Ein Unternehmen der LUKS Gruppe

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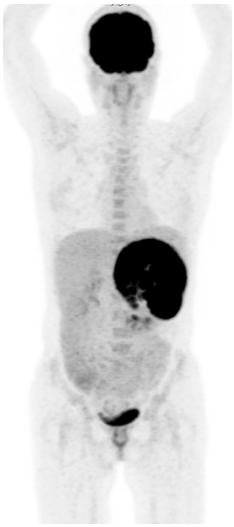
Pocketguide 'Art. Hypertonus und adrenales Inzidentalom'

Adrenokortikales Karzinom



Laura Hollenstein, Assistenzärztin
8. Februar 2023

herzlich, kompetent, vernetzt

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Facts

- Inzidenz: 0.5-2 / Mio / y
- Altersgipfel 4.-6. Lebensdekade, Frauen häufiger betroffen

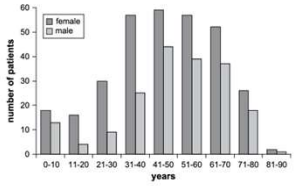

Fig. 1. Age and sex distribution at primary diagnosis of adrenocortical carcinoma (ACC); n = 507. Data from the German ACC Registry, August 2008.

- Auftreten meist sporadisch
- Assoziation mit Tumorsyndromen ~10% (Li-Fraumeni-Syndrom, Lynch-Syndrom, MEN 1)

Fassnacht et al. 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, 2018.
Fassnacht & Allolio. Clinical management of adrenocortical carcinoma. Best Practice & Research. Clinical Endocrinology & Metabolism, 2009.

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Klinik

Autonomous adrenal hormone excess	50–60
Hypercortisolism (Cushing syndrome)*	50–70
Androgen excess (virilization) in female patients*	20–30
Estrogen excess (feminization) in male patients*	5
Mineralocorticoid excess*	2–3
Non-specific symptoms from an abdominal mass	30–40
Incidentally detected by imaging for other purpose	10–15

Fassnacht et al. 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, 2018.

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Verdacht auf ACC: Work-up

Hormonal work-up	
Glucocorticoid excess	– 1 mg dexamethasone suppression test or free cortisol in 24-h urine[a] – Basal ACTH (plasma)[b]
Sex steroids and steroid precursors[c]	– 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 hypokalemia)
Exclusion of a pheochromocytoma	– Fractionated metanephrines in 24 h urine or free plasma-metanephrines
Imaging	– CT or MRI of abdomen and pelvis – Chest CT – FDG-PET/CT[d] – Bone or brain imaging (when skeletal or cerebral metastases are suspected)
keine Biopsie	- ausser bei extraadrenalem Tumorleiden

Fassnacht et al. 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, 2018.

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Diagnose

- häufig hochgradiger Verdacht
  - **Bildgebung**
  - Klinik
  - Labor

- Pathologie
  - lokale Infiltration und/oder Metastasen
  - ≥3 Weiss-Kriterien

High nuclear grade (Fuhrman criteria)
>5 mitoses per 50 HPF
Atypical mitotic figures
<25% of tumour cells are clear cells
Diffuse architecture (>33% of tumour)
Necrosis
Venous invasion (smooth muscle in wall)
Sinusoidal invasion (no smooth muscle in wall)
Capsular invasion

Fassnacht et al. 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, 2018.
Fassnacht et al. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2020.

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Staging

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0
	T3–T4, N0–N1, M0
IV	T1–T4, N0–N1, M1

T1: tumor ≤5 cm; T2: tumor >5 cm; T3: infiltration into surrounding tissue; T4: tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein; N0: no positive lymph node; N1: positive lymph node; M0: no distant metastases; M1: presence of distant metastases.

- bei Diagnosestellung
  - 50-60% ENSAT I + II
  - 20% ENSAT III
  - 20-30% ENSAT IV

Fassnacht et al. 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, 2018.
Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.

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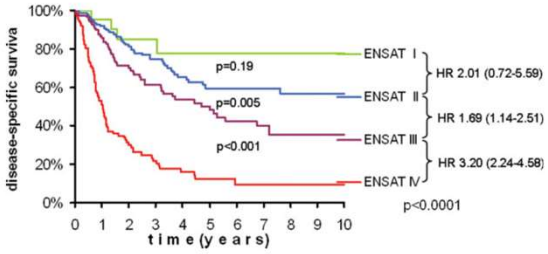
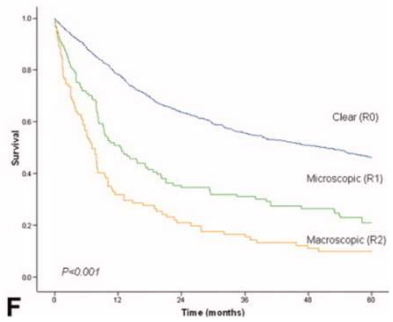
prognostische Faktoren

- ENSAT-Stadium



- Resektionsstatus



Fassnacht & al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma. Cancer 2009.
Bilimoria et al. Adrenocortical carcinoma in the United States. Cancer 2008.

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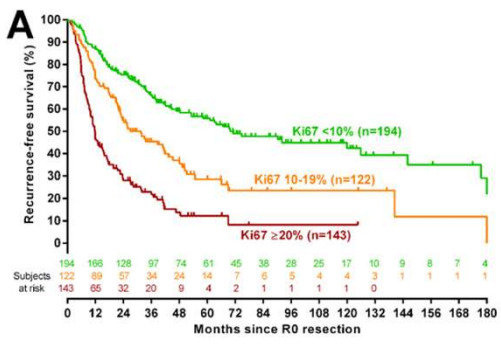
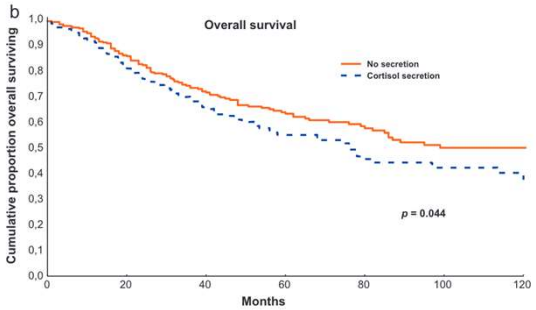
prognostische Faktoren

- Proliferationsmarker Ki67



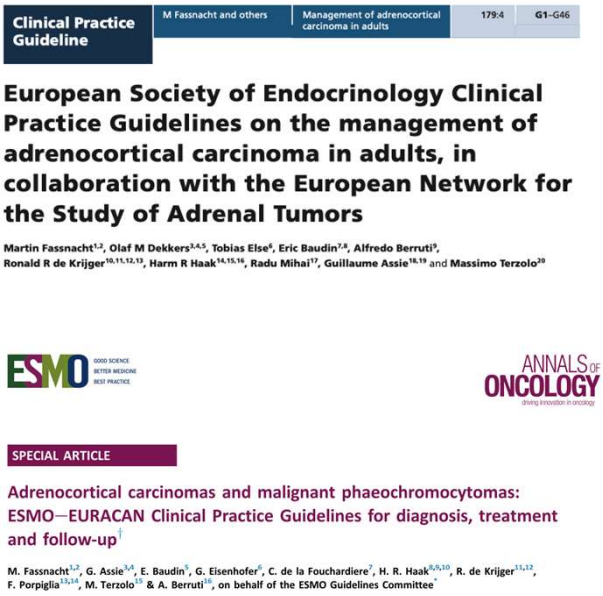
- Cortisol-Sekretion



No. of patients at risk	0	20	40	60	80	100	120
No secretion	327	252	159	106	71	45	40
Cortisol secretion	197	146	97	60	37	22	17

Beuschlein et al. Major Prognostic Role of Ki67 in Localized Adrenocortical Carcinoma After Complete Resection. J Clin Endocrinol Metab, 2015.
Berruti et al. Prognostic Role of Overt Hypercortisolism in Completely Operated Patients with Adrenocortical Cancer. European Association of Urology, 2014.

8



Clinical Practice Guideline | M Fassnacht and others | Management of adrenocortical carcinoma in adults | 179:4 | G1–G46

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

Martin Fassnacht[1,2], Olaf M Dekkers[3,4,5], Tobias Else[6], Eric Baudin[7,8], Alfredo Berruti[9], Ronald R de Krijger[10,11,12,13], Harm R Haak[14,15,16], Radu Mihai[17], Guillaume Assie[18,19] and Massimo Terzolo[20]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Fassnacht[1,2], G. Assie[3,4], E. Baudin[5], G. Eisenhofer[6], C. de la Fouchardiere[7], H. R. Haak[8,9,10], R. de Krijger[11,12], F. Porpiglia[13,14], M. Terzolo[15] & A. Berruti[16], on behalf of the ESMO Guidelines Committee*

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Review | M Terzolo and M Fassnacht | Management of non-metastatic ACC | 187:3 | R27–R40

ENDOCRINE TUMOURS

Our experience with the management of patients with non-metastatic adrenocortical carcinoma

Massimo Terzolo[1] and Martin Fassnacht[2,3]

[1]Internal Medicine, Department of Clinical and Biological Sciences, S. Luigi Hospital, Orbassano, University of Turin, Turin, Italy, [2]Division of Endocrinology and Diabetes, Department of Internal Medicine, University Hospital, University of Würzburg, Würzburg, Germany, and [3]Comprehensive Cancer Center Mainfranken, University of Würzburg, Würzburg, Germany

Correspondence should be addressed to M Terzolo
Email massimo.terzolo@unito.it

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Chirurgie

- ENSAT I + II immer
- ENSAT III meistens
- ENSAT IV wenn singuläre Metastase

- Zentrumspital, offene Chirurgie
- Lymphadenektomie periadrenal + hilär

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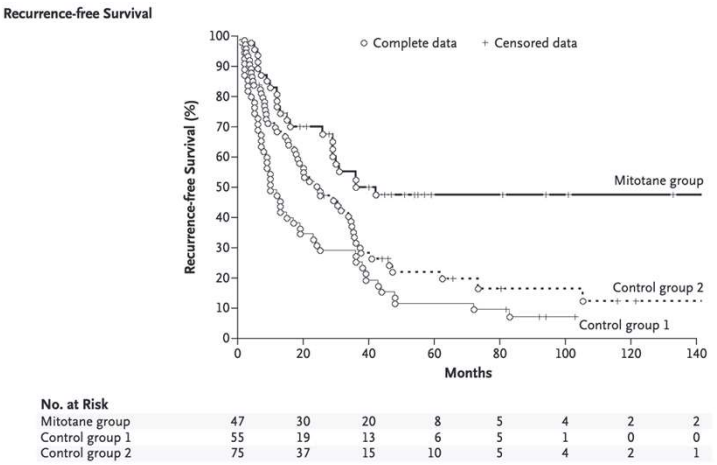
adjuvant Mitotan?

- retrospektive Multizenterstudie 2007
- R0- und R1-Resektion
- mitotane group (n = 47)
- control group 1 (n = 55, IT)
- control group 2 (n=75, DE)
- medianes rezidivfreies Überleben:
  - 42 vs. 10 vs. 25 Monate
- NW Grad 1+2



Terzolo et al. Adjuvant Mitotane Treatment for Adrenocortical Carcinoma. NEJM 2007.

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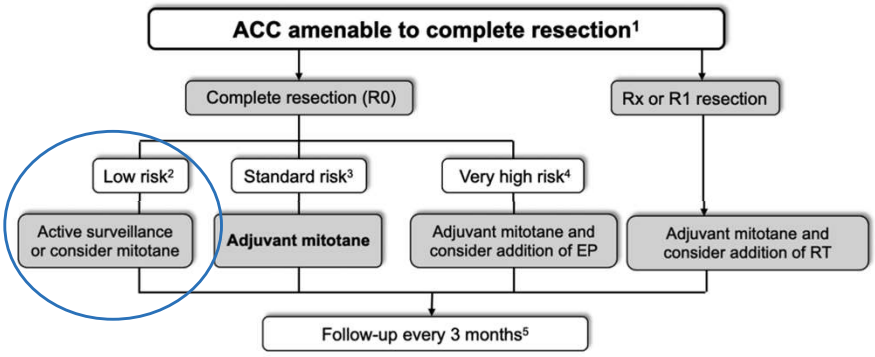

- low risk: ENSAT I /II + Ki67 <10%
- standard risk: ENSAT I/II + Ki67 10-30%; ENSAT III + Ki67 <30%
- very high risk: ENSAT I/II/III + Ki67% >30%; ENSAT IV, R1-Resektion

Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.

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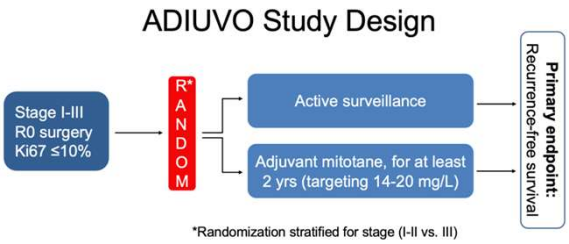
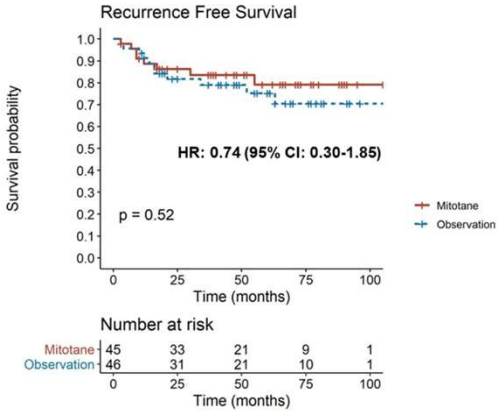
adjuvant Mitotan bei low-risk?





- März 2008 – Dezember 2018
- n = 91 (anstatt Ziel 200)
  - 45 Mitotan
  - 46 Observation
  - vergleichbare 'baseline characteristics'

Terzolo et al. Results of the ADIUVO Study, the First Randomized Trial on Adjuvant Mitotane in Adrenocortical Carcinoma Patients. Endocrine Abstracts, 2021.
Berruti et al. First randomized trial on adjuvant mitotane in adrenocortical carcinoma patients: The Adjuvo study. Meeting Abstract | 2022 ASCO Genitourinary Cancers Symposium.

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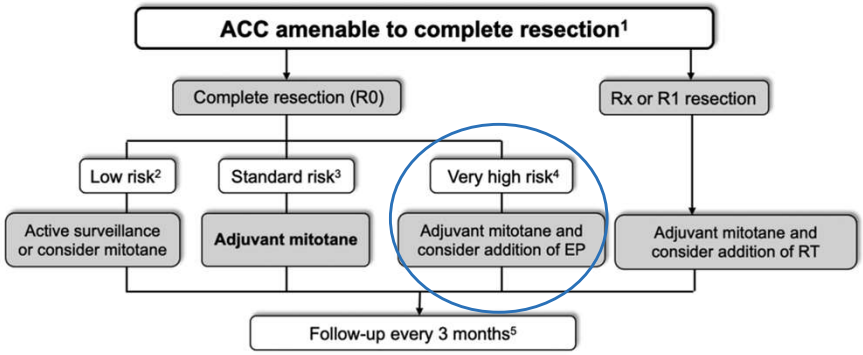

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Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.

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adjuvant CTx bei high risk?

- retrospektive Registerstudie
- Einschluss:
  - RO/R1/RX-Resektion 2002-02/2020
  - Start Platin-basierte CTx innerhalb 3 Mt
- n = 31 platin cohort
- n = 31 matched controls

Table 1. Baseline characteristics of the patients.

	Adjuvant platin therapy ($n = 31$)	Matched controls ($n = 31$)	*P* value platin vs matched controls
Sex (F:M)	16:15	19:12	0.44
Median age yrs (range)	41 (4–59)	44 (18–67)	0.79
Median tumour size mm (range)	124 (25–300)	120 (38–220)	0.79
Autonomous hormone secretion			
Cortisol +/− androgens− *n* (%)	15 (48.4)	12 (38.7)	0.068
Androgens	5 (16.1)	3 (9.7)	
Aldosterone	0	1 (3.2)	
Estrogens	0	0	
Inactive	7 (22.6)	15 (48.4)	
Unknown	4 (12.9)	0	
ENSAT tumour stage			
I, *n* (%)	0	0	1.0
II, *n* (%)	11 (35.5)	11 (35.5)	
III, *n* (%)	16 (51.6)	16 (51.6)	
IV, *n* (%)	4 (12.9)	4 (12.9)	
Venous tumour thrombus[a], *n* (%)	10 (32.3)	10 (32.3)	1.0
Resection status			
R0, *n* (%)	25 (80.6)	25 (80.6)	1.0
RX, *n* (%)	4 (13)	4 (13)	
R1, *n* (%)	2 (6.4)	2 (6.4)	
Ki67 index—median (range)	30 (10-80)	32.1 (8-80)	0.86
<20%	7 (25)	5 (17.9)	0.55
20–39%	10 (35.7)	14 (50)	
≥40%	11 (39.3)	9 (32.1)	
Number of patients with adjuvant mitotane (%)	28 (90.3)	28 (90.3)	1.0
Highest mitotane plasma concentration (mg/L)—median (range)			
In the first 3 months	12 (3–28)	10 (1–23)	0.87
No. of analysed patients	$n = 20$	$n = 23$	
Until progress/end of therapy	18 (3–34)	17 (1–27)	0.86
No. of analysed pts.	$n = 24$	$n = 24$	
No. of patients with mitotane level >14 mg/L during therapy (%)	17 (54.8)	17 (54.8)	1.0

Kimpel et all. Adjuvant platinum-based chemotherapy in radically resected ACC: a cohort study. British Journal of Cancer, 2021.

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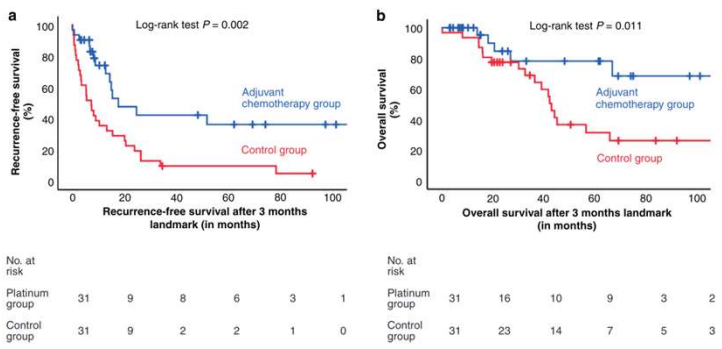
adjuvant CTx bei high risk?

- Medianes rezidivfreies Überleben
  - 17.3 vs. 7.3 Monate
- Gesamtüberleben
  - 5 Todesfälle in der CTx-Gruppe
  - 19 Todesfälle in der Kontrollgruppe
- NW Grad 1-3



Adiuvo-2 Trial
- randomisierte Studie
- ENSAT I-III, Ki67%>10%
- adjuvant Mitotan vs. Mitotan + Cisplatin/Etoposid

Kimpel et all. Adjuvant platinum-based chemotherapy in radically resected ACC: a cohort study. British Journal of Cancer, 2021.
ClinicalTrials.gov Mitotane With or Without Cisplatin and Etoposide After Surgery in Treating Patients With Stage I-III Adrenocortical Cancer With High Risk of Recurrence

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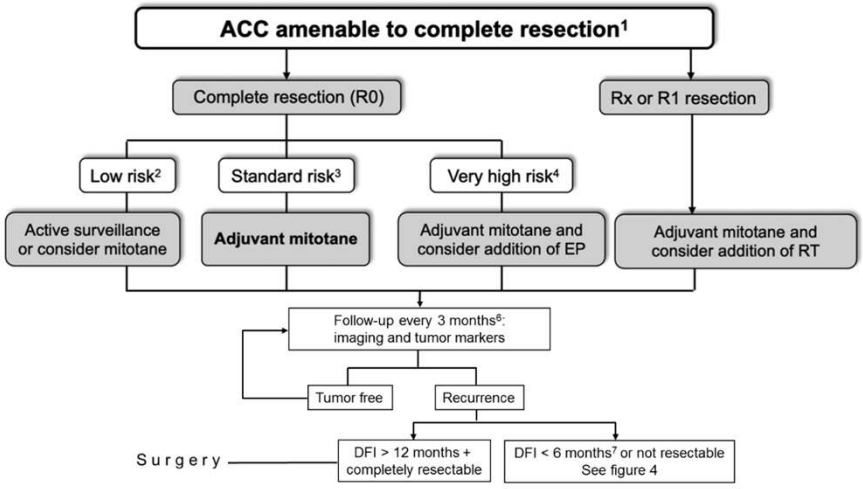

Fassnacht et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors, 2018.
Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.

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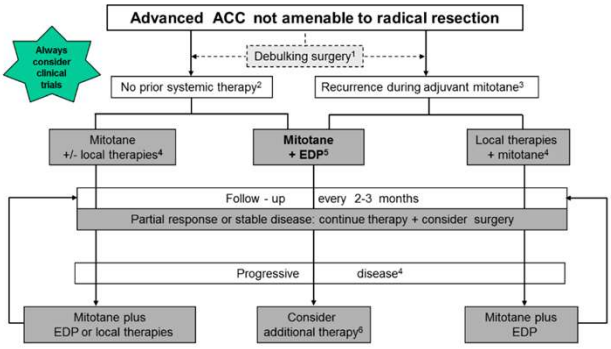
fortgeschrittener, nicht resezierbarer Tumor

- **Mitotan**
  - First-Line-Therapie
- Chemotherapie
  - **Etoposid, Doxorubicin + Cisplatin**
- Operation
  - Debulking
  - bei gutem Therapieansprechen
- lokale Therapien (RT, SIRT, RFA)
- bei Hormonexzess: Adrenostatika



Fassnacht et al. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2020.

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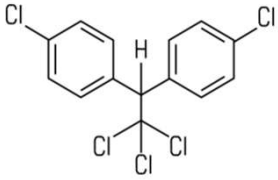
Mitotan

- Analoga des Insektizides Dichlordiphenyltrichlorethan (DDT)
- seit den 60er Jahren angewendet für NNR-Ca
- Wirkung:
  - selektiv zytostatischer Effekt auf adrenokortikale Zellen
  - Hemmung der Schlüsselenzyme für Steroidhormonsynthese
- Einnahme: Tabletten à 500mg (bis 6g), zu den Mahlzeiten
- Ziel-Spiegel 14-20 mg/L
- diverse NW
- cave: CYP3A4-Induktion
- Therapiedauer: 2-5 Jahre



Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.
SOP – Information für Patienten und mitbehandelnde Ärzte zu einer Therapie mit Mitotane (Lysodren®), Unversitätsklinikum Würzburg, Version 2021.

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NW Mitotan-Therapie

- NNR-Insuffizienz (Hydrocortison 40-60mg/d, ggf. Florinef)
- gastrointestinal (Inappetenz, Nausea, Emesis, Diarrhoe)
- neurologisch (Schwindel, Ataxie, Verwirrtheit, Visus- und Sprachstörungen)
- Hypothyreose
- ♂ Hypogonadismus -> freies Testosteron messen
- ♀ Ovarialzyste
- Leberwerterhöhung (insbesondere y-GT)
- Total-Cholesterin, LDL + HDL ↑

Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.
SOP – Information für Patienten und mitbehandelnde Ärzte zu einer Therapie mit Mitotane (Lysodren®), Unversitätsklinikum Würzburg, Version 2021.

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Laborkontrollen unter Mitotan-Therapie

Parameter	Interval	Comment
Mitotane blood level	Every 6–9 weeks[1]	Target: 14–20 mg/L
ACTH	Suspected glucocorticoid deficiency or excess	Glucocorticoid status is difficult to determine Target: ACTH in the normal range or slightly above (e.g. < 2 times the ULN)
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 (>3 times of baseline), there is an increasing risk of liver failure: Interrupt mitotane
TSH, fT4	Every 3–4 months	Reduction of fT4 is frequent. Thyroid hormone replacement is a debated issue
Renin	Every 6 months	If renin ↑↑ and K in the high normal range, add fludrocortisone Target: renin two to three times the normal range
Cholesterol (HDL, LDL), triglycerides	Every 3–4 months	If total and LDL cholesterol ↑↑, consider treatment with statins not metabolized by CYP3A4
Blood count	Every 3–4 months	Check for rare (and in only few cases severe) leucopenia, thrombocytopenia, and anemia
LH, testosterone, SHBG[2]	In case of symptoms of hypogonadism	Reduction of testosterone levels may be masked by increased SHBG and calculation of free testosterone is recommended. Testosterone replacement is a debated issue

[1]In the first 3 months, mitotane blood levels should be checked more frequently. Additional measurements may be needed in case of severe toxicity (in particular, neurological toxicity). [2]In male patients.

Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.

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Erholung NNR-Insuffizienz?

- retrospektive Studie
- 23 Patienten (Canada, Italien)
- min. 2y Mitotan-Therapie

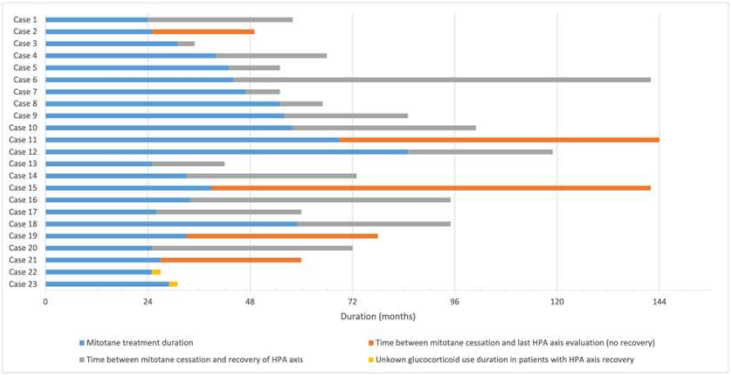

Figure 1. Schematic representation of mitotane exposure and HPA axis recovery timeline for each patient.

- 18/23 (78.3%) vollständige Erholung
- 3/23 (13%) laborchemisch Erholung, aber klinisch Bedarf
- 2/23 (8.7%) fehlende Erholung
- mittlere Zeitspanne nach Stopp Mitotan bis zur Erholung **2.7 Jahre**

Poirier et al. Recovery of Adrenal Insufficiency is Frequent After Adjuvant Mitotane Therapy in Patients with Adrenocortical Carcinoma. Cancers, 2020.

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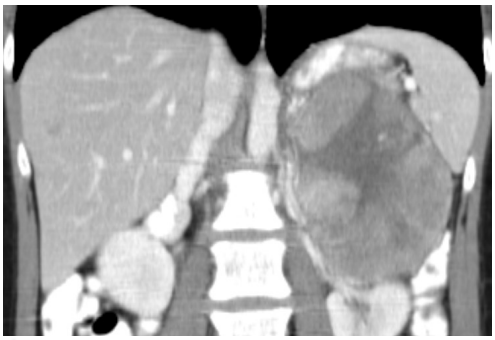
3 Fallbeispiele

23

weiblich, 44-jährig

- Symptomatik: Bauchschmerzen seit 1 Monat
- 01/12 CT Thorax/Abdomen
  - Nebennierentumor links
  - solitäre Lebermetastase
- keine Hormonaktivität



Nebennierenrindenkarzinom,
max. Durchmesser 14 cm,
mit ausgedehnter Tumornekrose (etwa 40 % des gesamten Tumors einnehmend), Angiosis carcinomatosa sowie
Infiltration des periadrenalen Fett-Bindegewebes
(Ektomie).

Tumorfreie Weichteilresektionsfläche bei Fadenmarkierung. Das Karzinom reicht mit seiner bindegewebigen Kapsel herdförmig bis 0,3 cm an die periphere zirkumferente Resektionsfläche heran.

- 03/12 Adrenalektomie links + Leber-Wedge-Resektion Segment VI
- ENSAT-Stadium IV, RO-Resektion, Ki67 3-5%

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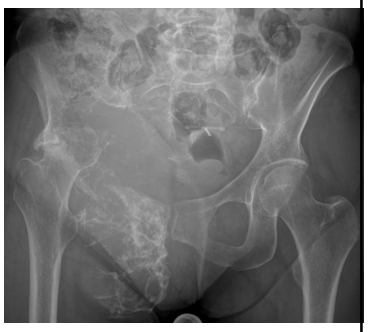
- adjuvant lokale Radiotherapie
- Mitotan 04/12-12/13
- bei Tumorprogredienz (Leber): Chemotherapie mit Etoposid, Doxorubicin + Cisplatin 12/12-02/13
- Radiofrequenzablation + SIRT bei Lebermetastasen 2013+14

- aktuell:
  - ausgedehnte Leber-, Lungen-, Lymphknoten- und ossäre Metastasen
  - palliativ Immuntherapie mit Nivolumab (allerg. Reaktion) 06/22
  - Pembrolizumab geplant



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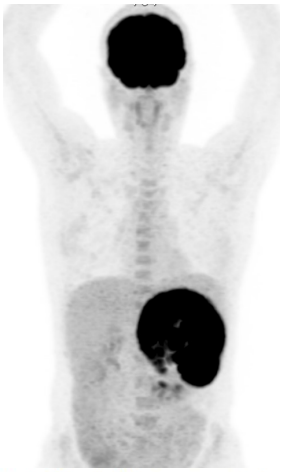
weiblich, 53-jährig

- Symptomatik:
  - tiefe Stimme, Hirsutismus
  - Gewichtsabnahme

- 05/17 offene Adrenalektomie

- **ENSAT-Stadium II, RO-Resektion, Ki67 > 5%**

- Mitotan 08/17-08/19



Eingesandtes Material: Nebennierentumor links (2)

Diagnose: **Nebennierenrindentumor, ausgehnt regressiv-nekrotisch verändert, Durchmesser: 17 cm, Gewicht: 2'218 g, ausgedehnte, teils eingeblutete Nekrosezonen (etwa 50-60 %), einzelne, teils atypische Mitosen (bis 5 Mitosen/50 HPF, Sehfelddurchmesser: 0.575 mm), ausgeprägte Pleomorphie und Hyperchromasie der Kerne, kleinherdige Kapselinfiltration und Einbruch in venöses Blutgefäss. Angrenzend miterfasste Nebenniere (Ektomie).**

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- 08/19 Lokalrezidiv (2cm), keine Metastasen
- Labor

- 09/19 Restadrenalektomie, R0
- adjuvant lokale Radiotherapie

ENDOKRINOLOGIE				
Cortisol Morgen	01.09.2022	Bereich: 166 - 507 nmol/L		
Cortisol Abend	28.06.2022	Bereich: 73.8 - 291 nmol/L		
Cortisol Stim. (1µg Synacten)	01.09.2022	Bereich: >550 nmol/L		
DHEA-S	22.05.2018	Bereich: 0.5 - 7 µmol/L		
DHEA-S	28.06.2022	Bereich: 0.96 - 6.95 µmol/L		1.35
TSH basal	20.11.2019	Bereich: 0.27 - 4.20 mU/L		
TSH basal	28.06.2022	Bereich: 0.27 - 4.2 mU/L		0.96
freies T3	05.12.2017	Bereich: 3.1 - 6.8 pmol/L		
freies T3	14.12.2021	Bereich: 3.1 - 6.8 pmol/L		
freies T4	20.11.2019	Bereich: 12 - 22 pmol/L		
freies T4	18.05.2022	Bereich: 12 - 22 pmol/L		
Freies Testosteron (berechnet)	03.09.2019	Bereich: 0.001 - 0.020 nm...		0.004
SHBG	22.05.2018	Bereich: 27.1 - 128 nmol/L		
SHBG	03.09.2019	Bereich: 27.1 - 128.0 nmol/L		200 ▲
Cortisol, Speichel	05.09.2019	Bereich: siehe Laborkarte...	<1.5	
Testosteron	03.09.2019	Bereich: 0.101 - 1.42 nmol/L		0.83
Aldosteron *	03.09.2019	Einheit: ng/l		128
Aldosteron/Renin Quotient *	03.09.2019	Einheit: ng/mU		6
Renin *	14.12.2021	Einheit: mU/l		21.0
17 OH-Progesteron *	03.09.2019	Einheit: ng/ml		3.0
Androstendion *	03.09.2019	Bereich: 1.0 - 11.5 nmol/l		4.6

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luzerner kantonsspital
LUZERN SURSEE WOLHUSEN

- 06/20 pulmonale Metastase OL rechts
- stereotaktische Bestrahlung

- 09/21 Progredienz Lungenmetastasen bds.
- 01/22 + 03/22 offene Metastasenresektion
  - 4 Metastasen NNR-Ca, max. 10mm
  - 4 pulmonales Adeno-Ca max. 4mm

- EGFR-Mutation im Bronchus-Karzinom -> Tyrosinkinaseinhibitor Osimertinib seit 04/22

- 06/22 Rezidiv Nebennierenloge links
- 08/22 Rezidivresektion 11mm

- 09/22 Nierenmetastasen links
- 11/22 Nephrektomie links

- aktuell: Weiterführung der regelmässigen Bildgebungen

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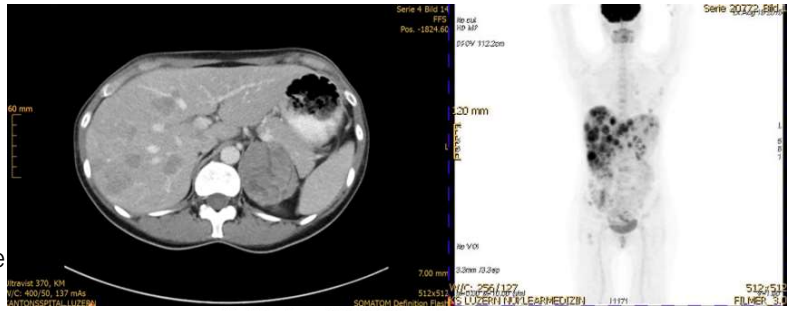
weiblich, 33jährig †

- Symptomatik seit 8 Wochen
  - proximale Myopathie, Plethora, Hirsutismus, tiefe Stimme, Akne
- Labor

- 07/15 Adrenalektomie li
- **ENSAT-Stadium IV, Ki67 ca. 40%**

- Mitotan
- Etoposid, Doxorubicin + Cisplatin

- 3 Monate nach Diagnose: Exitus letalis



Laborbefunde vom 08.06.2015 (Hausarzt):

Analyse	Resultat	Referenzbereich
Cortisol Morgen	930	171 - 537 nmol/l

Laborbefunde vom 19.06.2015 (Hausarzt):

Analyse	Resultat	Referenzbereich
Cortisol supprimiert (Dexamethason-Hemmtest)	952.2	< 84 nmol/l

Laborbefunde vom 17.07.2015:

Analyse	Resultat	Referenzbereich
Alkalische Phosphatase	122	35 - 104 U/l
Cortisol Abend	1738	64 - 327 nmol/l
Cortisol im Speichel (23.00 Uhr)	301	< 8.0 nmol/l
freies T4	10.1	10 - 23 pmol/l
DHEA-S	33.5	0.3 – 11.0 µmol/l (altersabhängig)
Gamma-Glutamyl-Transferase	66	6 – 42 U/l
Glukose	10.1	3.9 - 6.4 mmol/l
GPT (ALAT)	50	< 35 U/l
HbA1c	5.7	4.8 - 5.9%
hGH	0.08	0.13 – 9.88 µg/l
Kalium	2.1	3.4 - 4.5 mmol/l
Kreatinin	65	45 - 84 µmol/l
Natrium	144	136 - 145 mmol/l
17 –OH-Progesteron	folgt	0.3 – 15.1 nmol/l
Prolaktin	10.5	5 - 25 µg/l
SHBG	32.4	27.1 - 128 nmol/l
Testosteron total	4.64	0.101 – 1.67 nmol/l
TSH basal	0.17	0.27 - 4.20 mU/l

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luzerner kantonsspital
LUZERN SURSEE WOLHUSEN

Zusammenfassung

- seltene Tumorerkrankung
- hormonaktiv – hormoninaktiv

- interdisziplinärer Betreuung an Zentrumspital essentiell
- resezierbar:
  - Operation
  - Mitotan + Chemotherapie
    - individualisiert abhängig vom ENSAT-Stage, Resektions-Status, Ki67-Index
- nicht-resezierbar
  - Mitotan
  - Chemotherapie
  - lokale Therapien
- Mitotan
  - NW: NNR-Insuffizienz, gastrointestinal, neurologisch

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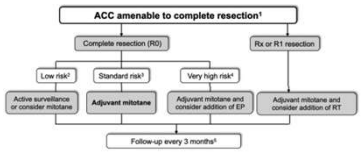
luzerner kantonsspital
LUZERN SURSEE WOLHUSEN

NNR-Ca (**T2**>5cm, **T3**: Invasion, Ln Meta, **T4** Meta) Lokale Radiatio, Mitotane (Lysodren BMS Tbl. 0.5-1g QID Blutspiegel 14-20mg/L, NW: GIT, Leber Neurol.-, ~~≈50% Remission, v.a. junge Pat~~)

ACC (ENSAT staging) resectable: individualized (depending on ENSAT, degree of resection, Ki67 index): **Surgery,** mitotane (Lysodren tab 0.5-1g QID, blood level 14-20mg/L, side effects: adrenal insufficiency, GIT, neuro), chemotherapy, local radiotherapy; unresectable: **mitotane** (s.a.), chemotherapy, local therapies (RT, SIRT, RFA).

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0
	T3–T4, N0–N1, M0
IV	T1–T4, N0–N1, M1

T1: tumor ≤5 cm; T2: tumor >5 cm; T3: infiltration into surrounding tissue; T4: tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein; N0: no positive lymph node; N1: positive lymph node; M0: no distant metastases; M1: presence of distant metastases.



- low risk: ENSAT I /II + Ki67 <10%
- standard risk: ENSAT I/II + Ki67 10-30%; ENSAT III + Ki67 <30%
- very high risk: ENSAT I/II/III + Ki67% >30%; ENSAT IV, R1-Resektion

Terzolo & Fassnacht. Our experience with the management of patients with non-metastatic adrenocortical carcinoma. European Journal of Endocrinology, 2022.

Parameter	Interval	Comment
Mitotane blood level	Every 6–9 weeks[1]	Target: 14–20 mg/L
ACTH	Suspected glucocorticoid deficiency or excess	Glucocorticoid status is difficult to determine Target: ACTH in the normal range or slightly above (e.g. < 2 times the ULN)
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 (>3 times of baseline), there is an increasing risk of liver failure: Interrupt mitotane
TSH, fT4	Every 3–4 months	Reduction of fT4 is frequent. Thyroid hormone replacement is a debated issue
Renin	Every 6 months	If renin ↑↑ and K in the high normal range, add fludrocortisone Target: renin two to three times the normal range
Cholesterol (HDL, LDL), triglycerides	Every 3–4 months	If total and LDL cholesterol ↑↑, consider treatment with statins not metabolized by CYP3A4
Blood count	Every 3–4 months	Check for rare (and in only few cases severe) leucopenia, thrombocytopenia, and anemia
LH, testosterone, SHBG[2]	In case of symptoms of hypogonadism	Reduction of testosterone levels may be masked by increased SHBG and calculation of free testosterone is recommended. Testosterone replacement is a debated issue

[1]In the first 3 months, mitotane blood levels should be checked more frequently. Additional measurements may be needed in case of severe toxicity (in particular, neurological toxicity). [2]In male patients.

Danke für die Aufmerksamkeit!

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