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Rare Diseases

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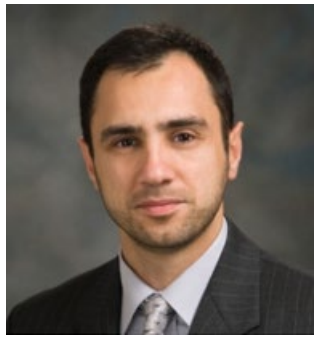
Clinical Management of Adrenocortical Carcinoma (ACC)

LYS-US-0020

Presenter



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Disclosures

Exelixis:
Research support

HRA Pharma Rare Diseases:
Consultant

Corcept Therapeutics:
Consultant

Calico:
Consultant

Objectives

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- Review the epidemiology, clinical features, diagnosis, staging, and prognosis of adrenocortical carcinoma
- Summarize the management of advanced adrenocortical carcinoma
- Discuss the use of mitotane in ACC (dosing, adverse effects, and monitoring)

Introduction to ACC

Definition

Epidemiology

Epidemiology of ACC

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ACC: malignant tumor of the cortex

Adrenocortical carcinoma (ACC) is a malignant tumor of the adrenal cortex[1]

ACC is an orphan disease

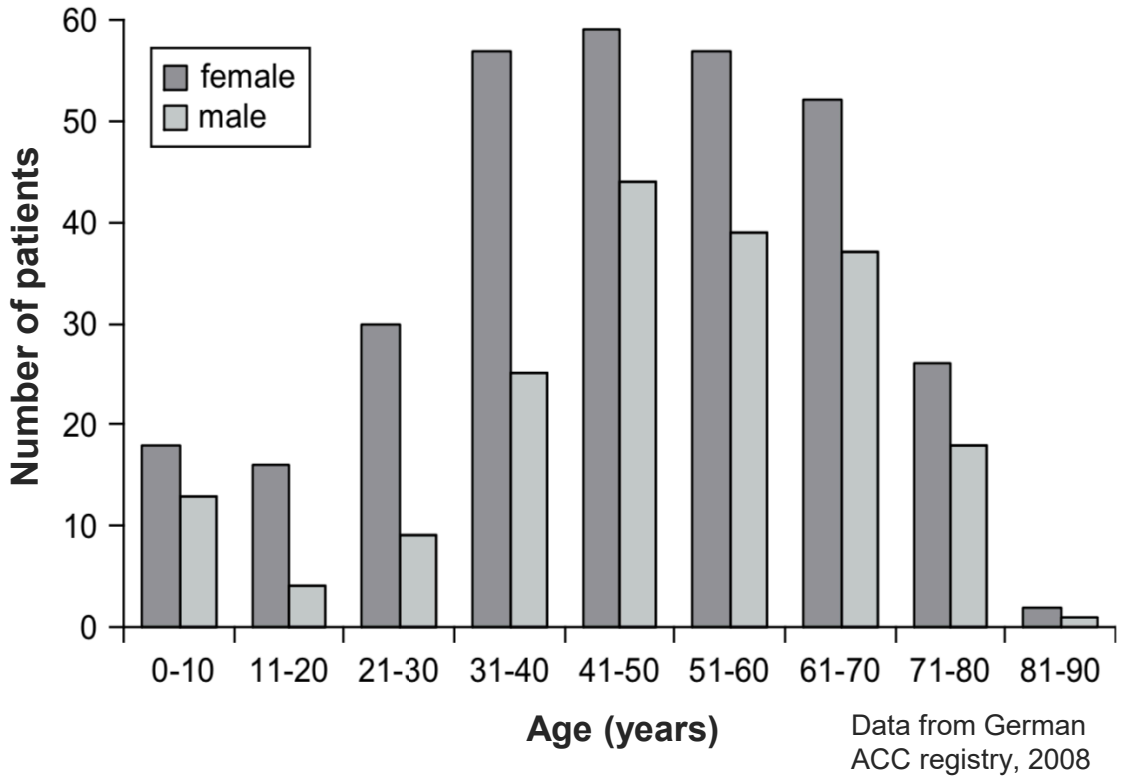
- Incidence: 1-2/million/year[1,2]
- ACC affects more women than men (ratio: 1.5:1)[2]

It has a **bimodal distribution**[1]

- Adults 40-55 years old[3,4]
- Children younger than 10 years

Worldwide incidence in children: 0.2 to 0.3 per million per year (although may be higher in particular populations)[3]

Age/Sex distribution at diagnosis of ACC[2]



Data from German ACC registry, 2008

ACC: adrenocortical carcinoma

1.Allolio B, Fassnacht M. *J Clin Endocrinol Metab.* 2006;91(6):2027-37.
2.Fassnacht M, Allolio B. *Best Pract Res Clin Endocrinol Metab.* 2009;23(2):273-89.
3.Else T, *et al. Endocr Rev.* 2014;35(2):282-326.
4.Jasim S, Habra MA. *Curr Oncol Rep.* 2019;21(3):20.

Diagnosis

Work-Up

Imaging

Diagnostic work-up for ACC

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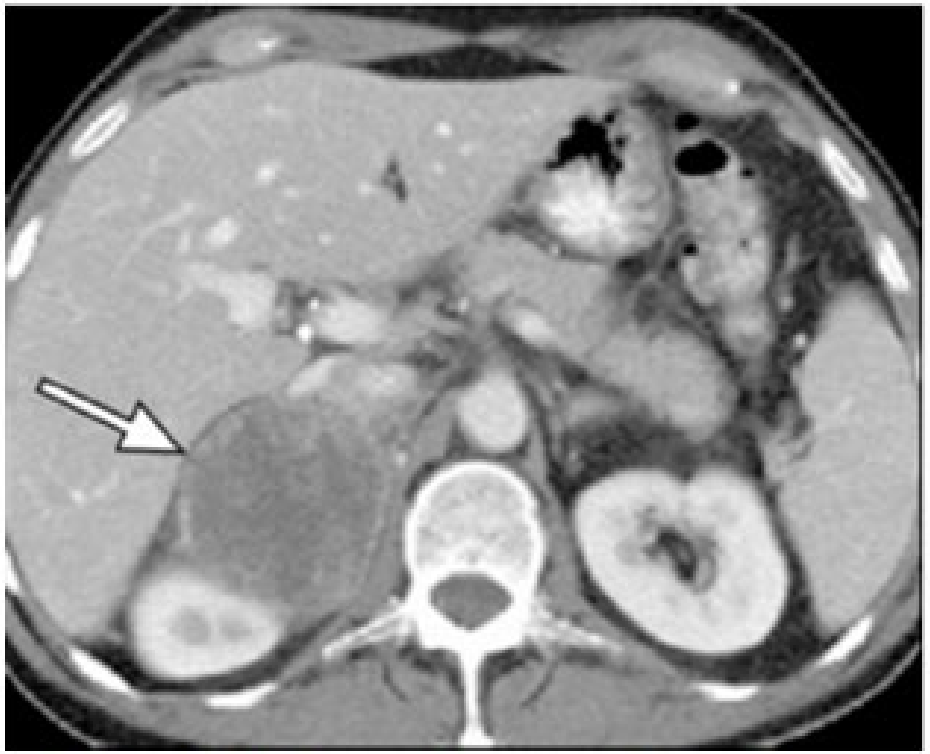
Hormonal work up	
Glucocorticoid excess	• 1-mg dexamethasone suppression test or free cortisol in 24-h urine[1] • Basal ACTH (plasma)[2]
Sex steroids and steroid precursors[3]	• DHEA-S • 17-OH-progesterone • Androstenedione • Testosterone (only in women) • 17-beta-estradiol (only in men and postmenopausal women) • 11-deoxycortisol
Mineralocorticoid excess	• Potassium • Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalaemia)
Exclusion of a pheochromocytoma	Fractionated metanephrines in 24h urine or free plasma-metanephrines
Imaging	
	• CT or MRI of abdomen and pelvis • Chest CT • FDG-PET/CT[4] • Bone or brain imaging (when skeletal or cerebral metastases are suspected)

1. The 1-mg dexamethasone test is the preferred method to exclude relevant hypercortisolism. However, if overt Cushing syndrome is evident, then cortisol in 24-h urine might be at least as good to quantify the cortisol excess. Alternatively, salivary or serum bedtime cortisol can be used.
2. ACTH can be skipped if hypercortisolism is excluded.
3. The most suitable set of precursors and sex hormones has not yet been established and local availability might be taken into account.
4. The panel did not agree on the systematic use of FDG-PET/CT.

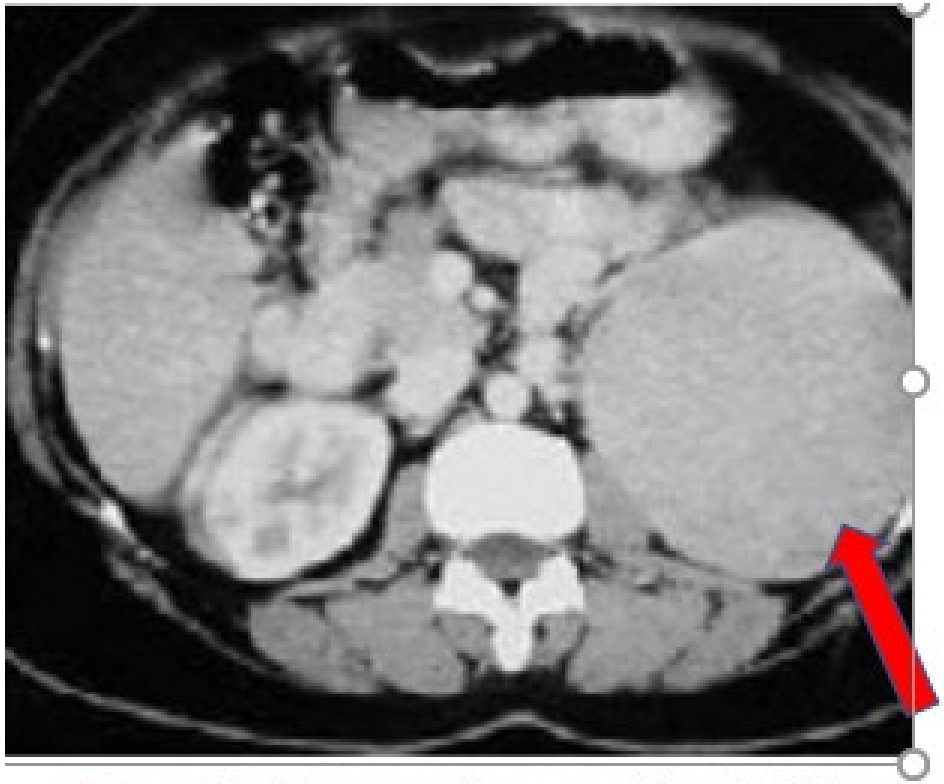
ACC: adrenocortical carcinoma; ACTH: adrenocorticotropic hormone; CT: computerized tomography; DHEA-S: Dehydroepiandrosterone sulphate, FDG-PET: fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging.

Fassnacht M, et al. *Eur J Endocrinol.*2018;179(4):G1-G46.

Imaging Diagnosis



Computed tomography scan showing large adrenocortical carcinoma, with internal haemorrhage, necrosis, and calcification[1]



Computed tomography scan with axial view of left adrenocortical carcinoma[2]

1.Elsayes KM, Caoili EM. *Appl Radiol.* 2011;40(9):14-9.
2.Panchani R, *et al. Indian J Endocrinol Metab.* 2012;16(Suppl 2):S378-81.

Staging classification
Prognostic factors

Staging systems for ACC[1]

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Stage	ENSAT
Stage 1	T1, N0, M0
Stage 2	T2, N0, M0
Stage 3	T1–2, N1, M0 T3– 4, N0, M0
Stage 4	T1– 4, N0 –1, M1

ENSAT requires extensive imaging; systematic lymph node resection; a complete surgical and pathological reports [2]

T1: ≤5-cm tumour; T2: >5-cm tumour; T3: tumour infiltration into surrounding tissue; T4: tumour invasion into adjacent organs; N0: no positive lymph nodes; N1: positive lymph node(s); M0: no distant metastases; M1: presence of distant metastasis[2]

1.Else T, *et al. Endocr Rev.* 2014;35(2):282-326.
2.Fassnacht M, *et al. Eur J Endocrinol.* 2018;179(4):G1-G46.

Prognosis

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Prognosis of ACC is generally poor and depends on the stage[1]

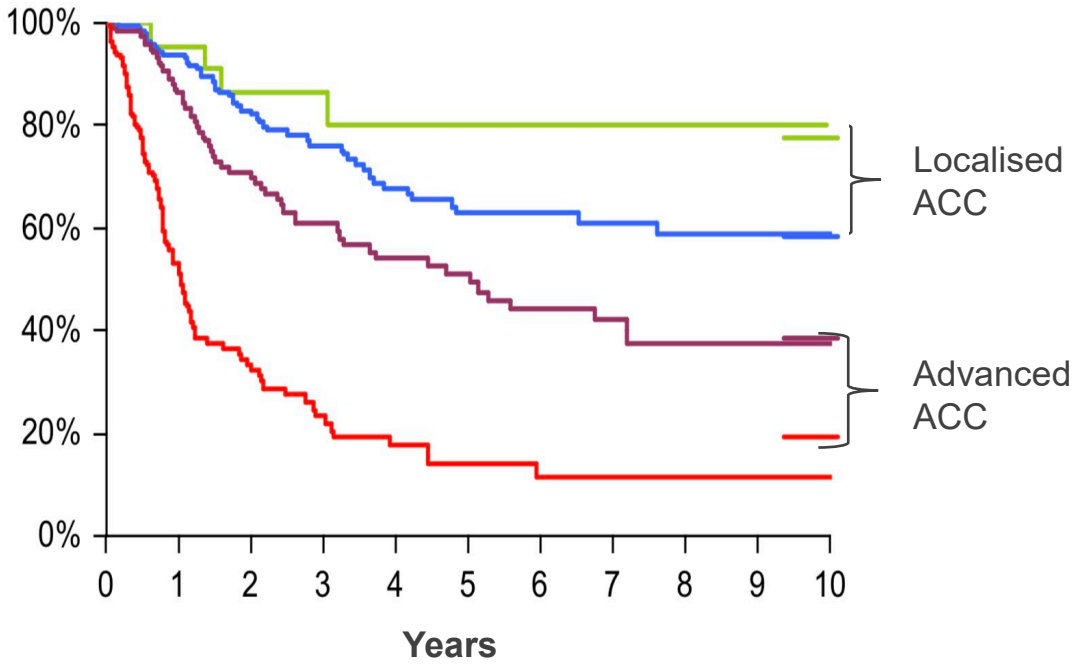
- Diagnosed at advanced stages in older series, but in the recent ones, highest percentage of patients were diagnosed in stage II through available imaging technology

Prognosis depends on stage[3]

- ACC has a poor prognosis
- Overall survival at 5 years is 13%-82%

Stage	5-year stage-dependent survival
I	82%
II	61%
III	50%
IV	13%

Disease-specific survival according tumour stage[2]



ACC: adrenocortical carcinoma

1.Fassnacht M. Allolio B *J Clin Endocrinol Metab.* 2006;91(6):2027-37.
2.Fassnacht M. Aliolio B *Best Practice & Research Clinical Endocrinology & Metabolism* 23 (2009) 273-289
3.Fassnacht M, *et al. Cancer.* 2009;115(2):243-50.

Hormonal Overproduction in ACC

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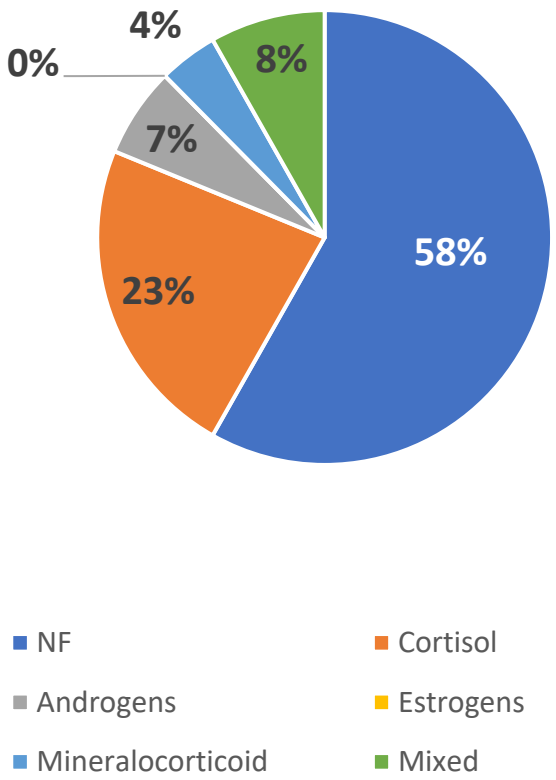
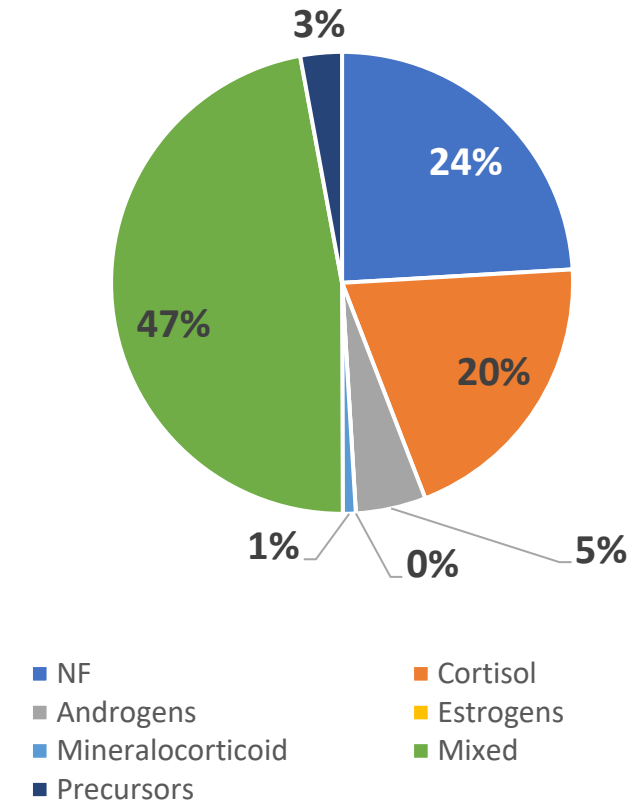
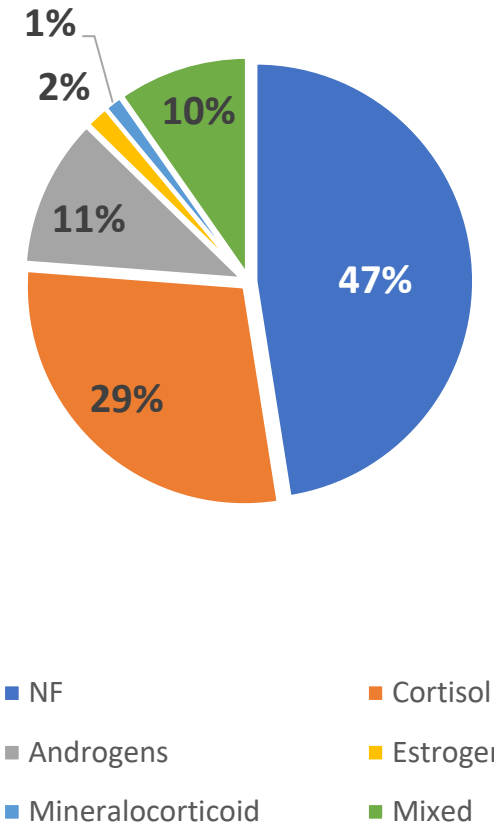
Adapted from Ayala-Ramirez et al
***EJE*, 2013**



Adapted from Abiven et al.
***JCEM*, 2006**



Adapted from Berruti et al.
***European Urol*, 2014**



Prognostic Factors: **Hormonal Activity**

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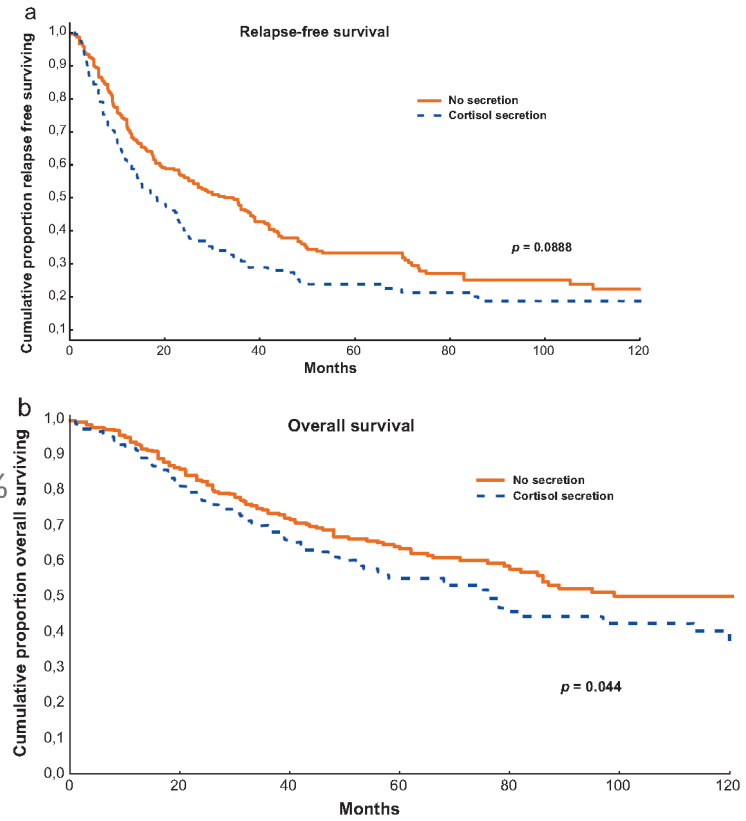
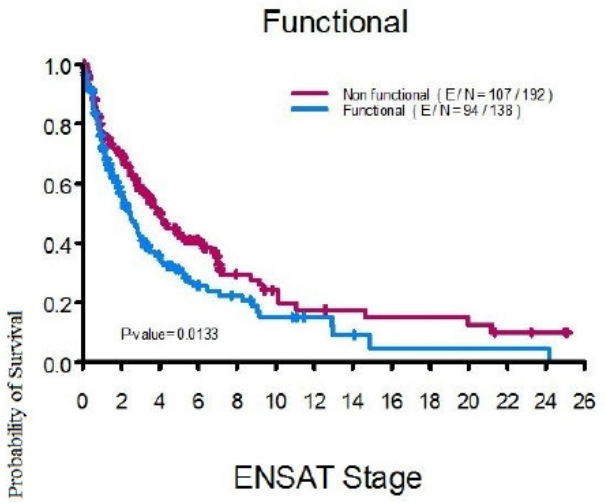
MV analysis: HR: 1.30; 95% CI, 1.04-2.62; $p = 0.02$)

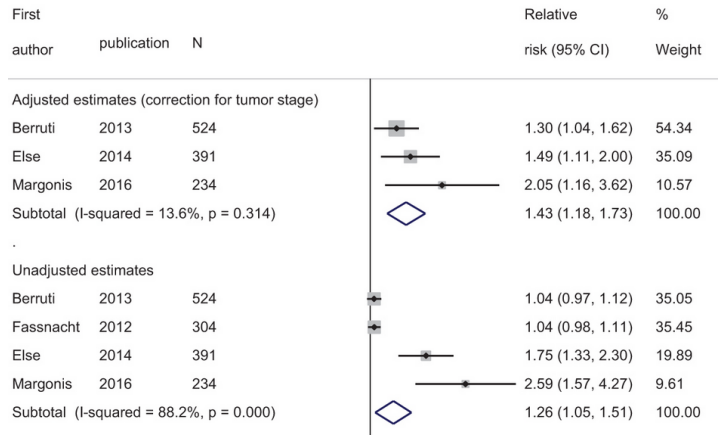


Berruti et al. *European Urology,* 2014



Ayala-Ramirez et al. *EJE*, 2013

RR of cortisol production for Recurrence Free Survival



Vanbrabant et al. *EJE*. 2018

Prognostic Factors: **Proliferation Rate (Ki67%)**

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Ki-67 immunohistochemistry has been proposed for prognosis purpose[1]

- The Ki-67 protein is highly expressed in cycling cells[1]
- It has thus been reliably used as a proliferation marker for grading multiple cancers and differentiating benign from malignant cancer[2]

1.Sun X, Kaufman PD. *Chromosoma*. 2018;127(2):175-86.
2.Else T, *et al. Endocr Rev.* 2014;35(2):282-326..

Prognostic Factors: **Proliferation Rate (Ki67%)**

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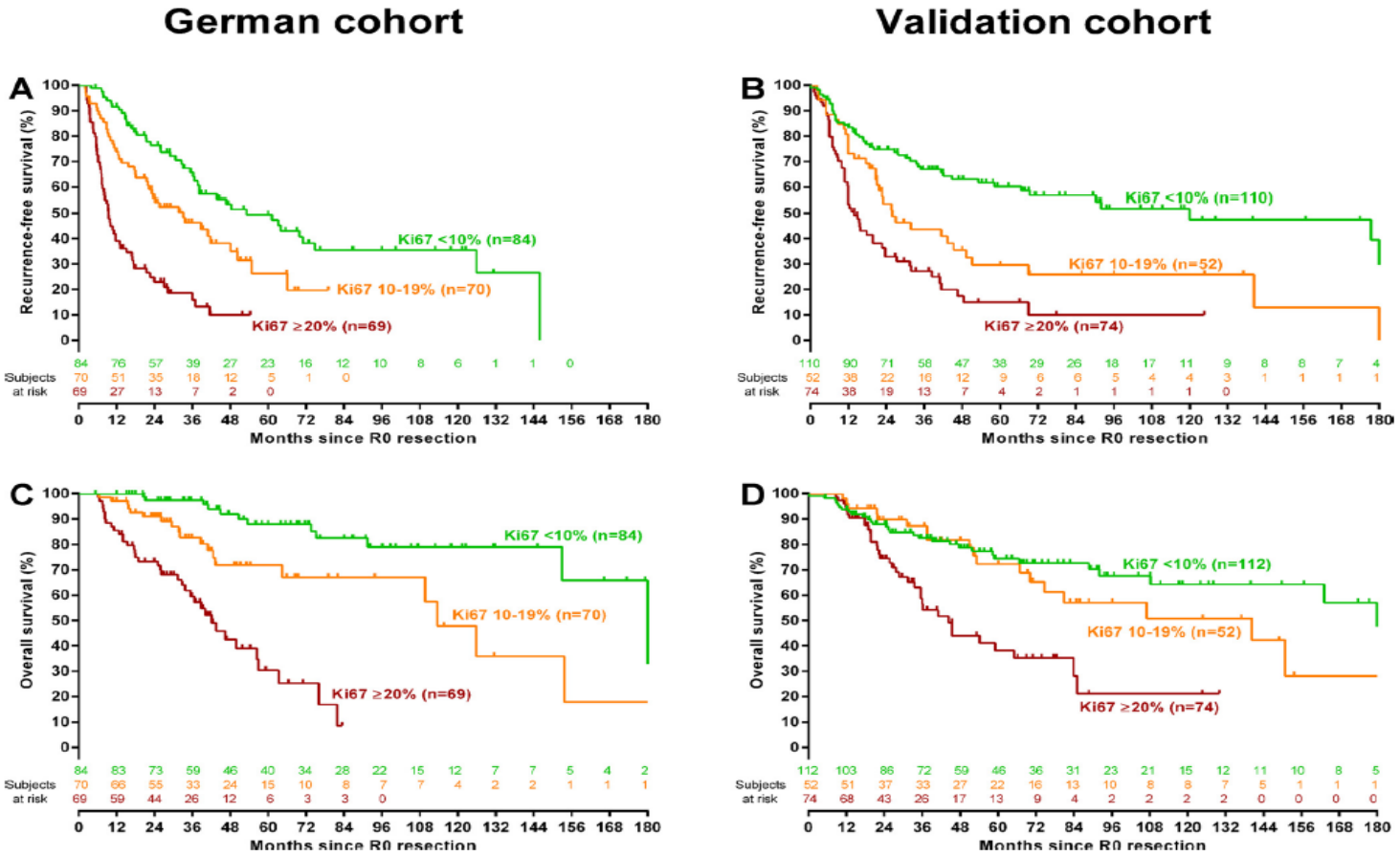

Major Prognostic Role of Ki67 in Localized Adrenocortical Carcinoma After Complete Resection

Beuschlein et al. *J Clin Endocrinol Metabol,* 2015

Prognostic Factors: **Resection Margin**

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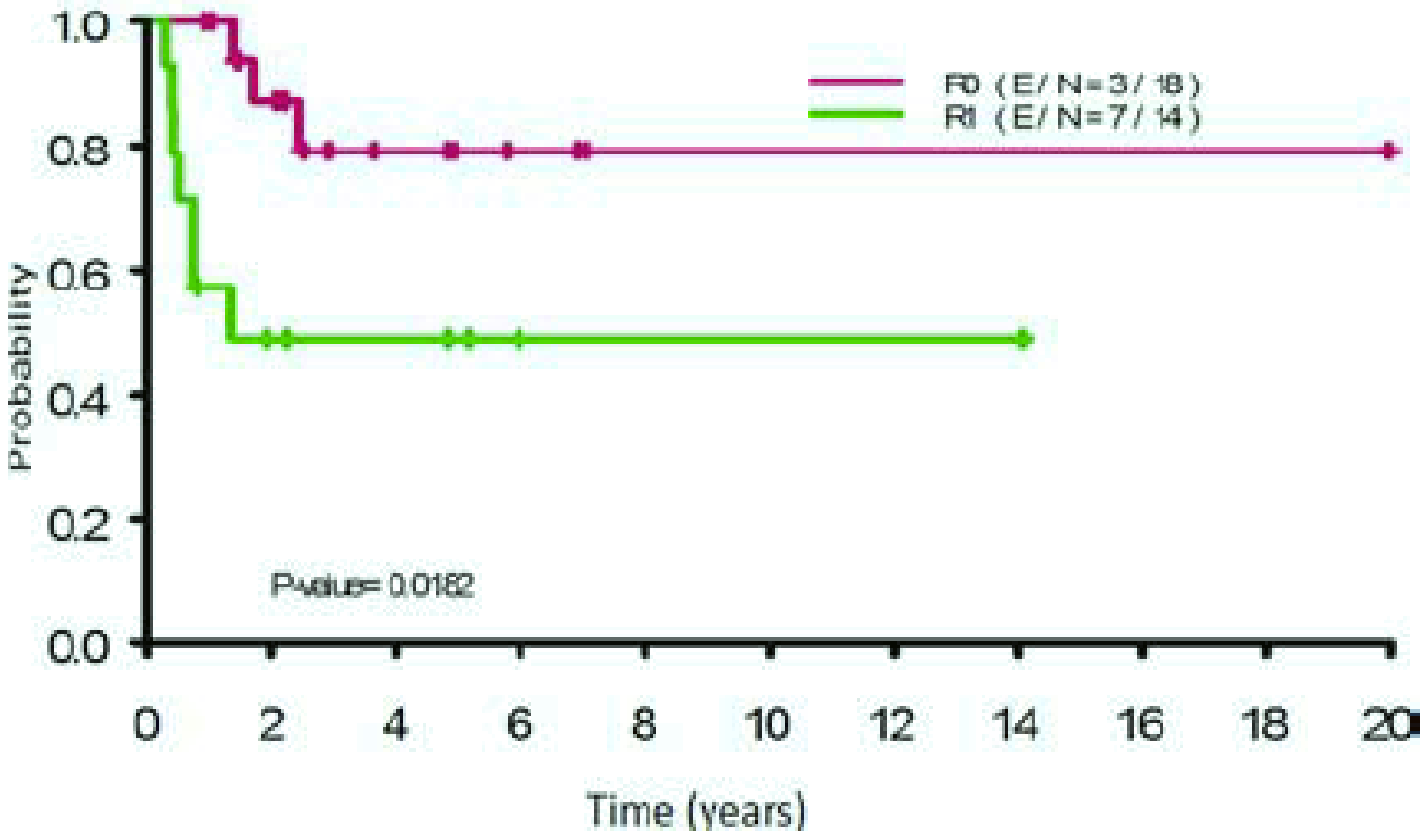

Effect of resection Margin on local recurrence
(R0: negative margin) vs.
(R1: microscopically positive)

Ayala-Ramirez M et al. *EJE* 2013

ACC Management

European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the Study of Adrenal Tumors.

Fassnacht M, *et al. Eur J Endocrinol.* 2018;179(4):G1-G46.

Recommended treatments for Localized ACC

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- Preoperative Management
- Surgical Management
- Surveillance

Fassnacht et al. *Eur J Endocrinol,* 2018

Recommendations advanced ACC not amenable to Resection

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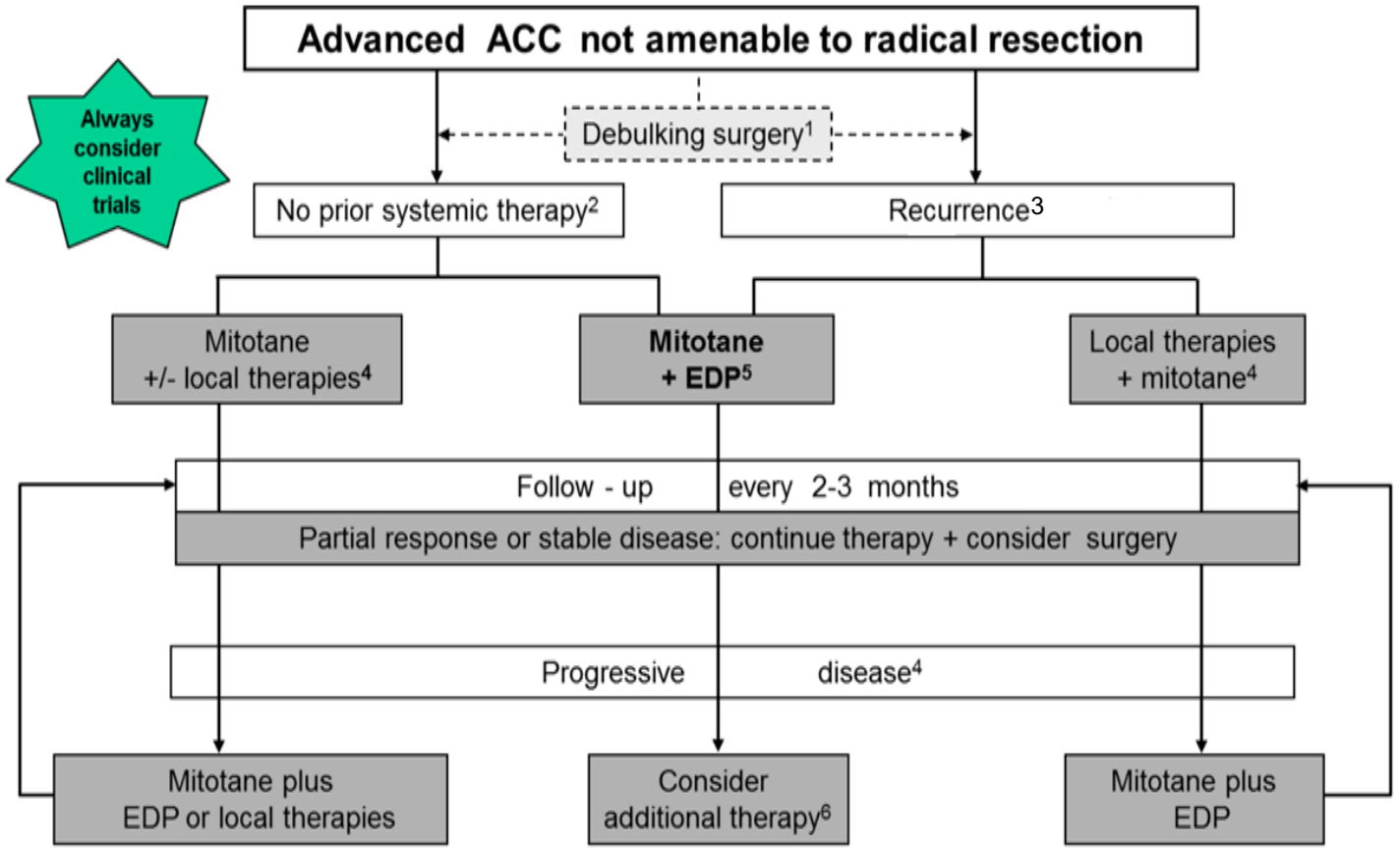

1. Only in **selected patients (with severe hormone excess)**
2. The following factors might guide the decision: site of disease involvement, tumor burden, symptoms, tumor grade/Ki67 index
3. The following factors might guide the decision: site of disease involvement, tumor burden, symptoms, tumor grade/Ki67 index, and importantly kinetics of tumor growth
4. Radiotherapy, radiofrequency ablation, cryo-ablation, microwave ablation, (chemo-) embolization
5. Few panellists favored cisplatin + etoposide
6. Contact specialized center

ACC: adrenocortical carcinoma: EDP: etoposide, doxorubicin, cisplatin

Adapted from Fassnacht M, et al. *Eur J Endocrinol.*2018;179(4):G1-G46.

Systemic Chemotherapy: FIRM-ACT Trial
EDP-Mitotane vs. Sz-Mitotane

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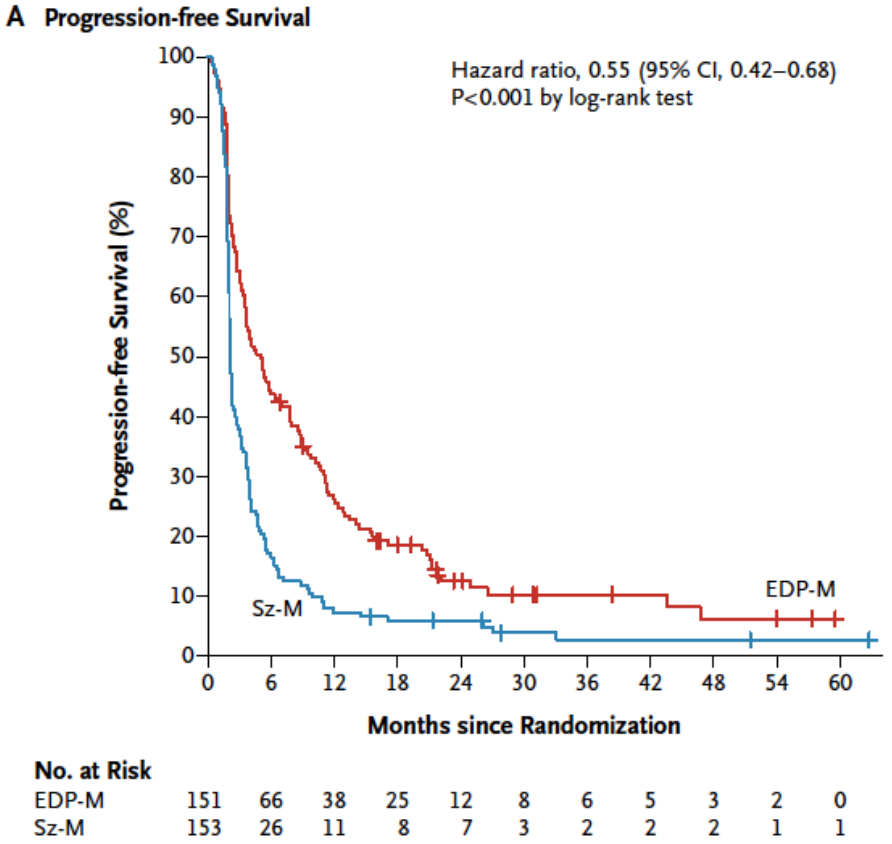
- Response Rate 23% vs. 9%
- Median PFS 5 vs. 2.1 months
- Overall Survival 14.8 vs. 12 months



Fassnacht et al. *NEJM*, 2012

Only FDA approved treatment for inoperable, functional or nonfunctional, adrenal cortical carcinoma (ACC)

WARNINGS: ADRENAL CRISIS IN THE SETTING OF SHOCK OR SEVERE TRAUMA: In patients taking LYSODREN, adrenal crisis occurs in the setting of shock or severe trauma and response to shock is impaired. Administer hydrocortisone, monitor for escalating signs of shock and discontinue LYSODREN until recovery.

Mitotane Mechanism of Action

Mitotane is an Adrenal Cytotoxic Agent and Steroidogenesis Inhibitor

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The mode of action is not fully understood[1]

Data available suggest that mitotane:

- Modifies the peripheral metabolism of steroids and inhibits key enzymatic steps in cortisol synthesis[2]
- Directly suppresses the adrenal cortex[2]

Administration of mitotane alters the extra-adrenal metabolism in man, leading to:

- A reduction in measurable 17-hydroxy corticosteroids[3]
- Increase of 6-β-hydroxycortisol (inactive metabolite)[3]

1.Lysodren® U.S. Package Insert
2.Hahner, Fassnacht. *Curr Opin Investig Drugs*, 2005
3.Fassnacht, Allolio. *Best Prat Res Clin Endocrinol Metab*, 2009

Improvements in the Understanding of Mitotane's MOA

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Original Research

- Mitotane alters mitochondrial respiratory chain activity by including cytochrome *c* oxidase defect in human adrenocortical cells[1]
- Morphofunctional effects of mitotane on mitochondria in human adrenocortical cancer cells[2]

Mitotane alters complex IV of mitochondrial respiratory chain, leading to morphofunctional alterations[1,2]

- Mitotane inhibits Sterol-O-Acyl Transferase 1 triggering lipid-mediated endoplasmic reticulum stress and apoptosis in ACC cells[3]

In adrenocortical cells, SOAT1 is a key target for mitotane[3]

- Alteration in lipid homeostasis → ER stress → apoptosis
- Steroidogenesis blockade

1. Hescot S, et al. *Endocr Relat Cancer.* 2013
2. Poli G, et al. *Endocr Relat Cancer.* 2013
3. Sbiera S, *et al. Endocrinology.* 2015

Mitotane Dosing and Plasma Monitoring

Mitotane PK

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- Lipophilic and is stored in adipose tissues, fat is the primary site of distribution[1]
- Prolonged half-life: median 53 days, range (18 – 159 days)[1]
  - This delays the impact on mitotane plasma levels after dose changes and after treatment discontinuation
- Long onset of action (3-5 months)[2]
- Fat tissue can act as a reservoir for mitotane, resulting in a prolonged half-life and potential accumulation of mitotane. Despite a constant dose, mitotane levels may increase. Monitoring of mitotane plasma levels (e.g. every two months) is recommended after interruption of treatment, as prolonged release of mitotane can occur.[2]
- Caution and close monitoring of mitotane plasma levels are highly recommended when treating overweight patients[2]

1.Lysodren® U.S. Package Insert
2.Paragliola et al. *Eur Endocrinol,* 2018

Mitotane Dosage & Administration

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- Initial dose: 2 to 6 grams orally daily, in 3 or 4 divided doses[1]

2-6 g/day / 3-5 months[1]

Increase dose incrementally to achieve a blood concentration of **14 to 20 mg/L** or as tolerated. It can take 3 to 5 months[1].

Clinical Effectiveness Assessment

Imaging assessment with thorax, abdomen and pelvis CT every 3 months for 2 years[2].

Optimal Blood Concentration

1.Lysodren® U.S. Package Insert
2.Fassnacht M, et al. *Eur J Endocrinol.*2018;179(4):G1-G46.

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Optimal Plasma Concentration Target

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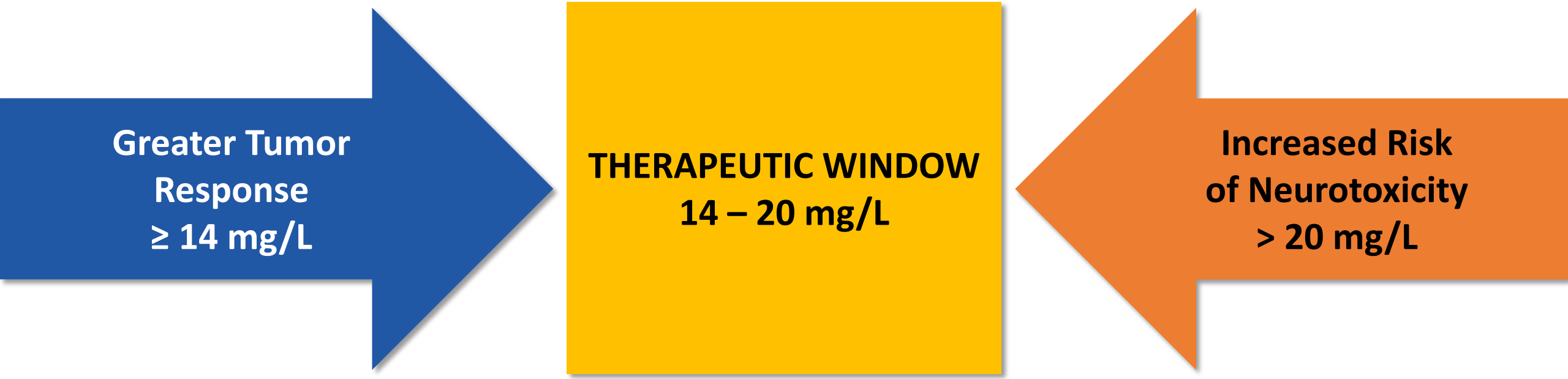
Mitotane Plasma Level Monitoring is to be performed on a regular and individual basis to reach/maintain an optimal therapeutic window[2]



1.Lysodren® U.S. Package Insert
2.Fassnacht M, Allolio B. *Best Pract Res Clin Endocrinol Metab.* 2009;23(2):273-89.

Mitotane Warnings Precautions

Mitotane – Indication, Warnings/Precautions

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Indicated for the treatment of inoperable ACC of both functional & non-functional types

WARNINGS: ADRENAL CRISIS IN THE SETTING OF SHOCK OR SEVERE TRAUMA: In patients taking LYSODREN, adrenal crisis occurs in the setting of shock or severe trauma and response to shock is impaired. Administer hydrocortisone, monitor for escalating signs of shock and discontinue LYSODREN until recovery.

- CNS Toxicity
- Adrenal Insufficiency
- Embryo-Fetal Toxicity
- Ovarian Macrocysts in Premenopausal Women

For more information please refer to the full U.S. Prescribing Information

Adrenal Insufficiency

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- Mitotane is an adrenal cytolytic drug[1]
- Generally spares the zona glomerulosa with selective loss of ACTH dependent adrenal zones (fasciculata and reticularis)[1]
- In addition the drug inhibits key steroidogenic enzymes, most notably CYP11A1, decreasing conversion of cholesterol to pregnenolone[2]
- Consider beginning hydrocortisone replacement at the outset of mitotane therapy. Mitotane is strong inducer of Cytochrome P4503A4 (CYP3A4)[3]
- Causes rapid inactivation of >50% administered hydrocortisone[3]
- Usually requires at least double usual maintenance dose (i.e. 40-50 mg hydrocortisone a day in divided doses)[3]

1.Hahner S, Fassanacht M. *Curr Opin Investig Drugs*, 2005
2.Asp V et al. *Toxicol Appl Pharmacol*, 2009
3.Fassnacht M, et al. *Eur J Endocrinol.*2018;179(4):G1-G46

Mitotane Drug Interactions

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- **Warfarin:**
  Mitotane has been reported to accelerate the metabolism of warfarin[1]
- **CYP 3A4 Substrates:**
  Mitotane is a strong inducer of cytochrome P450 3A4[1]
  - Concomitant use of LYSODREN may decrease the concentrations of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid the concomitant use of LYSODREN with certain CYP3A4 substrates where minimal concentration changes may lead to therapeutic failure. If concomitant use cannot be avoided, increase the CYP3A substrate dosage in accordance with approved product labeling.
- **Hormone Binding Protein:**
  Mitotane has been shown to increase plasma levels of sex hormone binding proteins[2]

1.Lysodren® U.S. Package Insert
2.Fassnacht, Allolio. *Best Prat Res Clin Endocrinol Metab*, 2009

Adverse Events and Monitoring Plan

Mitotane Adverse Events

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Most Common Adverse Effects

- Anorexia, nausea, vomiting, and diarrhea (80%)
- Depression, dizziness, or vertigo (15%-40%)
- Rash (15%)
- Neutropenia
- Hepatitis, elevation of liver enzymes
- Growth retardation, hypothyroidism
- Confusion, headache, ataxia, mental impairment, weakness, dysarthria
- Maculopathy
- Hypercholesterolemia, hypertriglyceridemia
- Decreased blood androstenedione and decreased blood testosterone in females, increased sex hormone binding globulin in females and males, decreased blood free testosterone in males
- Gynecomastia

Less Common Adverse Effects

- Hypertension
- Orthostatic hypotension, flushing
- Generalized aching, and fever
- Visual blurring
- Diplopia
- Lens opacity, retinopathy
- Prolonged bleeding time
- Hematuria
- Hemorrhagic cystitis
- Albuminuria
- Hypogonadism

Suggested Monitoring Plan

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Test	Indication	Interval
CBC	Hematological toxicity	Q 3 months
Electrolytes	Monitor steroid replacement	Q 1-3 months
ACTH, Plasma Renin Activity	Monitor steroid replacement	Q 1-3 months
LFTs	Hepatic toxicity	Q 3 months
TSH, Free T4	Hypothyroidism	Q 3 months
Lipid panel	Hyperlipidemia	Q 3 months
Testosterone	Hypogonadism	If clinically indicated
Mitotane level	Titrate dose	• Q month till reaching level then q 2-3 months • PRN if suspected toxicity

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Hahner, Fassnacht. *Curr Opin Investig Drugs*, 2005

Summary

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- A multidisciplinary team is needed to manage the complex medical issues seen in advanced ACC
- While there are no prospective data regarding hormonal management in ACC, therapy is suggested based on ESE/ENSAT 2018 guidelines
- Mitotane use should be supervised closely to achieve desired plasma level 14-20 mg/L and monitor adverse events
- Adrenal insufficiency is among the most common side effects during mitotane therapy and often requires higher than the average steroid replacement

Fassnacht M, et al. *Eur J Endocrinol.*2018;179(4):G1-G46.

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Clinical Management of ACC

THANK YOU!

INDICATION

LYSODREN® is an adrenal cytotoxic agent indicated for the treatment of inoperable, functional or nonfunctional, adrenal cortical carcinoma.

IMPORTANT SAFETY INFORMATION

Warning/Adrenal crisis in the setting of shock or severe trauma: In patients taking LYSODREN®, adrenal crisis occurs in the setting of shock or severe trauma and response to shock is impaired. Administer hydrocortisone, monitor for escalating signs of shock and discontinue LYSODREN® until recovery.

CNS Toxicity: CNS toxicity, including sedation, lethargy, and vertigo, occurs with LYSODREN® treatment. Mitotane plasma concentrations exceeding 20 mcg/mL are associated with a greater incidence of toxicity.

Adrenal Insufficiency: Treatment with LYSODREN® can cause adrenal insufficiency. Institute steroid replacement as clinically indicated. Measure free cortisol and corticotropin (ACTH) levels to achieve optimal steroid replacement.

Embryo-Fetal Toxicity: LYSODREN® can cause fetal harm when administered to a pregnant woman. Abnormal pregnancy outcomes, such as preterm births and early pregnancy loss, can occur in patients exposed to mitotane during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with LYSODREN® and after discontinuation of treatment for as long as mitotane plasma levels are detectable.

Ovarian Macrocysts in Premenopausal Women: Ovarian macrocysts, often bilateral and multiple, have been reported in premenopausal patients receiving LYSODREN®. Complications from these cysts, including adnexal torsion and hemorrhagic cyst rupture, have been reported. In some cases, improvement after mitotane discontinuation has been described.

Ovarian Macrocysts in Premenopausal Women: Ovarian macrocysts, often bilateral and multiple, have been reported in premenopausal patients receiving LYSODREN®. Complications from these cysts, including adnexal torsion and hemorrhagic cyst rupture, have been reported. In some cases, improvement after mitotane discontinuation has been described.

Lactation: Mitotane is excreted in human milk; however, the effect of LYSODREN® on the breastfed infant, or effect on milk production is unknown. Because of the potential for serious adverse reactions in the breastfed infant, advise nursing women that breastfeeding is not recommended during treatment with LYSODREN® and after discontinuation of treatment for as long as mitotane plasma levels are detectable.

Hepatic Impairment: Administer LYSODREN® with caution to patients with hepatic impairment.

Common adverse reactions (≥15%) include: anorexia, nausea, vomiting and diarrhea; depression, dizziness or vertigo; and rash.

LYSODREN® is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Please see Full Prescribing Information, including BOXED WARNING, for LYSODREN (mitotane) tablets.

To report SUSPECTED ADVERSE REACTIONS, contact Direct Success Pharmacy, Inc. at 1-844-LYSODREN (1-844-597-6373) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.