Adrenal cortical carcinoma

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In the name of
GOD

- السادختر ۴سال ویک ماهه باشکایت موی ناحیه پوبیس ازحدود ۶ماه قبل مراجعه کرده است.درمعاینه PH:III و AH:+ دارد.درمعاینه ژنیتالیا کلیترومگالی دارد.قد۹۹سانتی متر (صدک ۲۵-۵۰%) وزن ۱۶کیلوگرم (صدک ۵۰تا۷۵)

نتایج بررسیهای انجام شده به قرارزیراست:

- *17-OH-p:8ng/ml*
- *DHEAS:274microgr/dl*
- *Te:1.19ng/ml*
- *Na:139meq/l*
- *K:4.4meq/l*
- *ACTH:8.2pg/ml*
- *Prolactin:14.6ng/ml(macro:15%)*

Multislice CT scan of the abdomen and pelvis
(Without contrast)

The non- IV contras study is suboptimal for evaluation of abdominopelvic organs but as far as seen.

Clinical information: History of right renal mass

Study for comparison: Not provided

There is a large soft tissue lesion above the right kidney measuring
33 x 30 x 20 mm without obvious calcification probably due to adrenal mass.
Other abdominal organs as far as seen are unremarkable.
No obvious paraaortic lymphadenopathy is detected.
Minimal free preperitoneal fluid is seen (physiologic?).
Bony structures as far as seen are unremarkable.

IMP:

- **Right adrenal mass**

- سونوگرافی شکم ولگن باتاکید برادرنال:توده solid باحدودمنظم ولی هتروژن ولوبوله درادرنال راست باابعاد۳۲در۲۶ میلی مترمشهوداست.

- بیمار تحت CT scan شکم ولگن وتوراکس باپروتوکل ادرنال قرارگرفت .توده ادرنال راست به ابعاد۳۰*۲۰*۲۵با HF:35-40 و wash out:65% شناسایی شد.بقیه موارد:نرمال .

- بررسیهای تکمیلی انجام شده به قرارزیراست:

Biochemistry

Test	Result	Unit	Risk	Method	Reference Interval
Plasma Metanephrine	45	pg/mL		ELISA	<300
Plasma Normetanephrine	42	pg/ml		ELISA	<216

Urine Biochemistry

Test	Result	Unit	Risk	Method	Reference Interval
Volume (Urine -24 hrs)	300	ml/24hrs			666-2566
Creatinine (Urine-24 hrs)	0.2	g/24 hrs			0.6-1.8
Epinephrine (Urine-24hrs)	12	µg/24hrs		ELISA	<20
Norepinephrine (Urine - 24 hrs)	27	µg/24hrs		ELISA	<80
Metanephrine (Urine - 24 hrs)	24	µg/24hrs		Elisa	Up to 350
Normetanephrine (Urine - 24 hrs)	34	µg/24hrs		Elisa	Up to 600

Hormone Analysis

Test	Result	Unit	Risk	Method	Reference Interval
Cortisol D.S.T					
Cortisol D.S.T	5.89*	micg/dl		ECLIA	Up to 1.8
Plasma Renin Activity	1.2	ng/mL/hour		ELISA	0.06 - 4.69

* = Confirmed by Repeated Analysis

Immunology

Test	Result	Unit	Risk	Method	Reference Interval
Aldosterone (Upright)	68*	pg/ml		Elisa	70 - 300 (TIETZ 1999)

Specimen: The sample submitted for review and second opinion consists of 3 paraffin blocks labeled as 913 from Imam Hossein Hospital pathology laboratory which specified as "Adrenal mass resection"

Microscopic: Histologically sections show an encapsulated tumor composed of variably sized nests, large sheets and trabeculae of large cells. These cells have granular clear to eosinophilic cytoplasm with pleomorphic and intranuclear inclusions and mitosis. Increased variation in nuclear size and irregular invasive borders are also seen.

Diagnosis: Consulting H&E-stained slides specified as "Adrenal mass resection":
Adrenal cortical carcinoma, Weiss score 4
Tumor size: 35 mm
Nuclear grade: Grade IV
Clear or vacuolated cell: less than 25%
Diffuse architecture: more than 80%
Necrosis: Absent
Capsular invasion: Present
Vascular invasion: Absent
Ki-67: Positive in 10% of tumoral cells
Surgical margins are free.

History:

Known case of adrenocortical carcinoma

Macroscopic:

Received specimen in formalin labeled as mediastinal mass consists of two cylindric soft tan pieces each measuring in lenght 1.1, 0.6 cm and 0.2 cm in diameter (totally passed).

Microscopic:

Sections show thymus parenchyma consists of lymphoid tissue, some hassall's corpuscles and some lymphoid follicles with germinal center.

IHC staining No.1178 on block 8249 results as follow:
-Ki67:Mostly positive in germinal center
-TDT:Positive
-CD20:Positive in germinal center
-LCA:Positive
-BCL2:Positive in paragerminal center areas

Diagnosis:

Mediastinal mass core needle biopsy:
-Consistent with thymic tissue with lymphoid hyperplasia

- بیمارتحت ادرنالکتومی سمت راست باپروتوکل کانسرقرارگرفت .پس ازان تحت درمان بامیتوتان وهیدروکورتیزون قرارگرفت.

- مونیتورینگ درمان بامیتوتان به صورت دوره ای اجرا میشود.

ACC

- ***Rare***
- *1 to2 per million population per year .*
- *Develop at any age*
- *Bimodal age distribution(**before** the **age of five** and in the fourth to fifth decade of life) .*
- *Rapid progression in **adults** than in children.*
- ***Female**-to-male ratio (1.5 to 2.5:1) .*
- *May be due to proliferative effects of **estrogen**.*

Pathogenesis

- *Sporadic*
- *component of hereditary cancer syndromes.*
- *Li-Fraumeni syndrome (Sarcoma, Breast, Leukemia, and Adrenal gland [SBLA] cancer syndrome) / autosomal dominant/ inactivating mutations of the TP53 .*
- *Beckwith-Wiedemann syndrome (Wilms' tumor, neuroblastoma, hepatoblastoma, and ACC)/ abnormalities in 11p15.*
- *MEN1: parathyroid, pituitary, and pancreatic neuroendocrine tumors and adrenal adenomas, or carcinomas)/ inactivating mutations of the MEN1 gene on chromosome 11q.*

- *Amplification **SF-1** gene in tumors also has been reported .*

- ***Unilateral or bilateral** adrenal tumors can be found in 20 to 40 percent of patients with MEN1.*

Clinical presentation

- *60 percent of ACCs are sufficiently secretory .*
- *Majority are benign tumors, usually nonfunctional, but they can present with excess production of aldosterone or cortisol.*
- *Adults usually present with Cushing's syndrome alone (45 percent), or a mixed Cushing's and virilization syndrome (25 percent).*
- *Fewer than 10 percent present with virilization alone, but the presence of virilization in a patient with an adrenal neoplasm suggests an ACC rather than an adenoma.*

Clinical presentation

- ***Feminization*** *and* ***hyperaldosteronism*** *occur in fewer than 10 percent of cases .*

- *Most patients with* ***nonfunctioning*** *tumors present with clinical manifestations related to tumor growth (****abdominal or flank pain****) or with an* ***incidentally.***

- ***Constitutional*** *symptoms (weight loss, anorexia) are frequent.*

Clinical presentation in children

- *Children usually present with virilization (84 percent), while isolated glucocorticoid excess (Cushing's syndrome) is much less common (6 percent).*

Diagnostic evaluation

Hormonal evaluation

- Even in asymptomatic patients, recommends performing the following tests to determine the secretory activity of the tumor:

- FBS,cortisol, ACTH, 24-hour urinary free cortisol, DST(1mg dexamethasone), DHEAS, androstenedione, testosterone, 17-OH-P, and serum estradiol in men and postmenopausal women .

Diagnostic evaluation

- *It recommends that plasma metanephrines or urinary metanephrines and catecholamines obtained in all patients to exclude pheochromocytoma.*

- *Plasma aldosterone and renin should be obtained in patients with hypertension and/or hypokalemia.*

- *Hormonal evaluation provide tumor markers that can be useful during follow-up to estimate the presence of residual tumor or tumor recurrence after surgery.*

Radiographic studies

- CT scanning can usually distinguish adenomas from ACCs.
- MRI is complementary to CT, in that local invasion and involvement of the vena cava are more readily identifiable.
- PET scanning with fluorodeoxyglucose (FDG) is of value for identifying unilateral adrenal tumors with a higher index of suspicion for malignancy.
- FDG uptake is observed in all of the malignant and none of the benign lesions .
- It has been shown that a minority of benign cortical adenomas accumulate FDG, although to a lesser extent .

Radiographic studies

- ***Integrated*** *or "****fused" PET-CT*** *imaging improves the performance of PET because adrenal adenomas can be better differentiated from nonadenomas using a combination of CT attenuation measurements plus the intensity of FDG uptake, as described by the* ***standardized uptake value (SUV)*** *for the adrenal lesion.*

Radiographic studies

- The most common sites of distant spread for ACC are the liver, lungs, lymph nodes, and bone .
- CT imaging of the chest and liver, as well as bone scan, are included in the staging workup if an ACC is suspected.
- While PET is more sensitive than CT or radiographic bone scans for distant metastases in a variety of clinical settings, small lesions may be missed.

Radiographic studies

- ***FDG-PET-CT** is complementary to **regular CT** in the **follow-up** of patients with adrenal carcinoma.*

Fine-needle aspiration biopsy

- FNA cannot distinguish a benign adrenal mass from adrenal carcinoma.
- It can distinguish between an adrenal tumor and a metastatic tumor.
- FNA is sometimes performed when there is a suspicion of cancer outside the adrenal gland or in the patient undergoing a staging evaluation for a known cancer .
- Pheochromocytoma should always be excluded by biochemical testing before attempting FNA biopsy of an adrenal mass.

benign or malignant?

- Even when diagnostic material is available, the distinction between benign and malignant adrenocortical tumors may be difficult and should only be made by a pathologist experienced in using the microscopic Weiss criteria .

- The only definitive diagnostic criterion for a malignant adrenocortical tumor is distant metastasis or the presence of local invasion.

- In the absence of these findings, the Weiss histopathologic system is the most commonly used method for assessing the likelihood of malignant behavior .

Weiss system

The five criteria used in the updated Weiss system include:

- *>6 mitoses/50 high-power fields*
- *≤25 percent clear tumor cells in cytoplasm*
- *Abnormal mitoses*
- *Necrosis*
- *Capsular invasion .*
- *Each criterion is scored 0 when absent, or 2 for the first two criteria and 1 for the last three when present. the threshold for malignancy is a total score ≥3.*

Ki-67 labeling index (LI)

- *The Ki-67 labeling index (LI) has been used to select patients for adjuvant chemotherapy in addition to mitotane.*

- *While the absolute value of Ki-67 LI that permits the differentiation of a very high-risk ACC from low- or intermediate-risk ACC is not established , a high-grade ACC, which is defined in part by a high mitotic rate (and/or Ki-67 score ≥20 percent), is at a higher risk of recurrence than a low-grade ACC.*

Ki-67 labeling index (LI)

- *Cutoff values between benign and malignant lesions vary from 1.5 to 10 percent .*

Staging and prognosis

- **Children** :
- *Completely resected small tumors (200 g or smaller) : Excellent prognosis (five-year, event-free survival 91%).*
- *Completely resected large tumors (over 200 g) : Intermediate prognosis (five-year, event-free survival 52 %)*
- *Residual or distant metastatic disease : Poor prognosis*

Initial surgery

- ***Complete surgical resection** is the only potentially curative treatment .*
- ***It is particularly important to identify those with cortisol-producing tumors.***
- ***These patients, even those with mild hypercortisolism, have some degree of HPA axis suppression and require glucocorticoid coverage to prevent postoperative adrenal insufficiency .***

Initial surgery

- *For potentially resectable tumors invading adjacent organs, surgery often needs to be extensive, with en bloc resection of involved organs such as kidney, liver, spleen, pancreas, stomach, and colon .*
- *Intracaval extension or tumor thrombus is not a contraindication to surgery. resection may be facilitated by cardiopulmonary bypass .*
- *Suspicious lymph nodes should be resected, but the benefit of routine lymphadenectomy has not yet been established.*
- *ACCs often spread via lymphatic drainage.*
- *There was a significantly reduced risk for tumor recurrence and disease-related death in patients who underwent lymphadenectomy versus those who did not.*

occult micrometastases

- ***Although resection is technically possible for most patients with stage I to III disease it is not curative for many, presumably because occult micrometastases are present at the time of initial presentation, even with stage I disease .***

Routine debulking?

- *Even if the tumor cannot be removed entirely, some clinicians advocate maximal debulking as a means of improving survival , although others disagree as to the survival benefit of this strategy .*
- *Randomized trials to support routine debulking of nonresectable tumors are lacking, and decision making must be individualized.*
- *For patients with advanced functioning tumors, debulking may help to control hormone hypersecretion and increase the efficacy of further therapies .*
- *Patients with unresectable disease have a poor prognosis, surviving only three to nine months, and they are often better palliated with medical management.*

Neoadjuvant systemic therapy prior to surgery?

- The role of neoadjuvant systemic therapy prior to surgery for patients with locally advanced disease is not defined, and this is not considered a standard approach.

- In adults, one retrospective study suggested that patients with locoregionally advanced tumors with borderline resectable tumors might benefit from cisplatin-based neoadjuvant chemotherapy .

- Definitive evidence is still lacking, and therapeutic decisions should be individualized.

Laparoscopic versus open resection?

- *We suggest open rather than laparoscopic adrenalectomy for patients with ACC.*

- *The role of laparoscopic resection for ACCs is controversial, and open surgery remains the standard approach at least in our centers.*

- *European clinical practice guideline on adrenal incidentaloma recommends laparoscopic resection for tumors less than 6 cm even when ACC is suspected in the absence of local tumor invasion .*

Laparoscopic versus open resection?

- For tumors <6 cm without any evidence of local invasion (unknown if benign or malignant), laparoscopic adrenalectomy is reasonable if the surgeon has sufficient experience.

- This is not a widely accepted approach, and we suggest open rather than laparoscopic resection for known or highly suspected ACC, regardless of size .

Prognostic factors

- *The most important clinical factors that determine prognosis of ACC are **disease stage** and **completeness of resection .***

- *A modification has been proposed for the ENSAT staging system that incorporates histologic grade of differentiation **(table 2).***

Prognostic factors

- **Histology** : ***In addition to stage and completeness of resection, the biologic behavior of ACCs is also influenced by pathologic/morphologic factors.***
  (scoring system of Weiss) and ki 67.20%

Other factors

- *Older age at diagnosis and hypersecretion of cortisol have been recognized as adverse factors.*
- *Molecular predictors of malignant potential and survival are emerging, but none are ready for clinical use .*
- *Some reports suggest the value of mutated TP53, mutated b-catenin, ERCC1 , IGF2, SF1 , GLUT1, low expression of the SGK1 , and G0S2 hypermethylation are predictors of poor prognosis .*

TREATMENT AFTER INITIAL SURGERY*

- *Approach to adjuvant therapy :*
- *Decision to offer adjuvant therapy after resection is primarily based upon the risk of disease recurrence, which is influenced by three major prognostic factors: tumor stage, completeness of resection, and proliferation rate (as determined by the mitotic rate, MIB-1 staining, or Ki-67 expression)*
- *Patients at lower risk of recurrence typically have a good prognosis and may be candidates for surveillance. In contrast, those at higher recurrence risk may be candidates for adjuvant therapy, such as systemic therapy containing mitotane or radiation therapy.*
- *The use of molecular markers remains investigational.*

Patients with low recurrence risk

- *For most patients at low risk of recurrence after complete resection (stage I to III disease, microscopically complete [R0] resection, Ki-67 ≤10 percent), we suggest observation rather than adjuvant mitotane.*

Patients with low recurrence risk with potential risk of recurrence

- *Adjuvant mitotane may be appropriate for select patients who meet criteria for low-risk disease but also harbor some features that suggest a potential risk for recurrence.*

- *Examples include patients with stage III low-grade disease, or those with a large (>20 cm) stage II tumor with a borderline mitotic rate or Ki-67 score.*
- *If such patients are treated, a shorter duration would be appropriate(two years), with low threshold to discontinue mitotane if side effects are difficult to manage.*

Patients with low recurrence risk

- ***Observation alone** is also appropriate if patients also have a tumor **size <8 cm** and **no microscopic evidence of invasion** of blood **vessels** or the tumor **capsule**, in addition to the **criteria for low-risk disease.***

Patients with high recurrence risk

- ***Patients with high recurrence risk** : For patients at high risk of recurrence, we suggest the use of adjuvant **mitotane** use alone (without chemotherapy) rather than observation alone.*

Patients with high recurrence risk

Clinical features that indicate high recurrence risk include any one of the following:

- *Histologically high-grade disease (Ki-67 staining of >10 percent and <20 percent of tumor cells or >20 mitotic figures per 50 HPF regardless of tumor size .*
- *Incompletely resected disease .*
- *Intraoperative tumor spillage from tumor fracture or capsule rupture.*
- *Large, low-grade tumors with vascular or capsular invasion.*

Patients with very high recurrence risk

- *Although high-quality data are limited, patients at very high risk for an early recurrence (very high Ki-67 staining [≥20 percent]) and extensive vascular invasion/vena cava thrombus) may be offered an adjuvant regimen that includes the addition of cisplatin-based chemotherapy to mitotane.*

- *It is not known if cytotoxic chemotherapy alone or in combination with mitotane is more effective than adjuvant mitotane alone .*

Adjuvant mitotane

- ***Mitotane** (acongener of the pesticide **DDT**) is an adrenocorticolytic drug that has efficacy in patients with ACC .*

Duration

- ***High-risk ACC** : For patients with resected high-risk ACC, independent of stage, we aim to continue adjuvant mitotane for **three to five year**. The rationale for this duration is that it is very atypical for a patient with ACC to recur after four to five years.*

- ***Low-risk ACC** :**Observation** is preferred for most patients with resected low-risk ACC. However, for those with indications for adjuvant therapy, we aim for a minimum of **two years** of adjuvant mitotane . For patients **with low-risk disease and tumor spillage**, we will, at times, continue adjuvant therapy for up to **five years** if the drug is well tolerated .*

Dosage

- ***Suggested regimen*** *: While benefit of mitotane in the adjuvant setting has been reported using relatively low doses (1 to 3 grams daily) , current treatment protocols are based upon achieving* ***therapeutic mitotane serum levels.***

- *We suggest that all patients receiving mitotane (including those being treated for advanced disease) undergo therapeutic monitoring with plasma mitotane levels every four to six weeks.*

Mitotane initiation

- We initiate adjuvant treatment as soon as possible after surgery (within three months).
- Mitotane is initiated at 0.5 g twice per day and increased to 6 g/day over 4 to 12 weeks as tolerated, with monitoring of mitotane level every two to three weeks.
- Because of the long serum half-life and accumulation in adipose tissue, several weeks may be necessary to raise serum mitotane concentrations to the target level of 14 to 20 mcg/mL .
- When serum mitotane monitoring is not available, we suggest trying to push dosing to toxicity (up to 6 to 8 g per day) for patients with high-risk disease and adjust according to tolerability.

Mitotane

- ***Nausea** should be treated using **metoclopramide** or a serotonin (5-HT3) receptor antagonist such as **ondansetron.***

Monitoring response

- **Imaging** :

- Surveillance for ecurrence of disease should include contrast-enhanced CT scans (or MRI] of the chest, abdomen, and pelvis every three months for two to three years, then every four to six months for five years.

Monitoring response

- *The role of f (FDG -PET) in post-treatment monitoring is not yet established, some centers add integrated FDG-PET/CT at six-month intervals in the post-treatment follow-up strategy .*
- *integrated PET/CT detects more lesions than does PET or CT alone, and that PET should be considered a complementary examination to contrast-enhanced CT or MRI .(limited studies)*
- *PET was more sensitive than CT in detecting local recurrence, while CT was more sensitive in detecting small lung or peritoneal metastases .(one study)*

Monitoring

- **Biochemical** :
- *For patients with a completely resected, steroid-producing ACC, some groups monitor for recurrent hormone excess every three months for two years with steroid tumor markers such as cortisol in the morning before hydrocortisone dose, DHEAS, androstenedione, Te, estradiol, or mineralocorticoid based upon the steroid profile in the initial tumor.*

- *Other groups do not routinely screen for recurrent hormone excess unless or until there is evidence of recurrent disease.*

Monitoring

- *Mitotane, which increases serum CBG, may result in serum cortisol values that are artifactually elevated without significant changes in ACTH.*

- *Despite alterations in cortisol metabolism induced by mitotane, 24-hour urinary free cortisol excretion remains the best index of cortisol production currently available .*

Recommended monitoring during mitotane treatment*

Parameter	Interval	Comment
Mitotane blood level	Every 4 to 6 weeks¶	Target: 14 to 20 mcg/mL (mg/L).
Adverse effects	At every visit (initially, every 4 weeks; after 6 months, every 8 weeks)	Gastrointestinal adverse effects: Use antiemetics (eg, metoclopramide or a 5-HT3 blocker) or loperamide.
ACTH	Suspected glucocorticoid deficiency or excess	CNS side effects (ataxia, confusion, speech or visual problems): Interrupt therapy or reduce dosage. Glucocorticoid status is difficult to determine. Target: ACTH in the normal range or slightly above. Because of an increased glucorticoid clearance, high-dose glucocorticoid replacement is needed (most patients require at least 50 mg hydrocortisone per day).
Serum sodium and potassium	At every visit	
24-hour urine free cortisol	At every visit	Aim for mid-normal range.
GOT, GPT, bilirubin, 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 (greater than threefold of baseline), there is risk of liver failure: Stop mitotane.
TSH, fT3, fT4	Every 3 to 4 months	Disturbance of thyroid hormones is frequent. Thyroid hormone replacement is recommended in patients with clinical symptoms of hypothyroidism and low fT4 values.
Testosterone	Every 3 to 4 months	Hypogonadism frequently occurs. Replacement should be initiated in men with symptoms of hypogonadism.
Renin	Every 6 months	If renin is elevated, add fludrocortisone.
Cholesterol (HDL, LDL), triglycerides	Every 3 to 4 months (in an adjuvant setting)	If LDL or HDL cholesterol are highly elevated, consider treatment with statins.
Blood count	Every 3 to 4 months	Check for relevant leucopoenia, thrombocytopoenia, and anaemia (rare).

5-HT3: 5-hydroxytryptamine; ACTH: corticotropin; CNS: central nervous system; GOT: glutamic-oxaloacetic transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyltransferase; TSH: thyroid-stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; HDL: high-density lipoprotein; LDL: low-density

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

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
T1	N0	M0	I
T2	N0	M0	II
T1	N1	M0	III
T2	N1	M0	III
T3	Any N	M0	III
T4	Any N	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Toxicities

- Side effects : *The toxicity profile of mitotane limits tolerability, particularly at doses above 6 grams per day.*
- *The most common side effects are fatigue, nausea, vomiting, and anorexia, but skin rash, diarrhea, lethargy, sedation, confusion, dizziness, ataxia, gynecomastia, arthralgias, leukopenia, prolonged bleeding time, hematuria, and reversible growth arrest in children also occur .*
- *Other adverse effects include frequent hyperlipidemia LDL, HDL, TG, hypouricemia, and hepatotoxicity .*
- *If statins are used for the dyslipidemia, pravastatin and rosuvastatin should be considered as they have less drug interaction with mitotane.*

Toxicities

- *While increased concentrations of GGT and Alkp are almost invariably observed, a significant rise in transaminases or bilirubin is infrequent.*

Toxicities

- **Adrenal insufficiency** :
- ***Mitotane is a steroidogenesis inhibitor and adrenolytic drug. Glucocorticoid replacement therapy is necessary for patients treated with mitotane (unless the ACC is an advanced, glucocorticoid-producing tumor presenting as Cushing's syndrome).***
- ***Independent of the pharmacologic effects of mitotane, for patients with cortisol-secreting ACC, suppression of ACTH-adrenal axis will require replacement with glucocorticoids following complete tumor resection.***
- ***Very long-term use of mitotane usually induces atrophy and/or steroidogenic inhibition of the normal adrenal glands, thereby causing cortisol deficiency.***
- ***The zona glomerulosa is more resistant to the adrenolytic effect of mitotane, and aldosterone deficiency may not occur until after several months of therapy.***

Initiate glucocorticoid therapy

- *We suggest starting replacement glucocorticoid therapy when mitotane treatment is initiated because one cannot predict when a patient will become hypocortisolemic.*
- *For all patients who are receiving mitotane, we initiate replacement with hydrocortisone (30 to 40 mg daily in divided doses, two to three times per day). Of note, most patients eventually require a two- to threefold increase in hydrocortisone.*
- *In patients with residual ACC and persistent hypercortisolemia, glucocorticoid replacement should not be initiated until hypercortisolism is controlled with mitotane and steroid enzyme inhibitors.*
- *Several times the usual maintenance doses of glucocorticoids are sometimes needed as the induction of hepatic cytochrome P450 enzymes by mitotane increases the rate of metabolism of cortisol, dexamethasone , and fludrocortisone*

- ***Inadequately treated adrenal insufficiency** enhances mitotane-induced side effects and reduces drug tolerance .*

- ***A brief trial of a higher glucocorticoid dose** may mitigate some side effects that could be attributable to inadequate cortisol replacement and allow continuation of mitotane at the same dose.*

Monitoring

- *Close monitoring of blood sodium, potassium, creatinine, ACTH, and 24-hour urine free urinary cortisol levels is necessary to avoid adrenal insufficiency and acute hyperkalemia in patients treated with mitotane.*
- *Measurement of serum mitotane levels together with 24-hour urine free cortisol with an assessment of side effects should guide mitotane and hydrocortisone dosing.*
- *If side effects do not abate with glucocorticoid therapy, temporary discontinuation of mitotane is indicated, followed by reinstitution at a lower dose.*
- *Measuring cortisol levels in hair may eventually become useful to assess chronic hydrocortisone replacement in ACC .*

Monitoring

- ***Aldosterone** deficiency : Mitotane can also eventually cause aldosterone deficiency.*
- *Unlike glucocorticoid replacement, we do **not start mineralocorticoid** replacement **right away.***
- *We suggest monitoring **blood pressure at each visit**, **serum potassium at every three months,** and plasma **renin every six months** .*
- *Mineralocorticoid deficiency should be suspected if the patient **develops postural hypotension**, **hyponatremia**, or **hyperkalemia** and has an elevation in plasma **renin activity**.*
- *When clinical and biochemical signs of aldosterone deficiency become present, we suggest starting **fludrocortisone (0.1 to 0.3 mg daily**) to restore normal clinical and biochemical parameters . metabolism of fludrocortisone is increased by mitotane.*

Stopping mitotane and monitoring for recovery

- *After stopping mitotane therapy, hydrocortisone therapy should be continued but progressively decreased to more physiologic levels (as mitotane acceleration of glucocorticoid metabolism returns to normal) until the patient has no clinical or biochemical evidence of adrenal insufficiency.*
- *Patients should be evaluated for potential recovery of adrenal insufficiency every six months by measuring morning levels of serum cortisol before intake of hydrocortisone replacement.*
- *Although adrenal insufficiency may become permanent in some patients, depending upon the duration of mitotane therapy, it may recover in others.*

Reproductive issues

- *In men receiving mitotane therapy, **hypogonadism** is common, often requiring replacement testosterone therapy.*

- *In addition to its effect on CBG, mitotane increases serum SHBG. In addition to potential decreases in **free Te** levels, mitotane induces a **strong inhibition** of **5-alpha-reductase activity**, which may explain the relative inefficiency of testosterone replacement in mitotane-treated men .*

- *Te should be measured routinely in men receiving mitotane .*

Reproductive issues

- *The impact of mitotane on reproductive function in women is less clear. Increased levels of both (**LH**) and (**FSH**) have been observed, which in some premenopausal women has resulted in the development of **large ovarian cysts** . These cysts may be associated with lower abdomen discomfort and pain; cases of **ovarian torsion** requiring surgery have also been observed.*

pregnancy

- *There are concerns that pregnancy could lead to an increased likelihood of relapse, although data are minimal .*
- *The safety of mitotane during pregnancy is unknown.*
- *For women of reproductive age scheduled to receive adjuvant mitotane therapy after ACC resection, we suggest contraception during and for at least one year after mitotane as the drug has a long half-life and is deposited in adipose tissues.*
- *We suggest barrier methods of contraception as mitotane accelerates steroid metabolism and may decrease the contraceptive efficacy of hormonal contraception.*

Hypothyroidism

- *Hypothyroidism : mitotane increases serum TBG.*
- *Free T4 may be decreased .*
- *mitotane has a direct inhibitory effect on secretion of TSH.*
- *Thyroid function tests should be monitored periodically .*
- *Hypothyroidism with low TSH is frequent, and free T4 should be monitored.*
- *Thyroid hormone replacement is suggested in patients with clinical symptoms of hypothyroidism and low free T4 values.*

Drug interactions

- *Mitotane is a potent inducer of CYP3A4 metabolism. Limited data suggest that this can result in important drug-drug interactions .*
- *In a report of two patients with ACC who were receiving mitotane in combination with sunitinib (a drug metabolized by CYP3A4), serum sunitinib concentrations were decreased by approximately 80 percent of expected values .*
- *Although clinical data are currently unavailable, mitotane administration could reduce the efficacy of other drugs relevant to the management of patients with ACC, such as steroid hormone replacement, benzodiazepines, macrolide antibiotics, some opioids and statins, and dihydropyridine type calcium channel antagonists .*

Adjuvant radiation therapy

- ***Data** on the usefulness of adjuvant radiation therapy following surgical resection has been **limited**.*
- *The European Society of Endocrinology clinical practice guidelines panel suggest **against the routine use** of radiation therapy in patients with **stage I to II and R0 resection.***
- *They suggest considering radiation in addition to mitotane therapy in patients with **R1 or Rx** resection or in **stage III** .*

Postoperative radiation therapy

- We suggest the addition of postoperative radiation therapy (RT) for all patients with incompletely resected ACC, stage III disease with other characteristics of high recurrence risk, those who have tumor spillage at the time of resection, and for all patients with high-grade ACC (>20 mitotic figures per 50 HPF).

- The benefit of adjuvant RT is limited to improved local control; no clear survival benefit has been shown except in one study.

- We suggest starting RT as soon as possible following surgery (ideally within 12 weeks).


Thanks

- *we suggest that **adjuvant RT** should be considered a part of **multidisciplinary** management for patients with ACC.*

adjuvant RT

- *Our approach is similar to recommended adjuvant RT for all patients with microscopically incomplete (R1 or R2) or uncertain (Rx) margin status and for those with stage III disease (according to ENSAT criteria even if resection has been complete .*
- *They suggest that adjuvant RT be considered for patients who have had a complete (R0) resection of a tumor >8 cm in size with tumor invasion of the blood vessels (but not large tumor thrombus in the vena cava) and a Ki-67 proliferative index of >10 percent, and for patients who have intraoperative violation of the tumor capsule, tumor spillage, or dissemination of "necrotic" fluid.*
- *Because the risk of a local recurrence is highest in the first two years, they recommend starting RT no later than three months after surgery.*

adjuvant RT

- *There is disagreement as to the role of adjuvant RT in patients who have undergone laparoscopic rather than open resection, and there are no published data to help in resolving this point.*
- *There are different opinions regarding the safety and efficacy of laparoscopic resection of primary ACC.*
- *It is understandable that there are different opinions regarding the use of adjuvant RT in the setting of laparoscopic resection for a resected ACC that does not otherwise meet the criteria described above for adjuvant RT (tumor spillage at the time of resection, incompletely resected, high-grade lesion).*
- *The German ACC group does not recommend adjuvant RT in this situation.*

RECURRENT OR ADVANCED ADRENOCORTICAL CANCER

- *There is no curative therapy for metastatic or recurrent ACC.*
- *Symptoms of steroid excess can be controlled by medical therapy.*
- *In most cases, metastatic disease is fatal within one year, although there are rare long-term responses ascribed to chemotherapy with or without mitotane .*

Local therapy

- **Surgery** :*For patients with isolated, locally recurrent ACC that is surgically accessible, we suggest complete surgical resection followed by mitotane therapy.*
- *Where complete removal is feasible, **aggressive surgical resection** of locally recurrent disease, with the aim of achieving negative surgical margins, should be undertaken .*
- *The best candidates are those who have potentially resectable disease with a disease-free interval of at least **one year** after initial treatment.*

Local therapy

- ***Resection** may also be considered in the rare patient who presents with synchronous limited, potentially resectable **hepatic or pulmonary** metastases .*
- *Resection of locally recurrent disease may also be indicated for patients in whom surgery will be able to **remove a majority of tumor burden** or decrease **severe hypercortisolism** that is otherwise difficult to control;*
- *This approach should be **limited to selected patients** with uncontrollable symptomatic hormone excess or who are in imminent danger from organ invasion or compression.*
- *Aggressive resection of locally recurrent or distant disease may **prolong survival** in some patients.*

Radiation therapy

- *For palliation of symptoms from locally advanced or distant metastatic disease (eg, a bone metastasis), we use palliative radiation therapy (RT).*

- *The available data support the palliative benefit of RT for unresectable local tumor that is causing local symptoms or for distant symptomatic metastases, such as in bone .*

- *Stereotactic radiosurgery may be beneficial for patients who have a good performance status and limited metastases to the brain, lung, or liver.*

Radiofrequency ablation :

- *Percutaneous RFA may provide short-term local control of an unresectable primary tumor, particularly for those <5 cm in diameter .*
- *The long-term impact on survival is unknown.*
- *RFA has also been used to treat small liver metastases .*

Systemic therapy

- **Mitotane monotherapy** :

- **Primary treatment with mitotane may be indicated for patients who have histologically proven ACC in whom surgery is incomplete, not feasible, or contraindicated.**
- **The quality of the available literature on mitotane monotherapy is poor, and the results are highly variable.**

Mitotane monotherapy

- ***The main benefit of mitotane for patients with unresectable advanced disease is usually reduction in symptoms of hypercortisolism (weakness, myopathy, diabetes, immunosuppression, insomnia).***

- *We reserve **mitotane monotherapy** for the few patients who have a minimal burden (low number of tumor-involved organs) of low-grade (ie, low mitotic rate) disease and have recurred relatively late (two to three years) after surgery.*
- *These are the patients who are likely to have a **prolonged survival** .*
- *In the setting of extensive (multiple tumor-involved organs), rapidly progressive, high-grade disease, **mitotane** is almost always administered in combination with **cytotoxic chemotherapy** because of a generally accepted view that response rates are higher.*

- *For patients with **active disease** and **visible lesions**, **mitotane** is typically **continued lifelong** or until disease progression.*

- ***For patients whose disease progresses while receiving adjuvant mitotane, or whose disease is high grade or rapidly progressing (on or off mitotane), our usual practice is to initiate cytotoxic chemotherapy, oftentimes while continuing mitotane, given the higher response rates.***

Cytotoxic chemotherapy

- *Many cytotoxic drugs have been studied in patients with advanced ACC, either **alone or in combination with mitotane.***

- *Although they are frequently used, single agents such as cisplatin or doxorubicin are associated with response rates that are generally less than 30 percent and of short duration .*

- *Results are disappointing for chemotherapy combinations when not combined with mitotane*

Chemotherapy plus mitotane

- ***Better outcomes*** *than does mitotane alone.*

- *In the setting of* ***extensive*** *(multiple tumor-involved organs), rapidly* ***progressive, high-grade*** *disease, mitotane is almost always administered in combination with cytotoxic chemotherapy. (etoposide, doxorubicin, and cisplatin (EDP).*

Chemotherapy plus mitotane

- ***Although no chemotherapy regimen has been shown to improve overall survival (OS) in patients with advanced ACC, some of the more encouraging results have been with the combination of EDP plus mitotane:***

- ***Results with other chemotherapy drugs combined with mitotane seem to be less promising.***

Newer and investigational approaches

- **Immunotherapy** : *Programmed cell death ligand (PD-L1) is expressed in some ACCs and their associated tumor infiltrating lymphocytes, leading to interest in the use of checkpoint inhibitor immunotherapy in these patients.*

- ***Pembrolizumab** has shown a good safety profile and response rates ranging from 14 to 50 percent in phase II studies conducted in both adult and pediatric populations .*

IGF1R inhibitors

- ***80 percent** of ACCs overexpress **IGF-2**, which is known to signal predominantly through the IGF-1 receptor (IGF1R).*

- *phase I-II trial of the anti-IGF1R antibody **cixutumumab** demonstrated only limited overall efficacy .*

- *Although we **do not offer IGF1R inhibitors** in patient with advanced ACC, further studies may determine molecular markers that can predict which patients may benefit from this approach.*

VEGF inhibitors

- *Vascular endothelial growth factor **(VEGF)** is **upregulated in ACC** tumor tissue, and some studies have found that circulating VEGF levels are significantly greater in patients with ACC as compared with those with adrenal adenomas.*

- *While case reports suggested activity of the antiangiogenic agents thalidomide , **sorafenib,** and **sunitinib** , subsequent phase II trials have demonstrated limited efficacy of VEGF inhibitors.*

Radionuclide therapy

- *ACC can also be targeted with **therapeutic radionuclides.***

- *Examples of active radionuclides include iodine-131-metomidate and agents that target 11-beta-hydroxylase such as (R)-1-[1-(4-[131-I]iodophenyl)ethyl]-1H-imidazole-5-carboxylic acid azetidinyl .*

Medical treatment of hormone excess

- **Hypercortisolism** :
- *Adrenal function should be closely monitored in patients with ACC because they can have either adrenal insufficiency (caused by surgery or mitotane) or excess cortisol secretion (caused by persistent or recurrent tumor).*
- *In patients with hypercortisolism (either those who are not taking mitotane or those whose hypercortisolism is not controlled by mitotane), addition of a more specific **adrenal enzyme inhibitor** is often required.*
- *Control of hypercortisolism is important as patients can die prematurely of infections related to immunosuppression induced by their hypercortisolism and chemotherapy rather than by tumor burden.*

Medical treatment of hormone excess

- *we consider **metyrapone** as the first drug of choice in patients with ACC and hypercortisolism.*
- *While **ketoconazole i**s effective in benign adrenal disease, it is rarely able to control the hypercortisolism in ACC.*
- *Metyrapone, achieving eucortisolemia within **three to seven days.***
- *If eucortisolism is not achieved with metyrapone, combination therapy with ketoconazoleand mitotane can be utilized.*

Medical treatment of hormone excess

- *For patients with ACC, we suggest **metyrapone** starting at 250 mg four times daily and increasing up to 6 g per day.*
- *If metyrapone alone is insufficient or not tolerated, **ketoconazole** is started at 200 mg three times/day, increasing daily as needed to 400 mg three times/day.*
- *Higher doses are seldom more effective.*
- *Their effect can be assessed within a few days by measuring 24-hour urine cortisol on a frequent basis initially.*
- *Combination of both drugs and mitotane may be necessary to achieve adequate control.*
- *In severe uncontrolled cases, addition of **mifepristone**, a glucocorticoid receptor antagonist, can be beneficial .*
- *In acute situations with patients who are unable to take drugs orally, **intravenous etomidate** (which blocks 11-beta-hydroxylase) can be used in a low, nonhypnotic dose of 0.3 mg/kg per hour.*

- *Adrenal insufficiency is managed as described above using replacement mainly with hydrocortisone. Aldosterone deficiency is replaced with addition of fludrocortisone (0.1 to 0.3 mg daily) and adjusted to restore normal blood pressure and serum levels of potassium and renin.*
- *For patients who have increased hypercortisolism and are being treated with metyrapone, salt retention and hypertension can occur because of increased production of the mineralocorticoid deoxycorticosterone.*
- *We routinely use a mineralocorticoid receptor inhibitor (spironolactoneor eplerenone) or amiloride in this situation, adding diuretics and additional antihypertensive drugs if necessary.*

- *When potassium-sparing diuretics are used in association with potassium supplements.*

- *Frequent serum potassium monitoring is necessary as acute hyperkalemia can occur when hypercortisolism becomes controlled or when renal function is impaired.*

- *Adequate control of diabetes and high blood pressure are also important.*

- **Other** :A small percentage of adult ACC and a high percentage of pediatric ACC often presents with virilization with/without hypercortisolism. Virilization is best treated ***with specific androgen blockage*** with androgen receptor inhibitors (bicalutamide at 50 mg per day) or 5-alpha-reductase inhibition (finasteride at 5 mg per day).

- *While **spironolactone** is often used to control androgen effects in women with androgen excess in the setting of benign disease, it is often ineffective in the setting of ACC with very high serum androgen concentrations.*

- *Rare estrogen-producing ACCs are treated with any of the **antiestrogen** therapies (such as tamoxifen).*

PROGNOSIS

- *Overall, survival is **poor** for adrenocortical carcinoma (ACC)*
- *Five-year survival is approximately **45 to 60** percent for early stage disease and 10 to 25 percent for advanced stage disease .*
- *Past results suggested a poor prognosis even for patients with early stage disease .*
- *contemporary series suggest that **outcomes are improving** and that patients with these tumors are living longer.*

SPECIAL POPULATIONS

- **Clinicopathologic characteristics**
- ●**Familial cancer syndromes** – Most children with adrenocortical tumors have associated familial cancer syndromes (mainly Beckwith-Wiedemann syndrome and Li-Fraumeni syndrome)
- ●**Histopathology** – Unlike adults, severe histopathologic features in children, such as high Weiss score, are not reliable predictors of poor prognos.
- ●**Germline mutations in TP53** – 50 percent or more of pediatric patients with ACCs in North America have germline mutations in the *TP53* gene (which encodes the p53 tumor protein) .
- 8 percent of adults have these mutations . Loss of heterozygosity for 17p13 (the cytogenetic location of the *TP53*gene) occurs in 25 to 70 percent of sporadic ACCs.

Prognosis

- *The prognosis in children who have ACC appears to be better than that of adults, especially those for those with early-stage disease .*
- *Stage I disease (completely excised nonmetastatic tumors ≤200 g), presenting signs of virilization alone, and age less than three years were all associated with significantly better survival.*
- *The prognosis was poor for patients with metastatic or residual disease or larger resected tumors (weighing more than 200 grams).*

Management

- **Stage I disease** – Adrenalectomy alone
- **Stage II disease** – Adrenalectomy and retroperitoneal lymph node dissection
- **Stage III or IV (metastatic) disease** – Mitotane plus chemotherapy (etoposide, doxorubicin, and cisplatin [EDP]), followed by surgery of the primary tumor and metastases as clinically indicated.

Prognosis

- At median follow-up of 60 months, the five-year EFS and overall survival (OS) results were:
- ●**All patients** – 63 and 77 percent
- ●**Stage I** – 86 and 95 percent
- ●**Stage II** – 53 and 79 percent
- ●**Stage III** – 81 and 95 percent
- ●**Stage IV** – 7 and 16 percent


Thanks