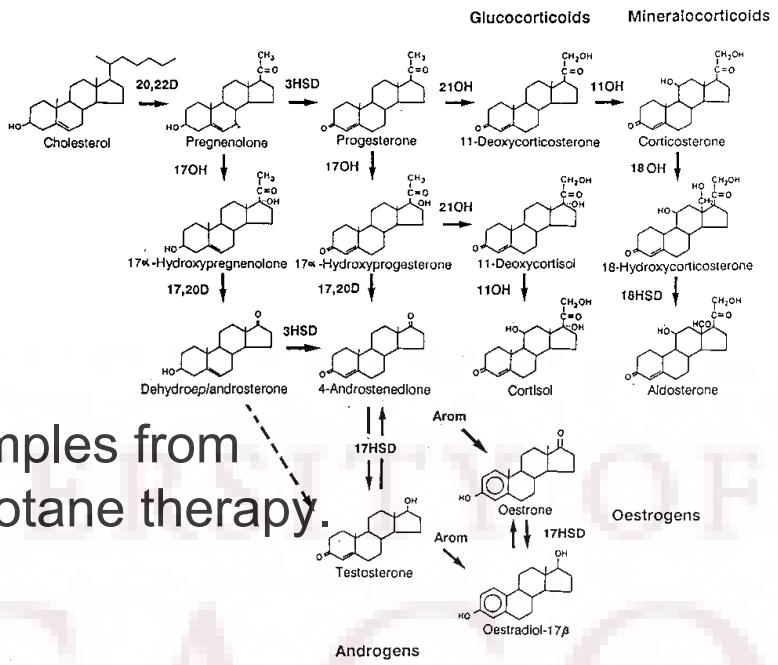
- How does mitotane affect steroidogenesis? And how long do the effects last?
- What are the expected outcomes for each therapy for ACC?

Mitotane

- Used as adjuvant therapy in patients with apparently complete surgical resection
  - Although most have resectable disease at presentation, >50% relapse and often with metastases
  - Recommended use in patients with potential residual disease and/or Ki67 more than 10%
  - No data regarding optimal duration, recommended at least 2 years
  - First prospective randomized trial is ongoing
- First-line treatment for metastatic ACC
  - 13%-35% response
  - May be combined with RFA
- Concomitant glucocorticoids are necessary
  - High dose replacement (50 mg) due to increased clearance
  - Fludrocortisone replacement may not be necessary
  - Monitor mitotane levels, LFTs, testosterone, TFTs, renin, cholesterol, CBC
  - Side effects: GI, lethargy, depression

Berruti et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii131-8.

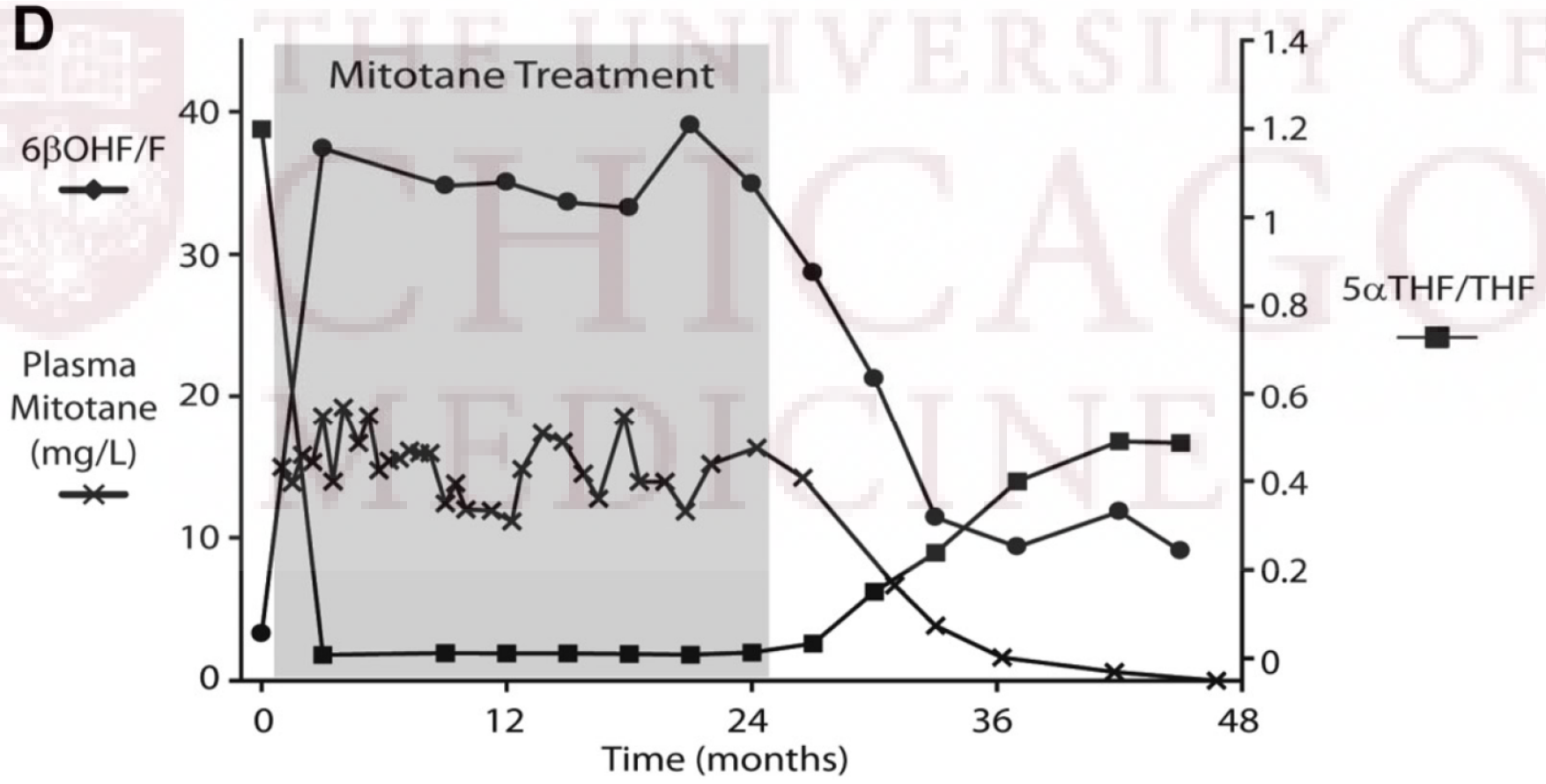
Mitotane



- Chortis et al. analyzed 24 hour urine samples from patients with ACC before and during mitotane therapy.
  - 23 in adjuvant setting
  - 104 for metastatic ACC
  - 88 controls
- No evidence for distinct enzyme inhibition, inc. 11β-hydroxylase
- Significant down-regulation of overall steroidogenesis
  - Decrease in total androgen and mineralocorticoid metabolites
  - May be due to inhibition of CYP11A1 (P450 side-chain cleavage enzyme), which would decrease conversion of cholesterol to pregnenolone
- Strong induction of cytochrome P450 3A4
  - Sharp increase of 6β-hydroxycortisol: 2→56%
- Strong inhibition of systemic 5α-reductase activity
  - Decrease in 5α-reduced steroids, similar to that with finasteride

Chortis et al. J Clin Endocrinol Metab. 2013 Jan;98(1):161-71.

Mitotane: Longitudinal study



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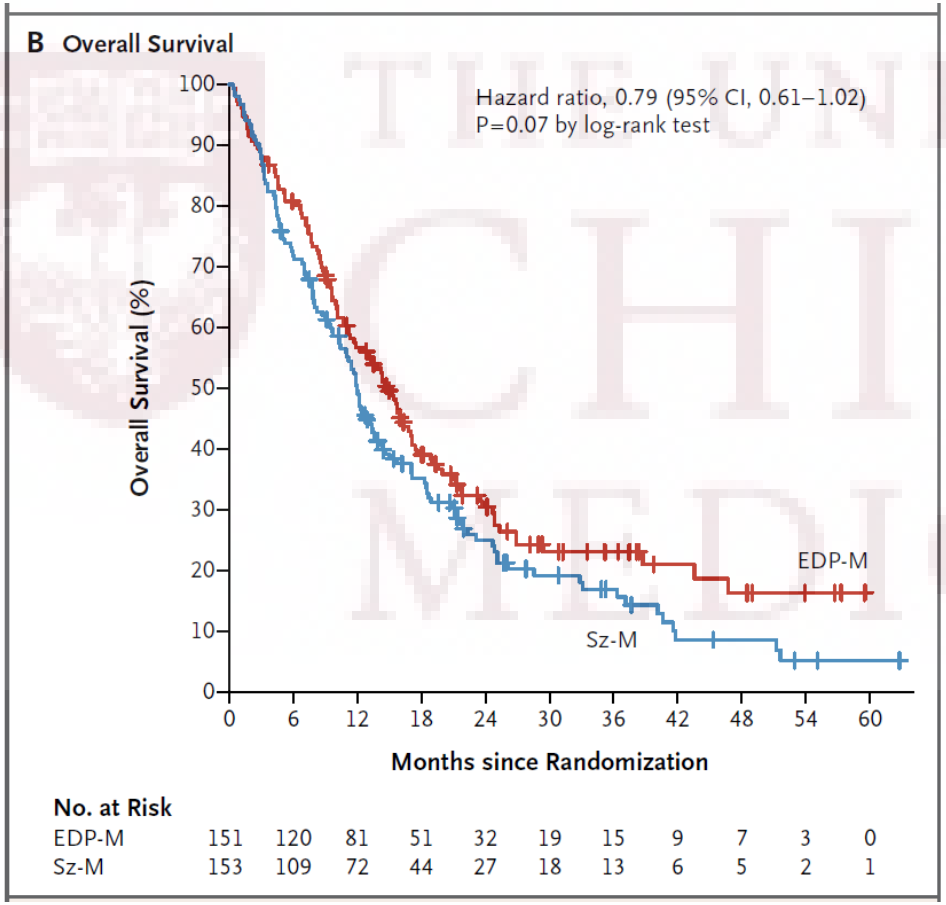
Chemotherapy



- 304 patients randomized to receive mitotane + etoposide/doxorubicin/ cisplatin v. streptozotocin
- EDP group had sig. higher response rate, longer median progression free survival (5 v 2 mo), but no difference in overall survival.

Fassnacht et al. N Engl J Med. 2012 Jun 7;366(23):2189-97.

mTOR inhibitors

- High expression of IGF2 in ACC
  - Effects mediated via PI3K/AKT/mTOR and RAS-MAPK pathways
- mTOR functions as a gatekeeper of cell growth, metabolism, and proliferation.
- De Martino et al. studied the effects of sirolimus and temsirolimus on growth and cortisol production in cell lines of human ACC.
  - mTOR inhibitors suppressed cell growth in a dose-/time-dependent manner in all cell lines.
    - Cell cycle arrest appears to be the predominant mechanism.
    - Effects were enhanced by blocking IGF2.
  - Sirolimus inhibited cortisol secretion.

De Martino et al. Endocr Relat Cancer. 2012 May 24;19(3):351-64.

References

- Berruti et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii131-8.
- Chortis et al. J Clin Endocrinol Metab. 2013 Jan;98(1):161-71.
- De Martino et al. Endocr Relat Cancer. 2012 May 24;19(3):351-64.
- Fassnacht et al. N Engl J Med. 2012 Jun 7;366(23):2189-97.