40 yo Woman with Weight Loss

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, 2018

Dr. Upala does not have any relevant financial relationships with any commercial interests

Learning Objectives

- Differential diagnosis of adrenal mass
- Review adrenocortical carcinoma
  - Presenting symptoms
  - Medical and Surgical treatment

HPI

- 40Yrs female with a past medical history of HTN, DM who presents with weight loss
- She presented 3 months ago with a chest pain to a hospital in South Illinois. Her chest pain was atypical and she was found to have high blood pressure and shingles. Her labs also was found to have a low potassium
- She was having symptoms of losing weight from 170 pounds to 127 pounds with feeling sometimes a panic attack, headache, high blood pressure and was placed on hydrochlorothiazide for that

HPI

- The patient was also diagnosed with diabetes mellitus around the same time and in the hospital she has been receiving low insulin sliding scale and sent home with metformin 500 twice daily with a good control. her A1c before was 6.1%, when she was diagnosed it was 9%
- For her low potassium, patient has been on supplements, lisinopril and Aldactone
- Patient reports rapid weight gain one year ago, along with acne and muscle weakness especially in the lower extremity. Her menses that were regular previously have ceased for the past year. She has not been on any hormonal therapy
- The patient denies any other family history of endocrine diseases except diabetes

Other History

- Past Medical History
  - HTN
  - T2DM
- Past Surgical history
  - None
- Family History
  - Father: T2DM
  - Mother: T2DM
- Allergy
  - No Known Allergies
- Social History
  - Never smoked
  - No alcohol intake
  - No recreational drugs
- Medication
  - Metformin
  - Spironolactone
  - Lisinopril
  - Potassium supplement
  - Acyclovir

Review of Systems

- Constitutional: No fevers, night sweats, appetite change, **+ weight loss, malaise, fatigue**
- HEENT: No photophobia, +**blurred vision**, no pain, hearing loss, difficulty swallowing, thirst, hoarseness
- Resp: No cough, dyspnea, increased WOB
- CV: **+CP, diaphoretic, palpitation, LE edema**, no DOE, orthopnea, PND, palpitations,
- GI: No abdominal pain, nausea, vomiting, diarrhea, constipation
- GU: No dysuria, urgency, polyuria, hematuria
- MSK: No myalgias, joint pain, back pain
- Neuro: No syncope, No numbness, paresthesias, seizures, **+tremors,**
- **+headaches**
- Heme: No adenopathy or easy bruising/bleeding
- Endo: No heat or cold intolerance, dry skin, dry hair, hair loss
- Derm: No rashes, ulcers, abdominal striae, hirsutism, acne
- Psych: No anxiety or depression

Physical Exam

BP 155/83 | Pulse 87 | Temp 36.6 °C (97.9 °F)| Resp 16 | Ht 149.9 cm (4' 11") | Wt 57.7 kg (127 lb 1.6 oz) | SpO2 99% | BMI 25.67 kg/m2

Physical Exam:
Vital signs reviewed
Constitutional: no acute distress
HEENT: EOMI, oropharynx clear
Neck: supple, no thyromegaly, no acanthosis nigricans
Cardiovascular: regular rate, no extra heart sounds
Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
Abdomen: bowel sounds present, soft, non-tender, no violaceous straie
Musculoskeletal: moving all extremities
Neurological: sensation intact to light touch
Skin: warm, dry
Psychiatric: not agitated

Initial Lab

Component	Value
WBC	11.0
RBC	4.14
Hemoglobin	10.9 (L)
Hematocrit	34.1 (L)
MCV	82.4
MCH	26.3
MCHC	32.0
RBC Dist Width	13.3
Platelet Count	320
Mean Platelet Volume	10.2
Differential Method	
No RBC or WBC abnormalities dete	
Lymphocytes	11 (L)
Monocytes	4
Eosinophils	0
Basophils	0
Abs Lymphocytes	1.32
Abs Monocytes	0.45
Abs Eosinophils	0.00
Abs Basophils	0.00
Neutrophils	84 (H)

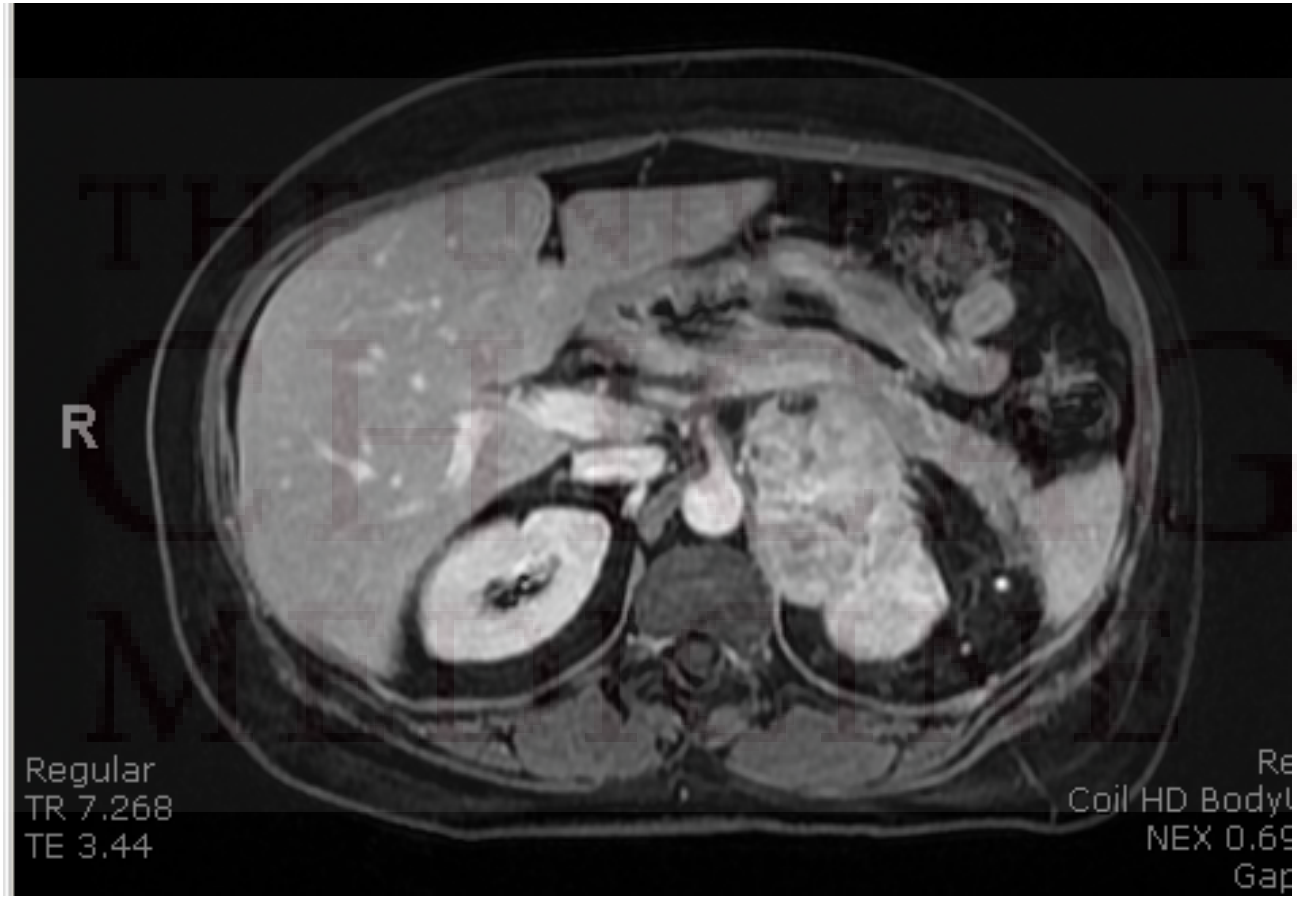
Component	Value
Sodium	145
Potassium, Ser/Plasma	3.1 (L)
Chloride	103
Carbon Dioxide	29
BUN	15
Creatinine	0.5
Glucose, Ser/Plasma	176 (H)
Calcium	8.9
GFR Estimate (Calc)	>120

Lab Component

Component	Value
Total Protein	7.2
Albumin	4.2
Bilirubin, Total	0.3
Alk Phos, Serum	76
AST (SGOT)	19
ALT (SGPT)	31

TSH: 1.06, A1c 7.2

Imaging



Imaging

- A CT scan was done at that hospital which revealed a large left adrenal mass of 8.6×6.3 cm and urology service has recommended removal of this mass
- MRI was done as well for further evaluation which revealed a large left adrenal mass that has a big part of it does not wash out the contrast

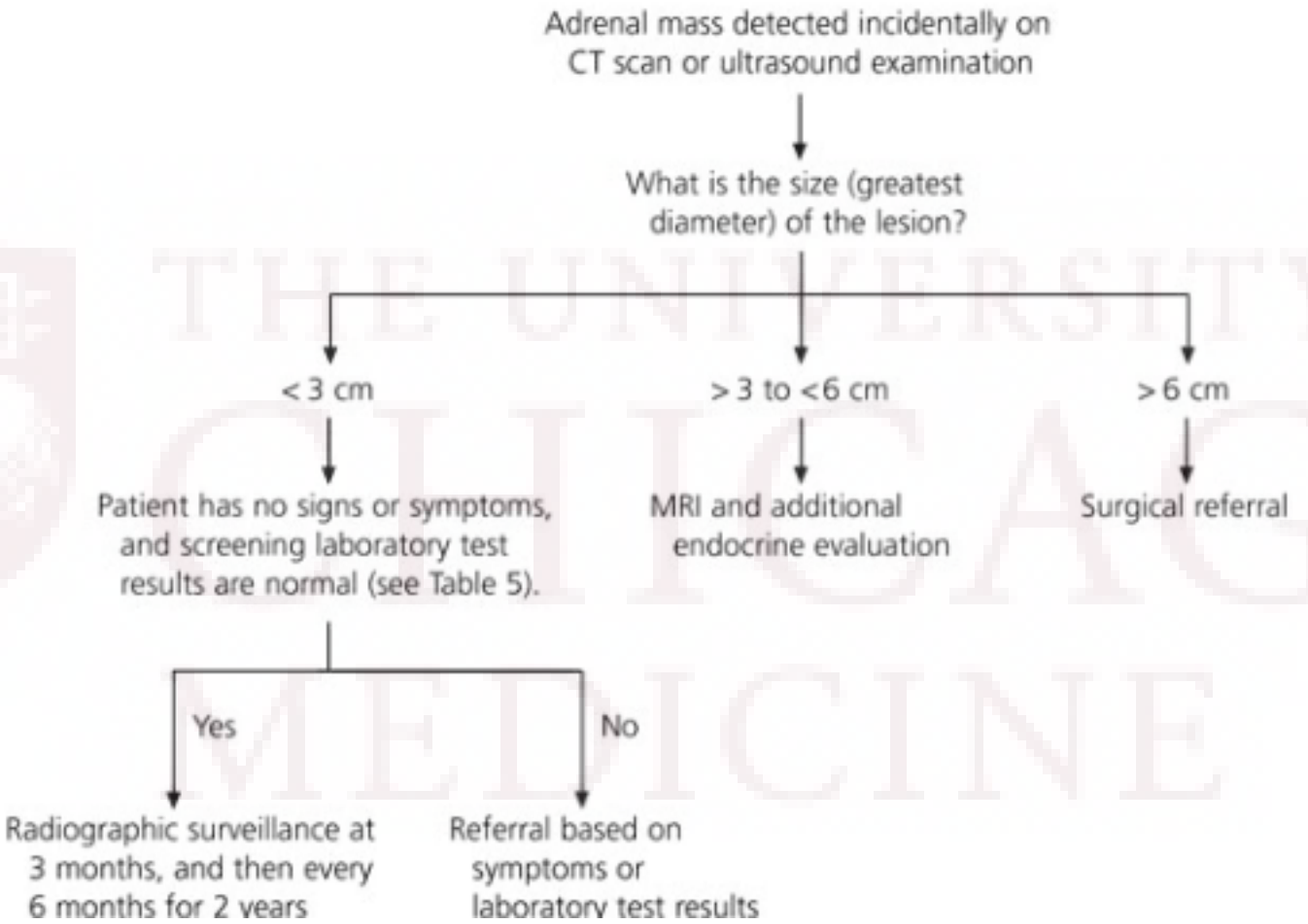
DDX

Adrenal Mass Differential Diagnosis

- **Adrenal Cortex**
  - Adenoma
  - Nodular Hyperplasia
  - Carcinoma
- **Adrenal Medulla**
  - Pheochromocytoma
  - Ganglioneuroma
  - Ganglioneuroblastoma
- **Metastases**
  - Breast, Lung, Lymphoma
  - Leukemia, other
- **Technical Artifacts**
- **Other**
  - Myelolipoma
  - Neurofibroma
  - Hamartoma
  - Teratoma
  - Xanthomatosis
  - Amyloidosis
  - Cyst
  - Hematoma
  - Granulomatosis
- **Pseudoadrenal**
  - Renal, Pancreas, Spleen etc

DDX?

DDX


Adrenal mass detected incidentally on CT scan or ultrasound examination
What is the size (greatest diameter) of the lesion?
< 3 cm
> 3 to < 6 cm
> 6 cm
Patient has no signs or symptoms, and screening laboratory test results are normal (see Table 5).
MRI and additional endocrine evaluation
Surgical referral
Yes
No
Radiographic surveillance at 3 months, and then every 6 months for 2 years
Referral based on symptoms or laboratory test results

Lab

- Work Up?

Lab

- Aldosterone : 136 (<21)
- Urine Aldosterone : 128 (2-20)
- Cortisol 4 am : 38.5
- Salivary cortisol : 3230 (<100)
- Plasma metanephrines : < 0.2 (<0.50)
- Plasma normetanephrines: 0.25 (<0.9)
- Renin : 3.7 (0.6-3)
- 24 hrs urine free cortisol : 2856 (3.5-45)
- ACTH : 1 (<52)

HPI

- She has had a hormonal evaluation that reveals very elevated 24 hour UFC
- Aldosterone level has been elevated but she had received aldactone while level was obtained
- Her plasma metanephrine were normal, making pheochromocytoma unlikely

Lab

1 mg overnight dexamethasone suppression test

- ACTH at baseline : 1 (<52)
- Cortisol 4 am : 40.4
- Cortisol 2 pm : 40

DDX

- Aldosterone secreting tumor
- Severe hypercortisolemia

Lab

- DHEA-S :433.9 (60.9-337)
- Adrenal cancer

Brief History

- 40 yo female, has had a 1 year history of rapid weight gain associated with amenorrhea, muscle weakness, new onset hypertension and DM2, significant hypokalemia and biochemical work up consistent with Cushing's syndrome
- Am cortisol post low dose DEX suppression is every elevated at 40, her 24 hour UFC is very elevated at 2856 and her late evening salivary cortisol is very elevated at 3230. Plasma ACTH is suppressed at 1. This is all consistent with adrenal Cushings
- She also has a reported 8 cm L adrenal lesion that was to be resected. Considering the size of mass and abnormal wash out on CT, there is concern for adrenocortical carcinoma

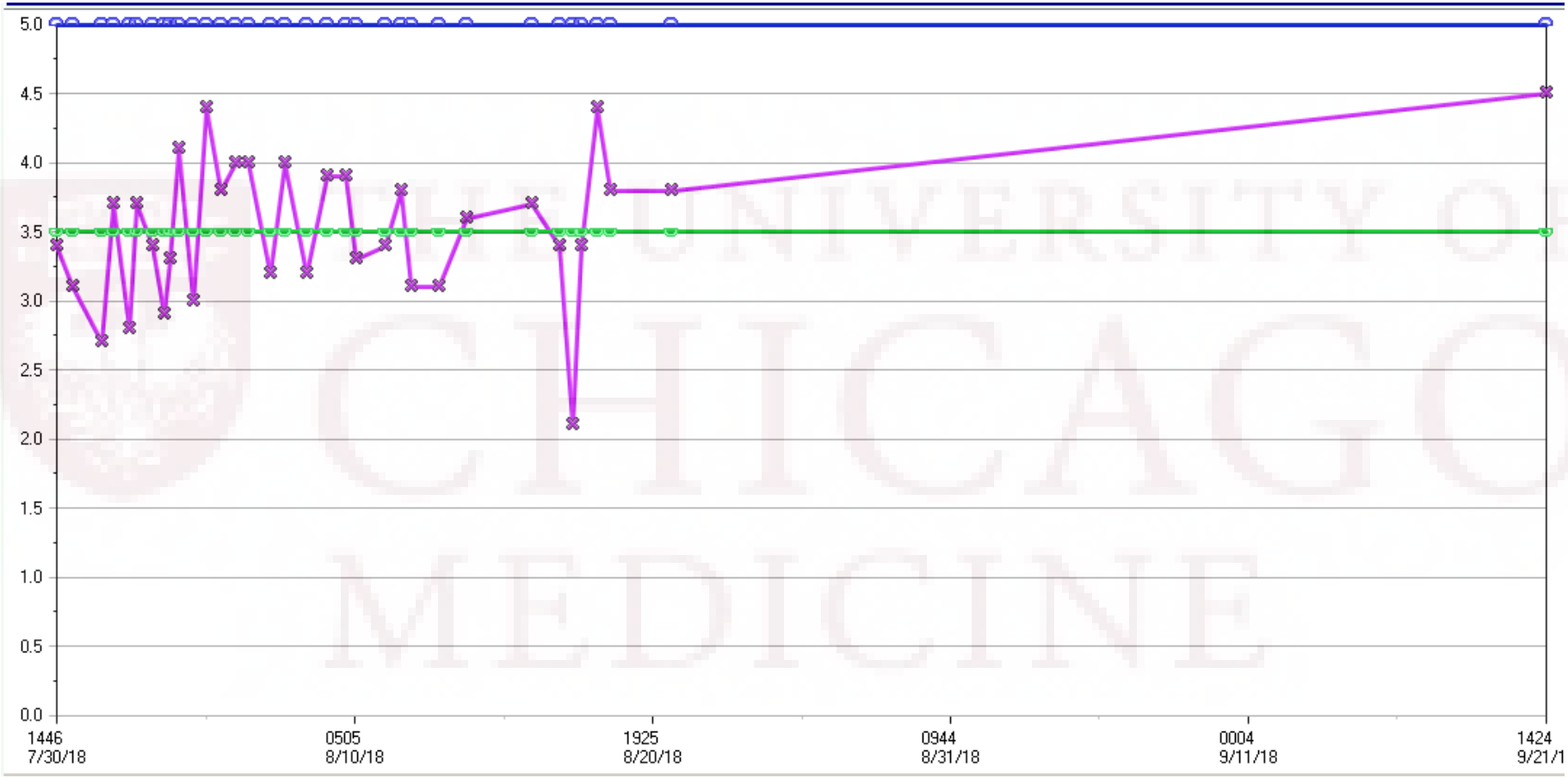
Management

- Continue potassium supplement and spironolactone
- DVT prophylaxis
- Stress dose steroids during surgery and post operative exogenous glucocorticoid therapy until recovery of HPA axis
- Surgery (robotic-assisted adrenalectomy)

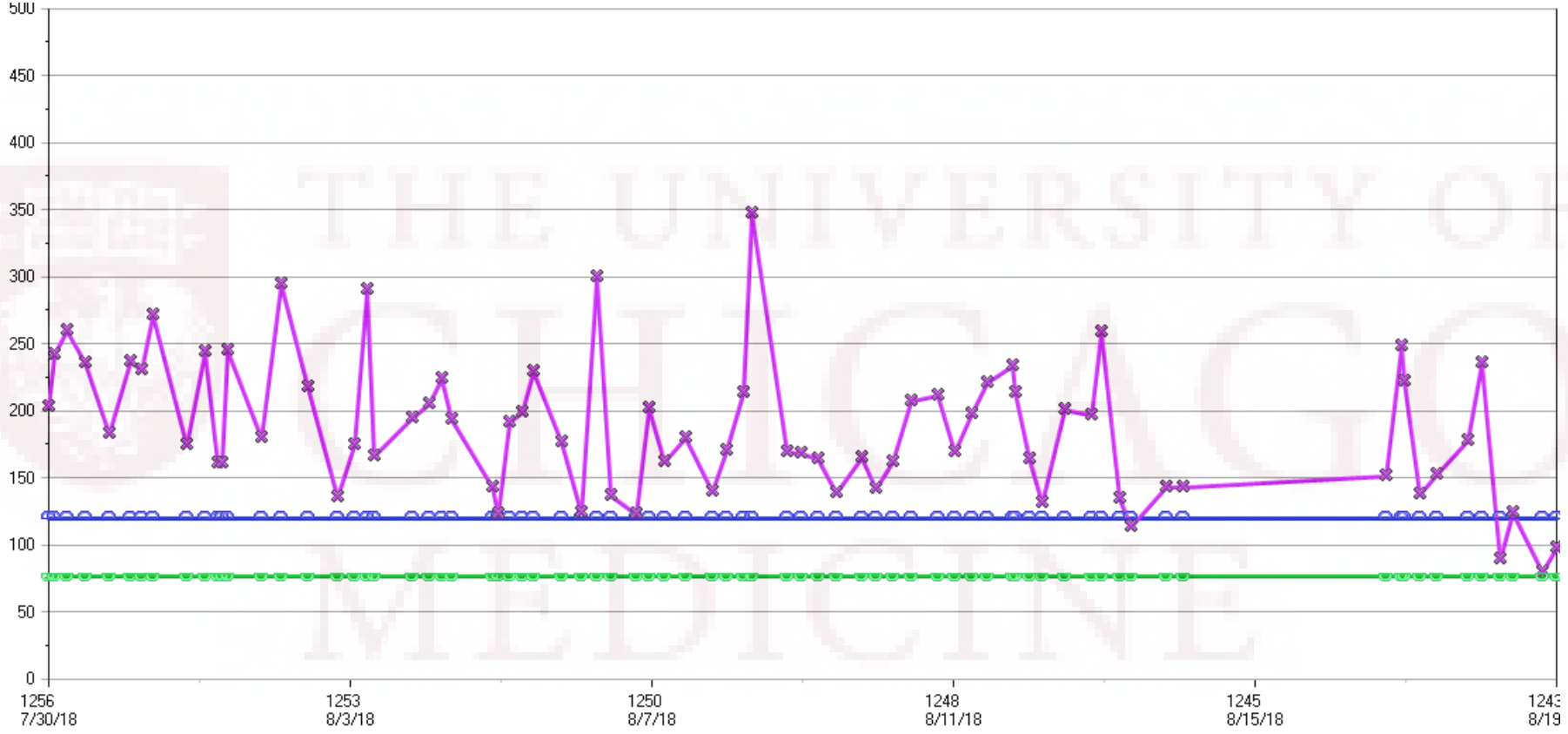
Pathology Report

- Left adrenal gland; robotic-assisted adrenalectomy:
  - Adrenocortical carcinoma (9.2 cm), high grade, invading into the peri-adrenal adipose tissue
  - Tumor involves the peripheral specimen
  - Tumor weight 152.8 grams
  - High grade (>20 mitosis/HPF)
  - Lymphovascular Invasion: Present
  - Regional Lymph Nodes: N/A
  - pTNM: pT3,NX

Potassium



Diabetes



THE UNIVERSITY OF CHICAGO MEDICINE

Merchant et al. 2013

Epidemiology

- Estimated incidence of 0.5-2 per 106 patients per year
- Peaks of age distribution at age <5 and in the 4th and 5th decades
- Scattered reports of gene associations, but rarity of lesion limits studies – no clear associations

Endocrinol Metab Clin N Am 37 (2008) 173–193

Clinical Presentation

- 60-65% of adrenocortical carcinomas are functioning lesions
- Cushings
- Virilization
- Feminization
- Hyperaldosteronism

Diagnosis

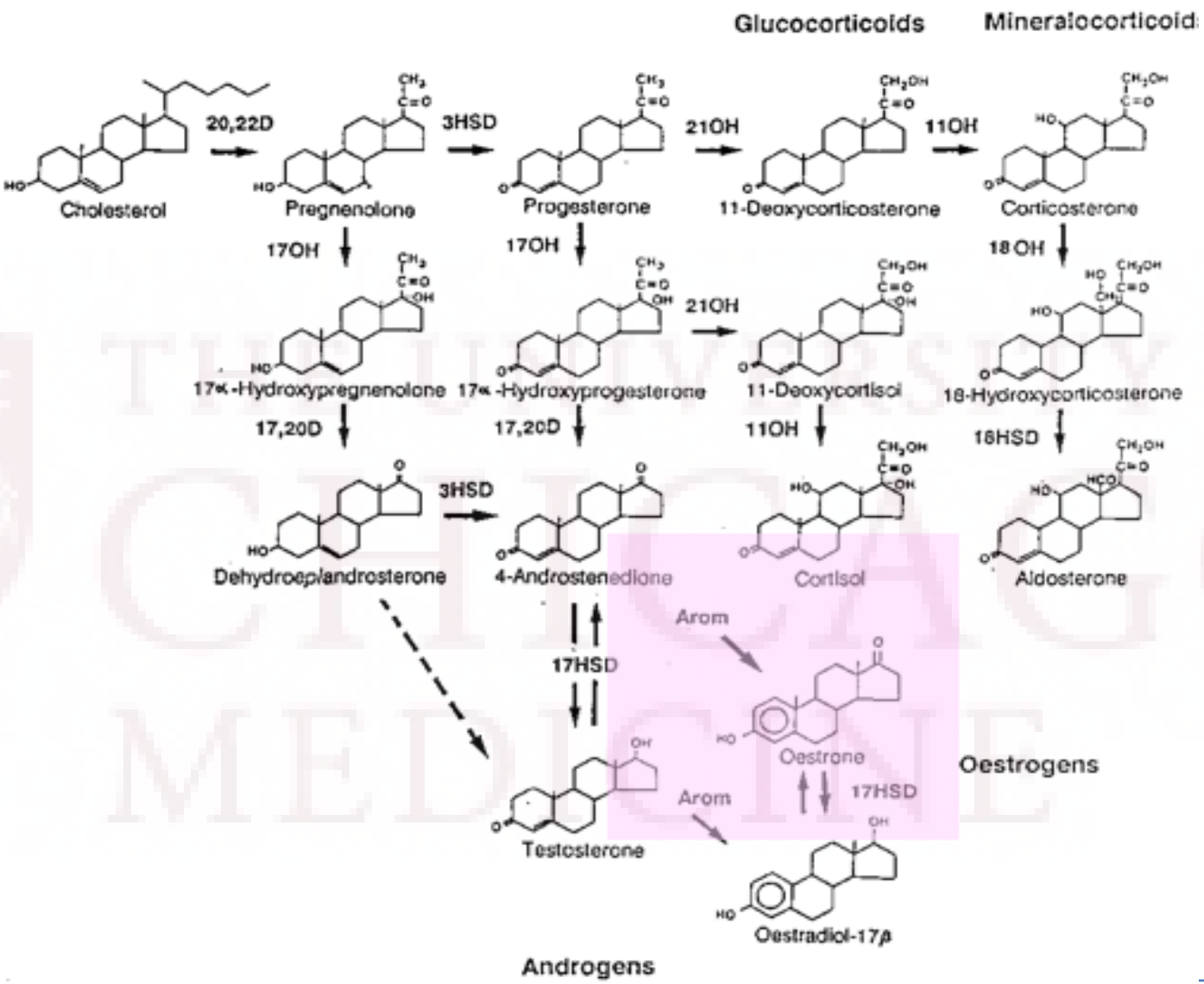
- Hormonal studies can be a first diagnostic test which confirms ectopic steroid hormone secretion, leading to an imaging and tissue diagnosis.
- They also can be a “tumor marker” which can be useful for monitoring response to therapy and suspicion of recurrence

Diagnosis

- 24 hour urinary cortisol excretion
- More than 90% of Cushinoid patients have free cortisol levels greater than 200mcg/ 24 hours 97% of normals have levels less than 100mcg/ 24 hours
- ACTH measured with serum cortisol will demonstrate ACTH independent nature of hypercortisolism

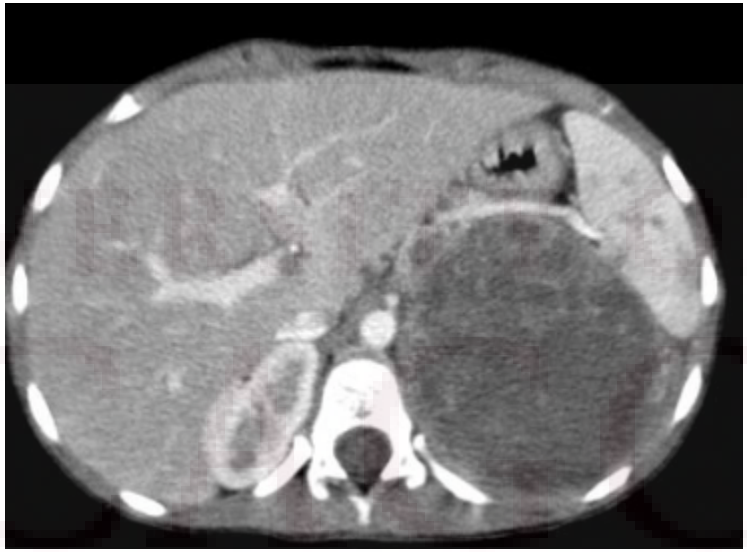
Diagnosis

- Other steroids are elevated:
  - androstenediol and adrosetenedione
  - DHEA and DHEA-S
  - 11- deoxycortisol
  - urinary 17- ketosteroids
  - aldosterone
- Many intermediate enzymes are defective or dysregulated, leading to inefficient steroid production and precursor accumulation


Glucocorticoids
Mineralocorticoid
Cholesterol
20,22D
Pregnenolone
3HSD
Progesterone
21OH
11-Deoxycorticosterone
11OH
Corticosterone
17OH
17OH
18 OH
17α-Hydroxypregnenolone
17α-Hydroxyprogesterone
21OH
11-Deoxycortisol
18-Hydroxycorticosterone
17,20D
17,20D
11OH
16HSD
3HSD
Dehydroepiandrosterone
4-Androstenedione
Cortisol
Aldosterone
Arom
17HSD
Oestrone
Oestrogens
Arom
17HSD
Testosterone
Oestradiol-17β
Androgens

Radiologic Findings

- CT detects 98% of adrenal carcinomas
- MRI scanning can also provide vascular invasion/ tumor thrombosis information
- Many incidental findings?
- Malignant lesions tend to be > 5cm, have irregular shapes/ blurred margins, and be heterogeneously enhancing



Staging

- Hormonal studies directed at symptoms
- 24h urine studies to r/o pheochromocytoma
- CT scanning to determine extent and resectability of lesion
- MRI may clarify vascular invasion; right sided lesions have a propensity to form venous tumor emboli

Staging

Adrenal cortical carcinoma TNM staging AJCC UICC 2017

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤5 cm in greatest dimension, no extra-adrenal invasion
T2	Tumor >5 cm, no extra-adrenal invasion
T3	Tumor of any size with local invasion but not invading adjacent organs
T4	Tumor of any size that invades adjacent organs (kidney, diaphragm, pancreas, spleen, or liver) or large blood vessels (renal vein or vena cava)
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Rossella L, Front Cell Dev Biol. 2015; 3: 45.

Clinical Questions

- Treatment option (surgery, chemical therapy, monitor)

Treatment Overview

- Surgical resection
  - Mainstay Tx
- Chemotherapy
  - Mitotane
- Radiation

Surgical Treatment

TABLE 7. *Adrenocortical carcinoma: survival rates from reported series*

Study	Institution/group	Year	n	5-y Survival (%)		
				Overall	Complete resection	Incomplete resection
Soreide et al.[6]	Norway	1991	99	16	62	0
Icard et al.[16]	French Endocrine Surgeons	1992	156	34	42	0
Zografos et al.[17]	Roswell Park	1994	53	19	38	0
Haak et al.[18]	Holland	1995	96	27	49	9
Crucitti et al.[19]	ACC Italian Registry	1996	129	35	48	7

ACC, adrenal cortical carcinoma.

- Complete surgical resection is the primary treatment modality

Surgical Treatment

Table 3. Survival of patients who underwent potentially curative resection for adrenal cortical carcinoma.

Study	Institution	Year	No.	Margin analysis	Median follow-up (months)	Overall survival (months)	5-Year actuaria survival (%)
Harrison [56]	MSKCC	1999	46	No	20	28[b]	36
Khorram-Manesh[a] [57]	Sweden	1998	18	No	85	—	58
Crucitti [58]	Italy	1996	91	No	—	28[c]	48
Lee[a][55]	MDACC	1995	16	Yes	43	46[b]	46
Zografos [36]	Roswell Park	1994	15	No	—	13[b]	38
Haak [59]	Netherlands	1994	47	No	—	—	49
Icard[a] [27]	France	1992	127	No	—	—	42
Icard [37]	France	1992	31	No	—	44[c]	45
Pommier[a] [26]	MSKCC	1992	53	No	28	28[c]	47
Gröndal[a] [60]	Sweden	1990	22	No	—	—	—
Henley [61]	Mayo Clinic	1983	31	No	—	—	32

MDACC: M.D. Anderson Cancer Center; MSKCC: Memorial Sloan-Kettering Cancer Center.
[a]Includes patients who underwent resection of synchronous metastatic disease.
[b]Median.
[c]Mean.

- Complete resection is the strongest predictor of survival

Surgical Treatment

Table 4. Patient survival following incomplete resection of adrenal cortical carcinoma.

Study	Institution	Year	No.	Median survival (months)
Crucitti [58]	Italy	1996	33	16
Lee [55]	MDACC	1995	7	8.5
Zografos [36]	Roswell Park	1994	28	2
Icard [27]	France	1992	28	< 12
Icard [37]	France	1992	10	< 4
Gröndal [60]	Sweden	1990	12	10
Henley [61]	Mayo Clinic	1983	14	< 6

Patients with incomplete resections included those who underwent incomplete resection of the primary tumor and those who underwent complete resection of the primary tumor in the presence of unresectable distant metastatic disease.

Incomplete resection is associated with a uniformly poor prognosis, with less than a 1 year median survival

Prognostic factors

- In a case review of 46 patients at MSKCC, 3 histologic factors correlated with survival:
  - Tumor > 12cm
  - 6 or more mitotic figures/ 10hpf
  - presence of histologic evidence of intra-tumoral hemorrhage
- 5 year survivals:
  - 0 factors: 83%
  - 1 factor: 42%
  - 2 factors: 33%

Radiation

- There are emerging case reports demonstrating improved outcomes when palliative XRT used for localized lesions

Chemotherapeutic Approach

- Mitotane
- Metyrapone (11B hydroxylase inhibitor)
- Ketoconazole
- Aminoglutehamide

Mitotane

- 1,1- dichloro-2-(o-chlorophenyl) ethane (o,p-DDD).
- Chemical relative to DDT
- Found to have adrenolytic activity in dogs in vivo (selectively destroyed the zonae reticularis and fasciculata)

Mitotane

- Inhibits the mitochondrial conversion of cholesterol to pregnenolone and the conversion of 11-deoxycortisol to cortisol (11B-hydroxylation). It produces selective adrenocortical necrosis in both the adrenal tumor and metastases

Mitotane

- Side effects are major and frequent, including:
  - CNS disturbance (vertigo, somnolence, ataxia)
  - Liver Toxicity
  - Renal Toxicity
  - Nausea, Vomiting
  - Diarrhea
  - Rash

Mitotane

Table 5. Effect of mitotane treatment on adrenal cortical cancer.

Study	Year	Institution	No.	Result/conclusion
Kasperlik-Zaluska [72]	1995	Poland	36	Suggested benefit of adjuvant mitotane
Haak [59]	1994	Netherlands	62	Response rate 21% (6/29) in setting of measurable disease
Vassilopoulou-Sellin [73]	1993	MDACC	13	No effect on survival
Pommier [26]	1992	MSKCC	29	PR 24%
Luton [74]	1990	France	37	PR 22%, no effect on survival
Venkatesh [75]	1989	MDACC	72	Stable disease or PR 29%
Karakousis [76]	1985	Roswell Park	10	Stable disease or response 40% ($n = 4$)
Van Slooten [77]	1984	Netherlands	34	Serum levels > 14 μg/ml associated with improved survival
Henley [61]	1983	Mayo Clinic	24	PR 4% ($n = 1$)

PR: partial response.

Cytotoxics

- Various systemic cytotoxics have been used for advanced disease, usually for those failing mitotane.
- Most studied have been Etoposide, cisplatin, and adriamycin.
- Paclitaxel and Temozolamide have recently demonstrated antitumor activity *in vitro*

Cytotoxics

- Original studies utilized Cisplatin and Doxorubicin with Cyclophosphamide or 5-FU. RR was 20%
- Cisplatin/ Etoposide reported to have an 11% response rate

Chemotherapy

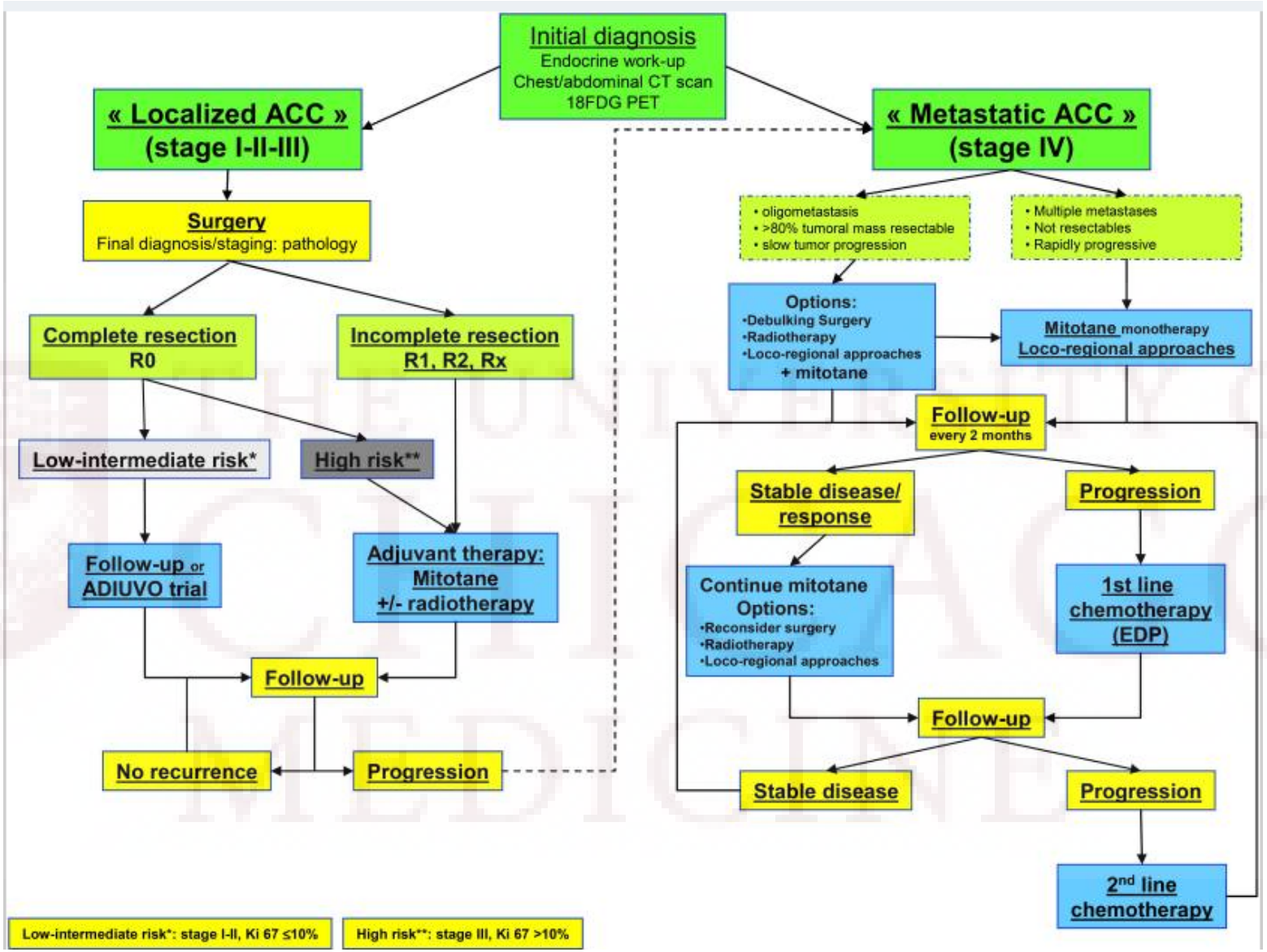
Table 6. Effect of chemotherapy on adrenal cortical cancer.

Series	Year	Institution	Regimen	No.	Response
Williamson [83]	2000	SWOG	ECM[a]	45	PR 5
Abraham [84]	1999	NCI	MEDV	28	CR 1, PR 4
Berruti [85]	1998	Italy	MEDP	28	CR 2, PR 13
Zidan [86]	1996	Israel	EP[b]	1	PR 1
Bukowski [87]	1993	SWOG	MP	37	PR 11
Berruti [88]	1992	Italy	EDP	2	PR 2
Schlumberger [89]	1991	France	DP5-FU	13	CR 1, PR 2
Hesketh [90]	1987	Boston University	EPB	4	CR 1, PR 1
Johnson [91]	1986	Vanderbilt	EC	2	PR 2

5-FU: 5-fluorouracil; B: bleomycin; CR: complete response; D: doxorubicin; E: etoposide; M: mitotane; NCI: National Cancer Institute; P: cisplatin; PR: partial response; SWOG: Southwest Oncology Group; V: vincristine.

[a]Mitotane given only after disease progression on EC and only to patients who had not received mitotane previously.

[b]Mitotane failure.


Initial diagnosis
Endocrine work-up
Chest/abdominal CT scan
18FDG PET
« Localized ACC »
(stage I-II-III)
« Metastatic ACC »
(stage IV)
Surgery
Final diagnosis/staging: pathology
• oligometastasis
• >80% tumoral mass resectable
• slow tumor progression
• Multiple metastases
• Not resectables
• Rapidly progressive
Complete resection
R0
Incomplete resection
R1, R2, Rx
Options:
•Debulking Surgery
•Radiotherapy
•Loco-regional approaches
+ mitotane
Mitotane monotherapy
Loco-regional approaches
Low-intermediate risk*
High risk**
Follow-up
every 2 months
Stable disease/
response
Progression
Follow-up or
ADIUVO trial
Adjuvant therapy:
Mitotane
+/- radiotherapy
Continue mitotane
Options:
•Reconsider surgery
•Radiotherapy
•Loco-regional approaches
1st line
chemotherapy
(EDP)
Follow-up
Follow-up
No recurrence
Progression
Stable disease
Progression
2nd line
chemotherapy
Low-intermediate risk*: stage I-II, Ki 67 ≤10%
High risk**: stage III, Ki 67 >10%

Recurrence

- Recurrences that are amenable to re- operation may be resected for long term survival
- 5 year survivals compare from 57% in those amenable to resection to 0% for those who are not

Recurrence

- MSKCC: 47 patients with recurrent/ metastatic disease
- Patients who had a complete second resection had a median survival of 74 months (5-year survival, 57%), whereas those with incomplete second resection had a median survival of 16 months (5-year survival, 0%)

Hospital Course

- Patient has been seen by oncology who has recommended radiation and mitotane therapy
- She met with radiation oncology and will start radiation soon for 6 weeks. She will start on mitotane afterwards
- She is off insulin and Tradjenta. Has been checking her blood sugars and values 69-90. Prior to adrenalectomy, she was requiring low dose insulin therapy for diabetes and was also on blood pressure medication that have been discontinued
- She is only on potassium 40 meq daily. Repeat K levels have been improved and her dose of potassium has been reduced
- She has been taking the hydrocortisone 10 mg in am and 5 mg at pm.

Summary

- Adrenocortical carcinoma is a rare disease that often presents late
- Primary curative therapy is surgical
- No role for adjuvant chemotherapy has been definitively demonstrated to date
- Palliative therapy with mitotane may be useful; its palliative effect may be entirely due to adrenolytic effect
- Re-operation appears to be the only long term curative option in recurrent cases
- Cytotoxic chemotherapy in the advanced/ metastatic setting has not been definitively demonstrated to be useful in controlled trials

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