31 yea-old female with RUQ pain

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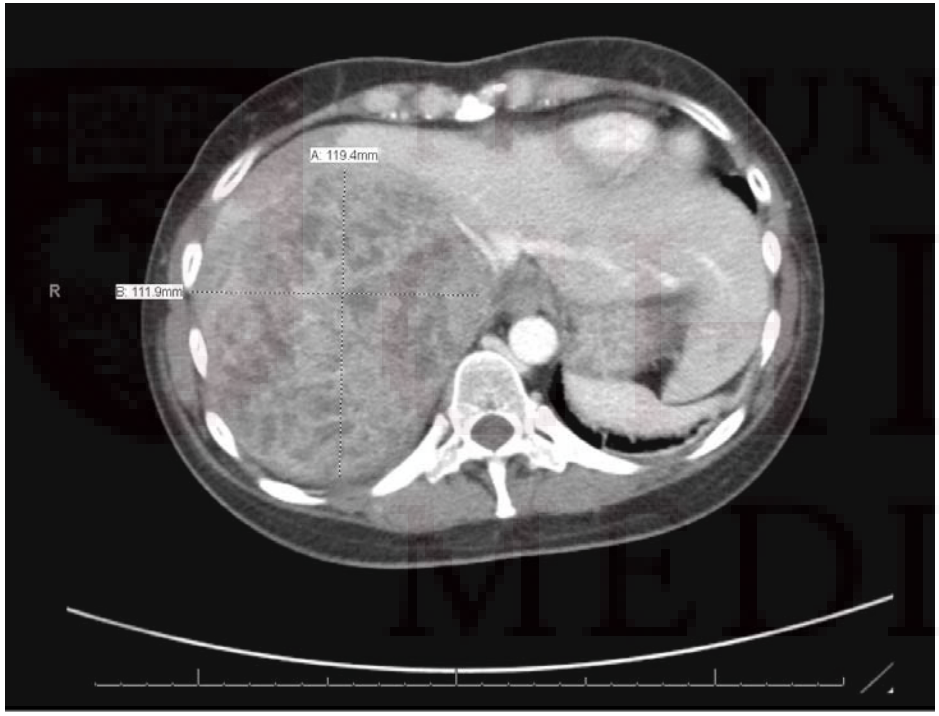
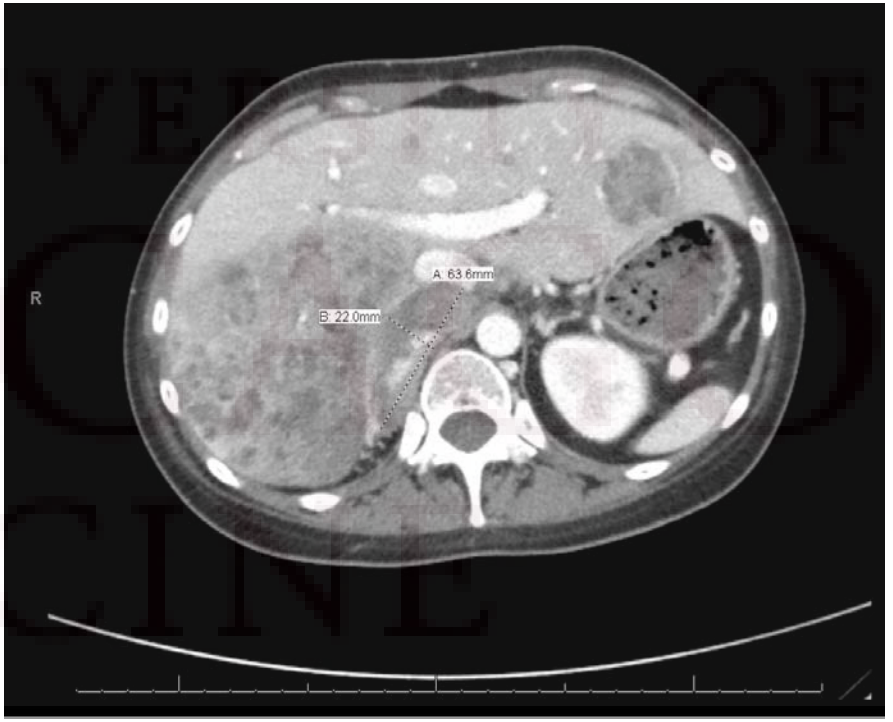
HPI:

- 31 year-old female presented with dull-intermittent RUQ pain for about 2-3 months to her PCP, US was ordered, which showed multiple liver masses.
- CT abdomen was ordered and revealed multiple bilobar masses in the liver measuring up to 11.9 x 11.2 cm in the right hepatic lobe, the intrahepatic IVC and right hepatic vein were compressed and deviated. Enlarged periportal lymph node measuring 1.8 x 1.6 cm, 6.4 x 2.2 cm R adrenal mass.
- FNA of one of the liver lesions was done: adrenal carcinoma (+ synaptophysin, + inhibin, + CD56, focally + CDX2, and + GATA3)

CT abdomen:





HPI:

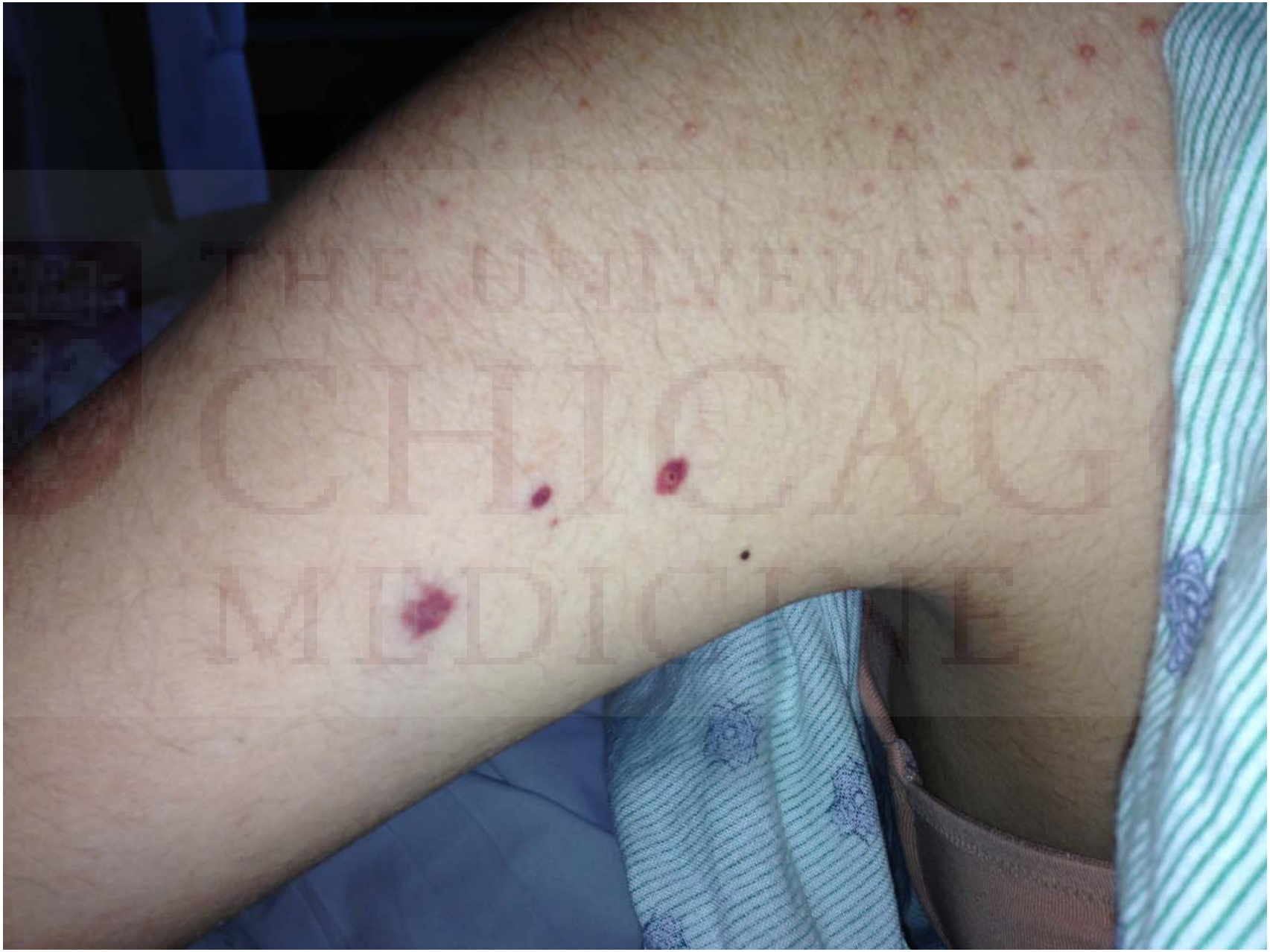
- ***PMH:*** None
- ***SH:*** Married, no children
- ***Home meds:*** multivitamins
- ***FH:*** paternal grandfather with DM2, maternal grandfather with a prostate cancer, paternal grandmother with colon cancer.

Review of systems:

- Constitutional: **+Weakness and fatigue.**
- Eyes: No blurry vision.
- ENT: No thirst.
- Respiratory: No shortness of breath, cough.
- Cardiovascular: No chest pain, palpitations.
- Gastrointestinal: No nausea, vomiting, **+RUQ pain**, diarrhea.
- Genitourinay: **no menstrual cycles for the last 3 months.**
- Musculoskeletal: No myalgias.
- Skin: **+Facial acne, acne on her upper chest and back. +Hirsutism. +Easy bruising.**
- Neurological: No headache. No peripheral neuropathy.

Physical exam:

- Vitlas: BP 142/90, Pulse 72, Temp 35.3 °C , Resp 18, Ht 154.9 cm, Wt 48 kg, BMI 19.99 kg/m2, SpO2 99%
- Constitutional: No acute distress.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended. No hepatomegaly. **RUQ tenderness.**
- Musculoskeletal/extremities: **LE edema 1+.**
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes.
- Skin: Skin is warm and dry. No acanthosis nigricans noted. **Facial acne, acne on her upper chest and back. Ferriman-Gallwey score 14. Red round maculas with dark center 1cm in diameter on her stomach and L upper arm. Bruises on her stomach.**



Labs:

142	104	16	134
4.0	28	0.5	

	11.1	
9.4		347
	35.4	

Ca 8.6 (8.4-10.2 mg/dL)
Mg 3.0 (1.6-2.5 mg/dL)
Phos 2.2 (2.5-4.4 mg/dL)

Total Protein 5.8 (6-8.3 g/dL)
Albumin 2.5 (3.5-6 g/dL)
Total Bilirubin 0.2 (0.1-1 mg/dL)
Bilirubin, conjugated 0.1 (0-0.3 mg/dL)
Bilirubin, unconjugated 0.1 (0.1-1 mg/dL)
Alk Phos 484 (30-120 U/L)
AST 46 (8-37 U/L)
ALT 49 (8-35 U/L)

HA1C 7%

ACTH 5.4 (<52 pg/mL) at 6AM

Cortisol 122.1 mcg/dL at 6AM

24hrs urinary cortisol 3053 (3.5-45 mcg/24hrs)

Renin 6.4 ng/mL/hr (Na-deplete, upright: Mean: 10.8 Range: 2.9-24, Na-replete, upright: Mean: 1.9, Range: <=0.6-4.3)

Aldosterone <4 (<21 ng/dL)

DHEA-SO4 1090 (45-270 ug/dL)

Labs:

Urine metanephrines and catecholamines:

Urine Norepinephrine 16 (15-80 mg/24hrs)
Urine Epinephrine 2.5 (<21 mcg/24hrs)
Urine Dopamine 103 (65-400 mcg/24hrs)
Urine Metanephrines 72 (<400 mcg/24hrs hypertensive)
Urine Normetanephrine 136 (<900 mcg/24hrs hypertensive)
Urine Total Metanephrine 208 (<1300mcg/24hrs)
Urine volume 1475 ml

Plasma metanephrines:

Normetanephrine <0.20 (<0.90 nmol/L)
Metanephrine <0.20 (<0.50 nmol/L)

Total testosterone 42 (20-60 ng/dL)
Free testosterone 24 (3-9 pg/mL)
Te binding globulin 15 (20-100 nmol/L)

- The pt was started on Lantus 13 units/day, Novolog 3 units with meals and Novolog CF 1:50>130.
- The pt was seen by oncology with a plan to start mitotane and then 1.5 weeks after that EDP.
- The pt was seen by reproductive endocrinology and discussed options for fertility preservation (oocyte retrieval vs ovarian cryopreservation vs depo Lupron treatment) and the pt was more interested in a third option.

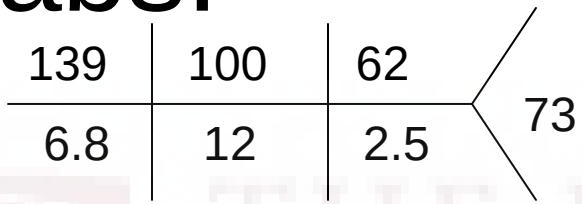
- The pt was started on mitotane 500mg QID on 10/15/2013
- On 10/17/2013 the pt developed AMS and was taken to ER
- In ER the pt was found to be hypotensive (BP not registered by cuff), she was given 1L NS and started on vanco/zosyn, she received 2L NS on her way to UofC

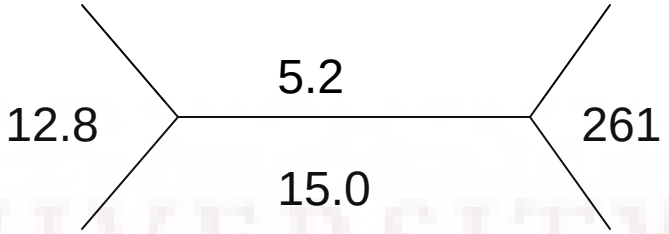
- In UofC ER she was hypotensive SBP 60`s, not protecting her airways
- The pt was intubated, central and A-line were inserted
- Shortly thereafter she had PEA arrest and CPR was started, she was coded for 30 mins

- She received 3 pushes of epi/2 bicarb/calcium, 2 units of RBCs due to HgB 4.2, she was started on levo, epi, vasopressin and dopamine and trasnferred to MICU

- Abx were changed to vanco/cefepime and flagyl

Labs:





AG 27
Ca 5.0 (8.4-10.2 mg/dL)
Mg 2.4 (1.6-2.5 mg/dL)
Phos 13.6 (2.5-4.4 mg/dL)

Total Protein 2.9 (6-8.3 g/dL)
Albumin 1.2 (3.5-6 g/dL)
Total Bilirubin 2.0 (0.1-1 mg/dL)
Bilirubin, conjugated 1.2 (0-0.3 mg/dL)
Bilirubin, unconjugated 0.9 (0.1-1 mg/dL)
Alk Phos 3377 (30-120 U/L)
AST 14384 (8-37 U/L)
ALT 3961 (8-35 U/L)
LDH >25000 (116-245 U/L)

CK 591 (9-185 U/L)

Lactic acid 9.8 (0.7-2.1 mEq/L)

Ammonia 272 (20-70 mcg/dL)

Cortisol 453.8 mcg/dL at 12AM

Blood cx: Enterobacter gergoviae x 1

- CT of the head showed extensive edema in the the bilateral occipital lobes and within the right cerebellar hemisphere (may represent recent multi-territorial infarcts and less likely posterior reversible encephalopathy syndrome)
- Repeat CT head after cardiac arrest showed subacute infarction in bilateral cerebral hemispheres in the distribution of the anterior and posterior circulations with sulcal effacement
- Bedside US of the abdomen did not show any intraabdominal fluid
- XR chest showed bilateral opacities/edema
- XR abdomen did not show any acute process

- The pt was stated on hydrocortisone 100mg Q8H on 10/17/2013
- The dose was increased to 150mg Q8H on 10/18/2013
- CVVH was started on 10/17/2013 due to severe acidosis and electrolyte abnormalities
- Dubutamine gtt was added on 10/18/2013
- Due to ? acute abdomen surgery was consulted, however the pt was too sick for surgery

- The pt was made DNR/DNI on 10/18/2013
- After discussion with the family, the pt was made comfort care only on 10/19/2013, pressors and CVVH were discontinued, the pt was extubated, fentanyl gtt was continued for comfort of the pt
- Patient pronounced deceased at 6:37 PM on 10/19/2013
- Autopsy was declined

- Adrenal carcinoma staging and prognosis
- Mitotane and adrenal insufficiency
- Mitotane and steroid replacement

- Adrenal carcinoma is a rare cancer with an incidence of 0.7-2 cases per 1mln population per year, M:F 1:1.5.
- Adrenal carcinoma is associated with certain genetic syndromes
  - (Beckwith–Wiedemann syndrome - abdominal wall defects-macroglossia-gigantism;
  - Familial adenomatous polyposis coli
  - Li–Fraumeni syndrome - sarcoma, breast cancer, brain and adrenal glands).

Diagnostic work up:

Table 2 | Diagnostic work-up in patients with suspected or proven adrenocortical carcinoma*

Hormonal work-up	Tests
Glucocorticoid excess (minimum 3 out of 4 tests)	Dexamethasone suppression test (1 mg, 2300 h) Excretion of free urinary cortisol (24 h urine) Basal cortisol Basal ACTH (plasma)
Mineralocorticoid excess	Potassium Aldosterone:renin ratio (only in patients with arterial hypertension and/or hypokalemia)
Sex steroids and steroid precursors	DHEAS 17OH-progesterone Androstenedione Testosterone 17β-estradiol (only in men and postmenopausal women)
Exclusion of a pheochromocytoma	Fractionated metanephrines in 24 h urine or free plasma metanephrines
Imaging	CT or MRI of abdomen‡ and CT of thorax Bone scintigraphy (if skeletal metastasis is suspected) FDG-PET (optional)

*Recommendation of the adrenocortical carcinoma working group of the European Network for the Study of Adrenal Tumors (ENSAT).[69] ‡Modern imaging is able to identify most adenomas correctly. However, measurement of Hounsfield units (HU), before contrast media and calculation of washout 10 min or 15 min after contrast media or MRI with chemical shift analysis is needed to provide optimal diagnostic yield. Abbreviations: ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; FDG, fluorodeoxyglucose.

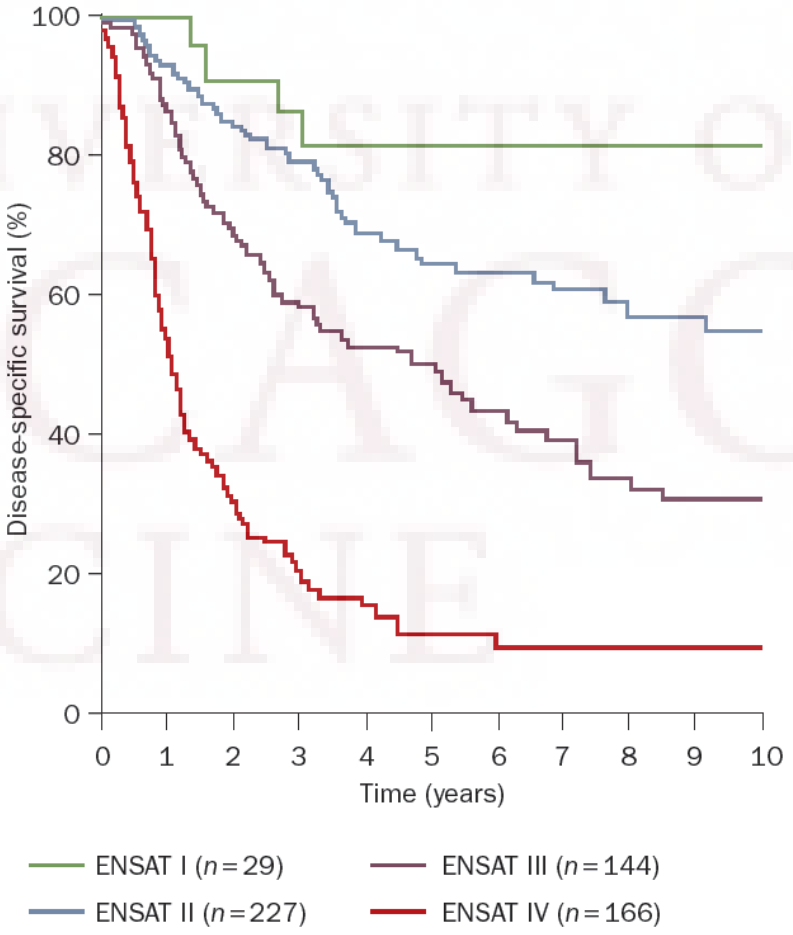
Adrenocortical carcinoma: a clinician's update. Fassnacht M, Libé R, Kroiss M, Allolio B. Nat Rev Endocrinol. 2011 Jun;7(6):323-35.

Staging and prognosis:

Table 3 | ENSAT staging for adrenocortical carcinoma

Stage	ENSAT tumor stage 2008
I	T1, N0, M0
II	T2, N0, M0
III	T1–2, N1, M0 T3–4, N0–1, M0
IV	T1–4, N0–1, M1

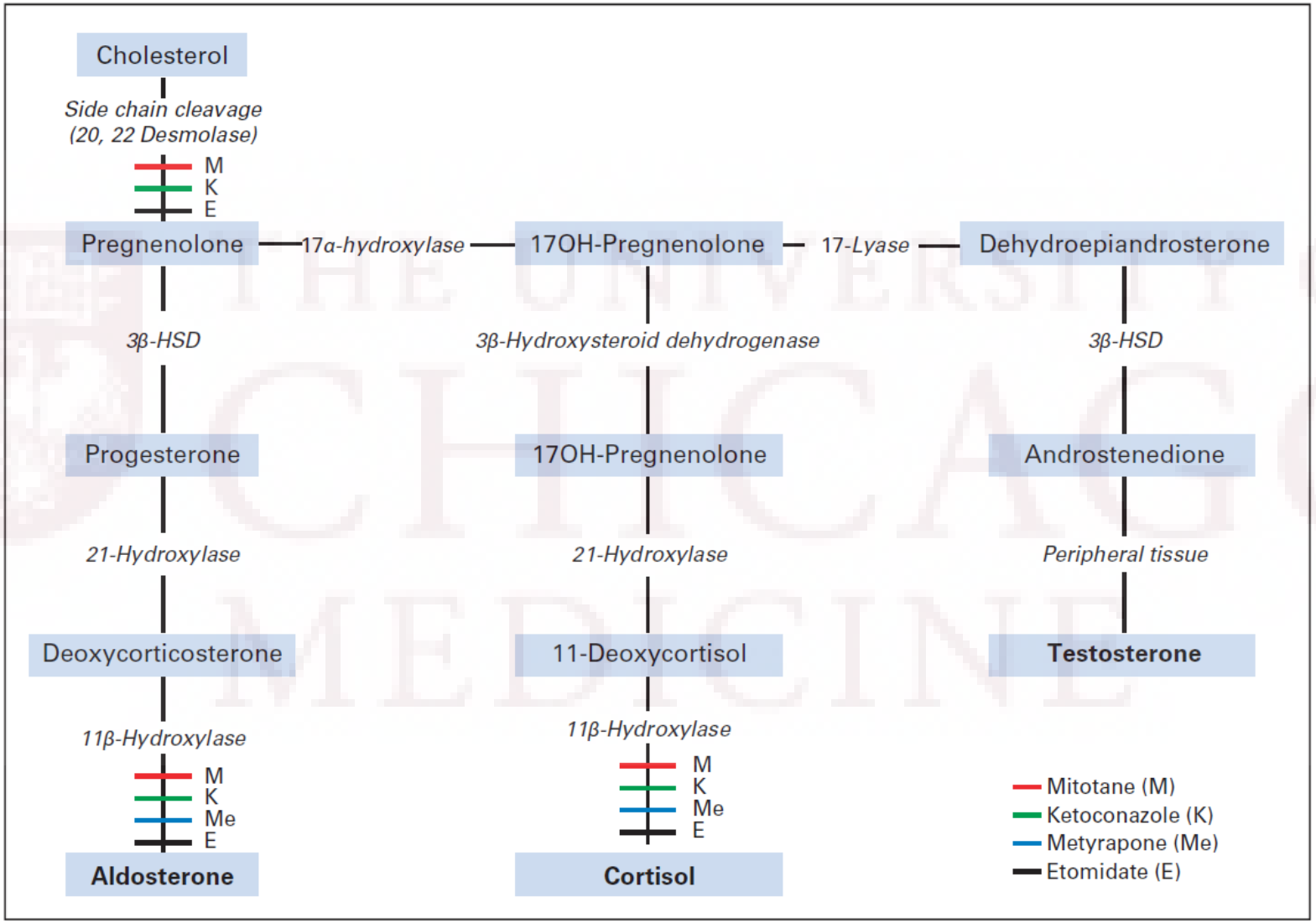
T1, tumor size ≤5 cm; T2, tumor size >5 cm; T3, tumor infiltration in surrounding tissue; T4, tumor invasion in adjacent organs or venous tumor thrombus in vena cava or renal vein. N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastases; M1, presence of distant metastasis. Abbreviations: ENSAT, European Network for the Study of Adrenal Tumors; M, metastasis; N, lymph node; T, tumor. Permission obtained from John Wiley and Sons © Fassnacht, M. *et al. Cancer* **115**, 243–250 (2009).



Adrenocortical carcinoma: a clinician's update. Fassnacht M, Libé R, Kroiss M, Allolio B. Nat Rev Endocrinol. 2011 Jun;7(6):323-35.

Mitotane:

- adrenal cytotoxic agent (directly suppresses the adrenal cortex, affects mitochondria in adrenal cortical cells)
- decreases steroid synthesis by inhibition of cholesterol side-chain cleavage (ie, human cytochrome P450 [CYP], cholesterol desmolase, or 20, 22 desmolase) and 11-hydroxylase (ie, P450 11 or CYP11b1)

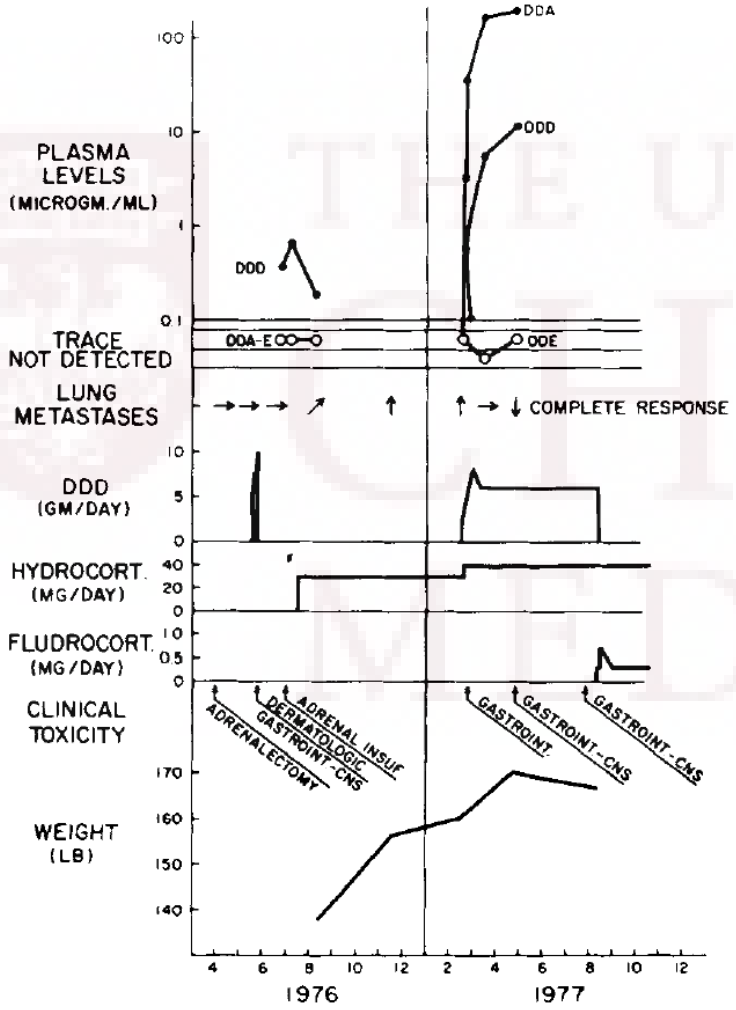


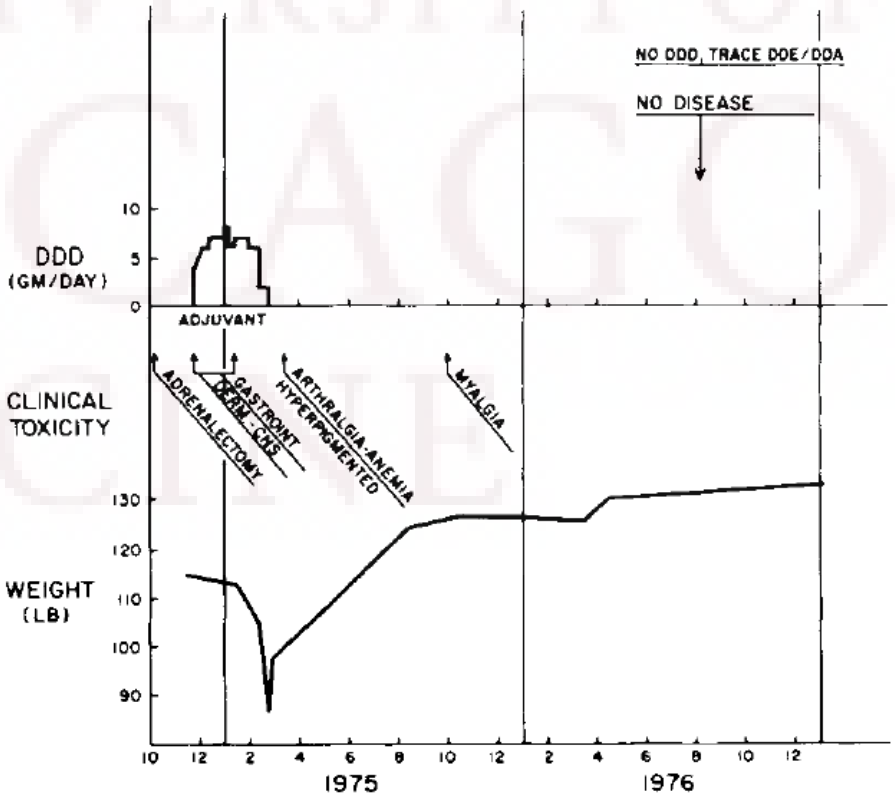
Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. Veytsman I, Nieman L, Fojo T. J Clin Oncol. 2009 Sep 20;27(27):4619-29.

Mitotane:

- Increases CBG and can falsely increase levels of total cortisol
- Increases TBG, competitively binds to TBG, TSH and free T4 remains unaffected
- Increases clearance of exogenously administered steroids, so replacement doses need to be increased by third

Mitotane and adrenal insufficiency:





o,p'-DDD (mitotane) therapy of adrenal cortical carcinoma: observations on drug dosage, toxicity, and steroid replacement. Hogan TF, Citrin DL, Johnson BM, Nakamura S, Davis TE, Borden EC. Cancer. 1978 Nov;42(5):2177-81.

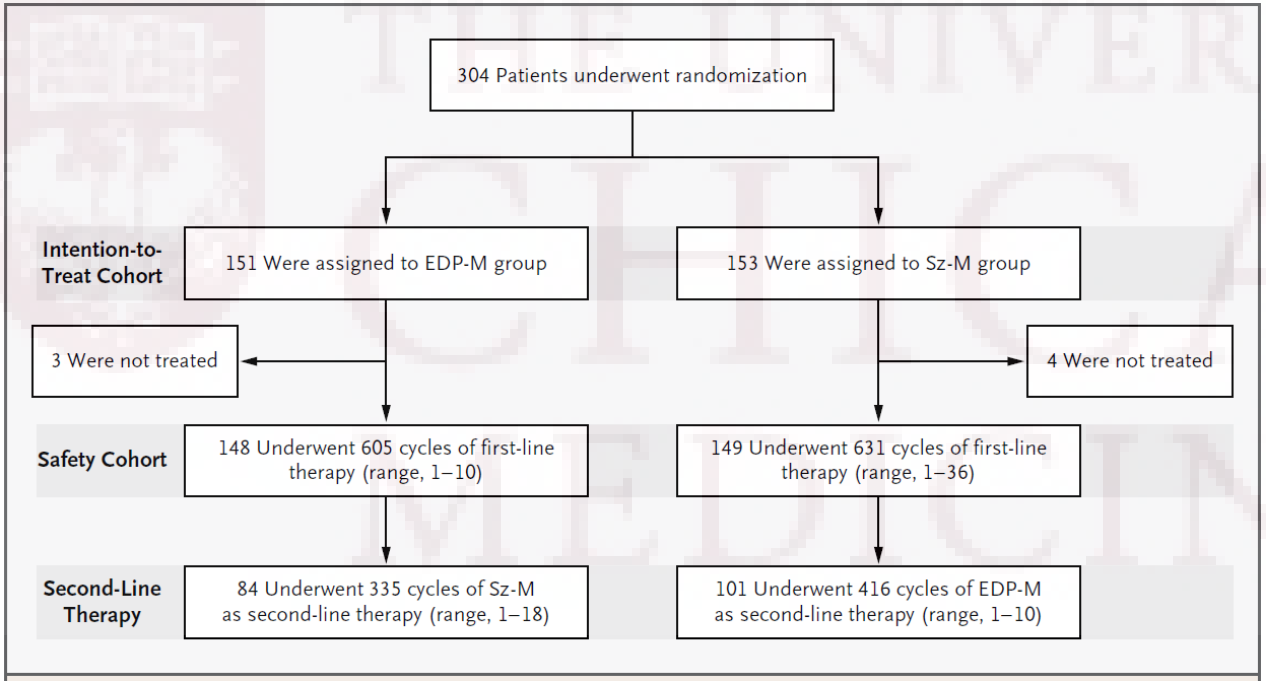
Mitotane treatment:

Mitotane dose regimen[a]	• Start with 1.5 g/d and increase dose within 4–6 days to 6 g/days • After 3 weeks, adjust dosage according tolerability and blood level (see below) • Maximum dose 12 g/days, but most patients do not tolerate >8 g/days • Target mitotane blood level 14–20 mg/l. Using this regimen, ~50% of patients achieve the target level within 3 months
Glucocorticoid and mineralocorticoid supplementation	• A total daily dose of 50 mg hydrocortisone (divided as 20–20–10 mg) or 75 mg cortisone acetate and more may be needed. Glucocorticoid replacement is monitored best with careful clinical assessment • Fludrocortisone may be added depending on the blood pressure, serum potassium levels, and plasma renin activity
Recommended blood monitoring during mitotane therapy	• Mitotane serum levels every 2–3 weeks in the first 3 months. After reaching a plateau, the interval can be extended (i.e. every 6 weeks) • Glutamate-Oxaloacetate Transaminase (GOT), Glutamate-Pyruvate Transaminase (GPT), bilirubin, Gamma-Glutamyl-Transferase (GGT). Initially every 4 weeks, after 6 months every 8 weeks. GGT is invariably elevated without clinical consequences. If other liver enzymes are rapidly increasing (>3-fold of baseline), there is a risk of liver failure: stop mitotane • TSH, fT3, fT4 every 3–4 months. Thyroid hormone replacement is recommended in patients with clinical symptoms of hypothyroidism • Testosterone, free testosterone, and sexual hormone binding globulin (SHBG) should be tested in male patients with symptoms of hypogonadism • Renin every 3 months. If renin increases in the presence of symptoms suggestive of mineralocorticoid deficiency, fludrocortisones should be added • Cholesterol (High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL)), triglycerides every 3–4 months (in an adjuvant setting). If LDL/HDL cholesterol consistently increases, consider treatment with statins not metabolized by CYP3A4 (e.g. pravastatin, rosuvastatin) • Blood count every 3–4 months

Plasma mitotane level	CNS (grade 2)/GI side effects (grade 3/4)		Grade 3/4 CNS side effects
	Absent	Present	Present
<14 mg/l	Increase daily dose by 1 g[b]	Reduce daily dose by 1 g	Stop mitotane[c]
14–20 mg/l	Maintain dose	Reduce daily dose by 1.5 g	Stop mitotane[c]
>20 mg/l	Reduce daily dose to 50%–75% of the most recent dose	Stop mitotane[c]	Stop mitotane[c]

Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, Pentheroudakis G; ESMO Guidelines Working Group.

Chemotherapy regimens for advanced adrenal carcinoma:



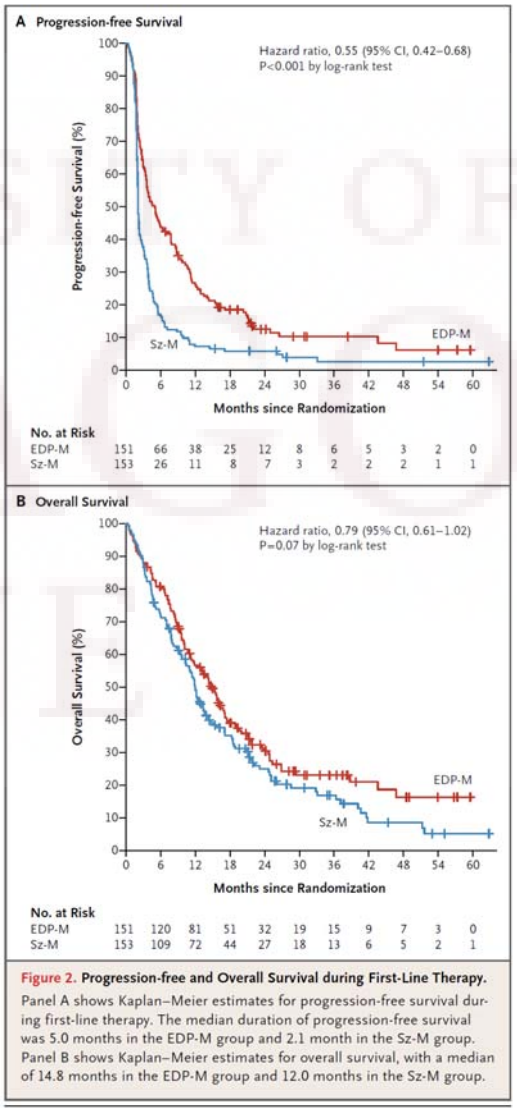


Figure 2. Progression-free and Overall Survival during First-Line Therapy.
Panel A shows Kaplan–Meier estimates for progression-free survival during first-line therapy. The median duration of progression-free survival was 5.0 months in the EDP-M group and 2.1 month in the Sz-M group. Panel B shows Kaplan–Meier estimates for overall survival, with a median of 14.8 months in the EDP-M group and 12.0 months in the Sz-M group.

Combination chemotherapy in advanced adrenocortical carcinoma. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, Welin S, Schade-Brittinger C, Lacroix A, Jarzab B, Sorbye H, Torpy DJ, Stepan V, Schteingart DE, Arlt W, Kroiss M, Leboulleux S, Sperone P, Sundin A, Hermsen I, Hahner S, Willenberg HS, Tabarin A, Quinkler M, de la Fouchardière C, Schlumberger M, Mantero F, Weismann D, Beuschlein F, Gelderblom H, Wilmink H, Sender M, Edgerly M, Kenn W, Fojo T, Müller HH, Skogseid B; FIRM-ACT Study Group. N Engl J Med. 2012 Jun 7;366(23):2189-97.

Take home points:

- Mitotane is an adrenal cytotoxic agent
- Steroid replacement treatment should be initiated at same the time of mitotane based on expert opinion
- Steroid replacement dose might need to be increased by third due to increased clearance
- Significant side effects are observed with mitotane treatment
- Careful monitoring is recommended

References:

- Adrenocortical carcinoma: a clinician's update. Fassnacht M, Libé R, Kroiss M, Allolio B. Nat Rev Endocrinol. 2011 Jun;7(6):323-35.
- Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. Veytsman I, Nieman L, Fojo T. J Clin Oncol. 2009 Sep 20;27(27):4619-29.
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- Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, Pentheroudakis G; ESMO Guidelines Working Group.
- Combination chemotherapy in advanced adrenocortical carcinoma. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, Welin S, Schade-Brittinger C, Lacroix A, Jarzab B, Sorbye H, Torpy DJ, Stepan V, Schteingart DE, Arlt W, Kroiss M, Leboulleux S, Sperone P, Sundin A, Hermsen I, Hahner S, Willenberg HS, Tabarin A, Quinkler M, de la Fouchardière C, Schlumberger M, Mantero F, Weismann D, Beuschlein F, Gelderblom H, Wilmink H, Sender M, Edgerly M, Kenn W, Fojo T, Müller HH, Skogseid B; FIRM-ACT Study Group. N Engl J Med. 2012 Jun 7;366(23):2189-97.