THE ADRENOCORTICAL CARCINOMA

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Conference presented at 27-th National Congress of
Italian Society of Endocrine Surgery, Cagliary, Italy, October 2008

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Abstract:
Adrenocortical carcinoma (ACC) is a rare tumor with a poor prognosis. Overall incidence is about 0.5-2 / milion inhabitants. ACC could be secreting (about 60% from all the cases) or non-secreting (diagnosed espacially as an incidentaloma during an ultrasound or CT-scan exam). The paper discuss the difficulties of positive diagnosis for ACC, from point of view of histological exam (Weiss criteria), biological markers (e.g. Ki67, p53), imagery techniques (CT-scan, IRM, scintigraphy). Treatment of the ACC is also challenging; radical surgery is possible in early stages. Large „en bloc" resections it is also recommended in locally advance stages. The place of adjuvant therapy and reoperations for recurrence is also discussed. The experience in ACC surgery of the Department of Surgery from Padova University is also presented. Conclusions: ACC carries a poor prognosis for patients commonly presenting with large, locally invasive tumors, and metastatic disease. A precocious diagnosis using imagery and histologic criteria, aggressive surgery and novel therapies may help to increase survival, which has remained unchanged over the last 20 years.

KEY WORDS: ADRENOCORTICAL CARCINOMA, DIAGNOSIS, PRONOSTIC FACTORS, ADRENALECTOMY[*]

[*]Conference presented at 27-th National Congress of Italian Society of Endocrine Surgery, Cagliary, Italy, October 2008

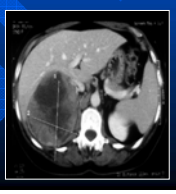
ADRENOCORTICAL CARCINOMA

- Incidence: 0.5-2 / milion inhabitants /year
- Preoperative Diagnosis - "Difficult"
- Histological Diagnosis - "Difficult": FOLLOW UP
- Surgery is "Radical"(?): ⇨ RECCURENCES ⇩ REINTERVENTIONS

ADRENOCORTICAL CARCINOMA

- SECRETING (60%)
  - 30% HYPERCORTISOLISM
  - 22% VIRILITY
  - 10% FEMININITY
  - 3%HYPERALDOSTERONISM
  - 35% MIXTED SECRETIONS

- NON-SECRETING (40%)
  - INCIDENTALOMA



THE SURGERY OF ADRENOCORTICAL CARCINOMA

What had been changed ?

NEW ISSUES

- ✓ IMPROVEMENT of HISTOLOGICAL DIAGNOSIS
- ✓ IMPROVEMENT of RADIOLOGICAL DIAGNOSIS
- ✓ AGGRESSIVE SURGERY
- ✓ ADJUVANT TERAPY(?)

ADRENOCORTICAL CARCINOMA

HISTOLOGICAL DIAGNOSIS

WEISS CRITERIA

1. HIGH DEGREE OF NUCLEATION
2. >5 MITOSIS PER 50 HPF
3. ATIPICAL MITOSIS
4. CITOPLASMATIC EOSINAFILY (>75% cellule tumorali)
5. FIBROSIS AND TRABECOLARY STRIPS
6. NECROSIS
7. VENOUS INVASION
8. SINUSOIDAL INVASION
9. CAPSULAR INFILTRATION

WEISS < 3

WEISS > 4

0 1 2 3 4 5 6 7 .....

Adenoma

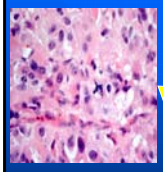
Carcinoma

Weiss, 9

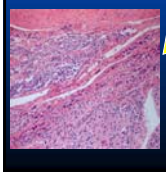
ADRENOCORTICAL CARCINOMA

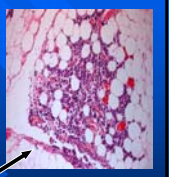
HISTOLOGICAL DIAGNOSIS

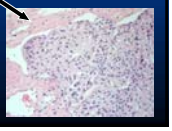
WEISS CRITERIA



HIGH DEGREE OF NUCLEATION
>5 MITOSIS PER 50 HPF
ATYPICAL MITOSIS
CYTOPLASMATIC EOSINOFILIA
FIBROSIS
NECROSIS
VENOUS INVASION
CAPSULAR INFILTRATION







ADRENOCORTICAL CARCINOMA

HISTOLOGICAL DIAGNOSIS

WEISS < 3

WEISS > 4

0 1 2 3 4 5 6 7 .....

Adenoma

Carcinoma

???

PROBLEMATIC CASES:

Just the present or the appearance of recurrence or the systemic metastasis could confirm the diagnosis of MALIGNITY

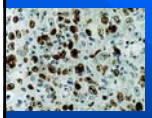
We need other MARKERS !!!

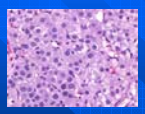
ADRENOCORTICAL CARCINOMA

HISTOLOGICAL DIAGNOSIS

■Ki-67

■p53





➢Higher in Carcinoma (36%) lower in Adenoma (0%)

➢Correlation with Survival

Diagnosis criteria

Prognosis factor

Martins 2005
Stojadinovic 200

ADRENOCORTICAL CARCINOMA

HISTOLOGICAL DIAGNOSIS

■ Insulin like Growth Factor II (IGF 2)

Growth factor

(cromosome 11 p15)

➢Higher in Carcinoma (90%) lower in Adenoma (0%)

➢Correlation with survival

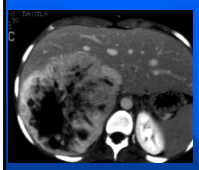
Diagnosis criteria

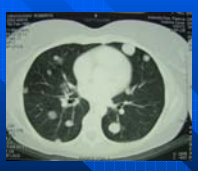
Prognosis factor

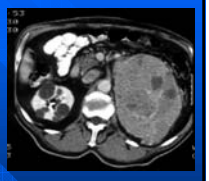
Sidhu 2003

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS



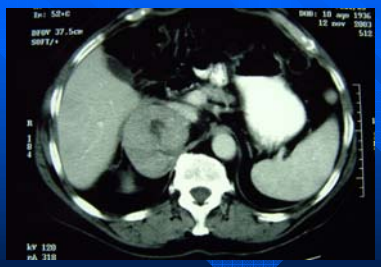




General speaking, it is easy to establish the diagnosis of "adrenal tumor"and in some cases to establish the diagnosis of adrenal carcinoma (e.g. invasion, metastasis).

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

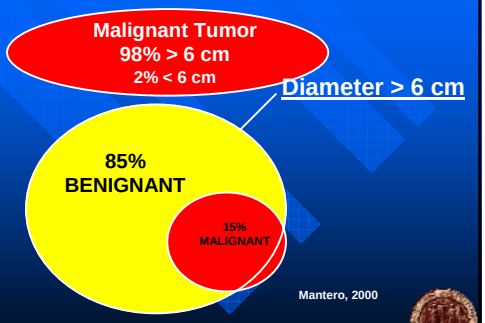


It is difficult to differentiate a carcinoma from a benign tumor (incidentaloma).

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

VOLUMETRIC Criteria



Mantero, 2000

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

LIMITS of the CUT-OFF POINT

< 6cm → FOLLOW UP → 2-4%: Carcinoma

> 6cm → SURGERY → 85%: Benignant tumor

TABLE 5. Diagnostic power of different cut-off values for mass size (CT measurement) in the differentiation of primary adrenocortical cancer from benign masses

Mass size (cm)	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)
4	93	42	16	98
5	81	63	21	96
6	74	73	25	96

Mantero, 2000

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the CT-SCAN

- Size
- Regular form
- Clear-cut
- Homogeneous lession

DENSITY - HU*

without contrast

correlation with lipidic content

ADENOMA: High lipidic content

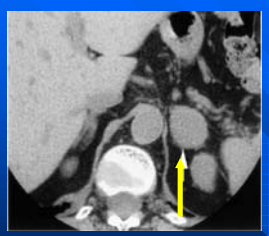
CARCINOMA: Low lipidic content

* Hounsfield units

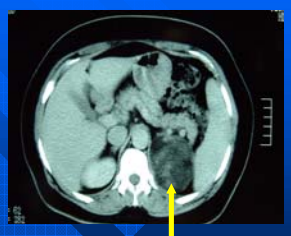
ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the CT-SCAN



25 HU:
SMALL MALIGN TUMOR



2 HU:
LARGE BENIGN MASS

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the CT-SCAN

• DENSITY without contrast < 10 HU

Benign vs Malign

SENSIBILITY - 71%
SPECIFICITY - 98%

Boland 1998

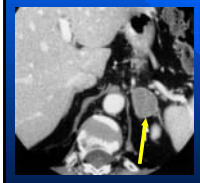
ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

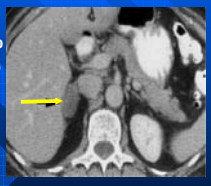
ROLE of the CT-SCAN

DENSITY (HU) with contrast < 30 HU

Benign vs Malign



SENSIBILITY – 69%
SPECIFICITY - 97%



75 HU:
MALIGN TUMOR

21 HU:
BENIGN MASS

Al-Hawary 1998

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the IRM

- Size
- Vascular Invasion

•Hyperintensity in T2

The intensity in T2 is correlated with fluid content

ADENOMA
Low Fluid Content

CARCINOMA
High Fluid Content

Al-Hawary 2005

ADRENOCORTICAL CARCINOMA

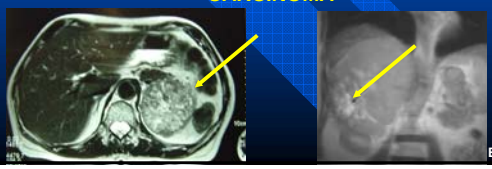
IMAGERY DIAGNOSIS

ROLE of the IRM

Hyperintensity in T2
+
Chemical Shift

Diagnosis accuracy of 98%

ADRENOCORTICAL CARCINOMA

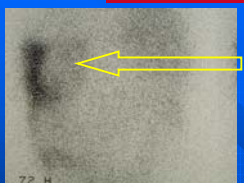


Elsayes 2004

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the SCINTIGRAPHY



Low level of radionuclid into the tumor.

Management of incidentally discovered adrenal masses and risk of malignancy

Gennaro Favia, MD, Franco Lumachi, MD, Stefano Basso, MD, and Davide F. D'Amico, MD, *Padua, Italy*

Technique	*No. of patients*	*TP (n)*	*TN (n)*	*FP (n)*	*FN (n)*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
CT scan	68	15	45	3	5	75.0	93.7	83.3	90.0
MRI	26	7	18	0	1	87.5	100	100	94.7
NCS	54	9	25	0	0	100	100	100	100
FNAB	19	7	12	0	0	100	100	100	100

Limits:
High Price

Surgery, 2000

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

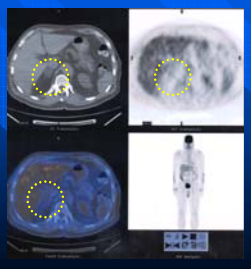
ROLE of the PET-CT

PET (18FDG) → marker of cell metabolism

TC → morphological correlation

Advantage:
Accuracy in diagnosis
(86-96%)

Limits:
High price
Low disponibility



Bergstrom 2000
Jana 2005

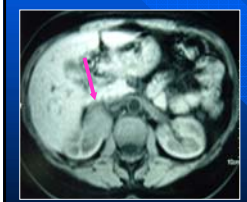
ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the PET-CT

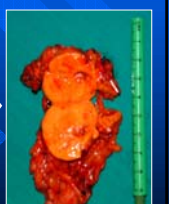
Endocrinosurgery PD (2003-2007)
n=20 cases

Sensibility : 75%; Specificity: 75%



RMN
(suspicion of renal infiltration)

PET
(negative)

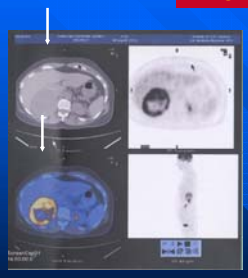


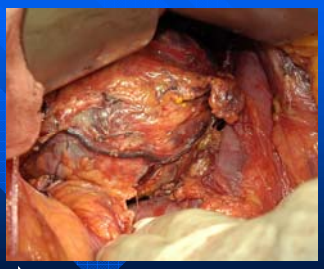
ADENOMA

ADRENOCORTICAL CARCINOMA

IMAGERY DIAGNOSIS

ROLE of the PET-CT



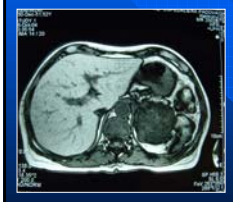


PET-TC positive Carcinoma ⇨ ADRENOCORTICAL

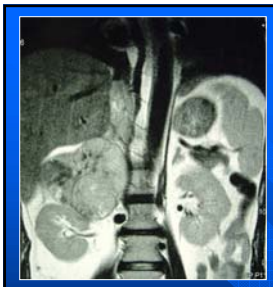
ADRENOCORTICAL CARCINOMA

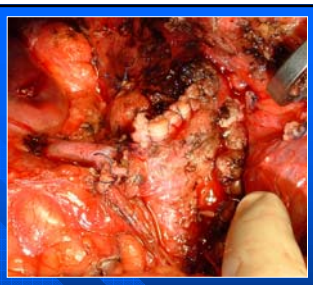
SURGICAL TREATMENT

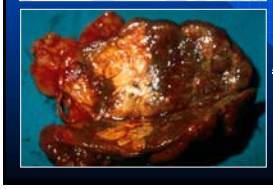
- "RADICAL" SURGERY ➡ "En bloc" large resection



Adrenal carcinoma - Left Adrenal Gland
Adrenalectomy + Nephrectomy



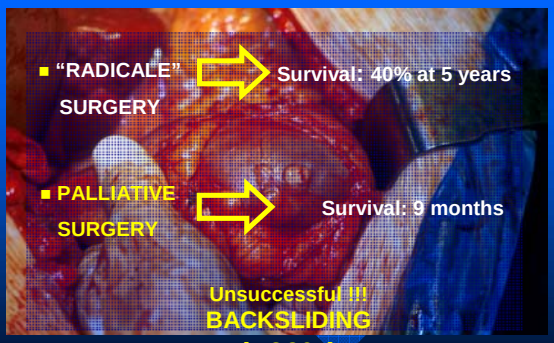




Adrenal carcinoma - Right Adrenal Gland
Open Adrenalectomy
+ resection and thrombectomy

ADRENOCORTICAL CARCINOMA

SURGICAL TREATMENT



- "RADICALE" SURGERY ⇨ Survival: 40% at 5 years
- PALLIATIVE SURGERY ⇨ Survival: 9 months

Unsuccessful !!!
BACKSLIDING
(>60%)

Dackiw 2001

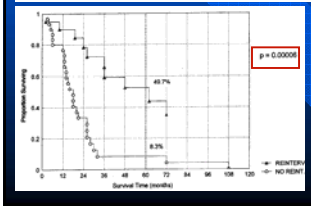
ADRENOCORTICAL CARCINOMA

SURGICAL TREATMENT

ROLE of the OPERATION

Role of reoperation in recurrence of adrenal cortical carcinoma: Results from 188 cases collected in the Italian National Registry for Adrenal Cortical Carcinoma

Conclusions. *Although the prognosis of this tumor is still poor, surgery is the only effective therapy; reoperation allows survival comparable to that observed in patients without recurrent disease. An aggressive strategy for recurrent ACC is advisable until prospective studies demonstrate a real effectiveness for chemotherapy. (Surgery 1997;122:1212-8.)*

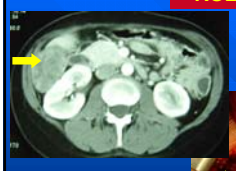


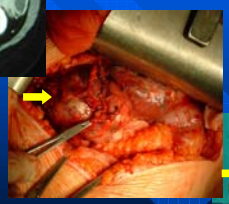
"FOLLOW "
The Backslides!!!

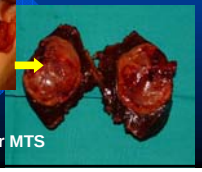
ADRENAL CARCINOMA

SURGICAL TREATMENT

ROLE of the OPERATION





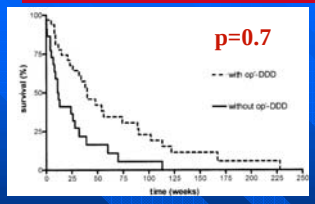


ADRENOCORTICAL Carcinoma
2-nd Reoperation - Hepatic Resection for liver MTS

ADRENCORTICAL CARCINOMA

ADJUVANT THERAPY

ROLE of the MITOTANE



NO effects in survival (p=0.7)

…but…

Icard 2001

ADRENCORTICAL CARCINOMA

ADJUVANT THERAPY

ROLE of the MITOTANE

Berruti at al *Endocr Relat Cancer*. 2005; 12(3): 657

Etoposide, doxorubicin and cisplatin plus mitotane in the treatment of advanced adrenocortical carcinoma: a large prospective phase II trial.

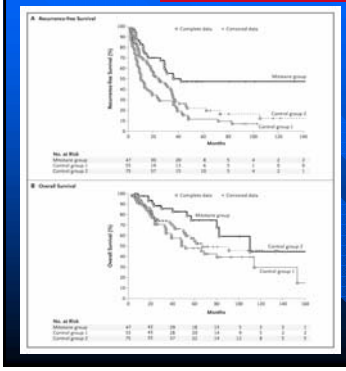
"Down-staging"

Increase up the median survival (p<0.002)

ADRENCORTICAL CARCINOMA

ADJUVANT THERAPY

ROLE of the MITOTANE



Disease Free-Survival (p<0.01)

Survival
Vs German Group (p<0.01)
Vs Italian Group (p=NS)

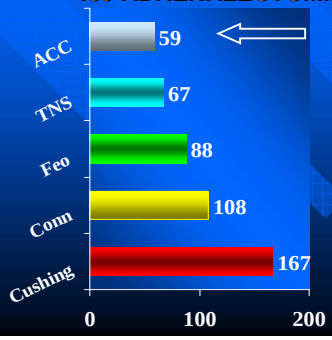
NEJM 2007

ENDOCRINOSURGERY

University of Padova

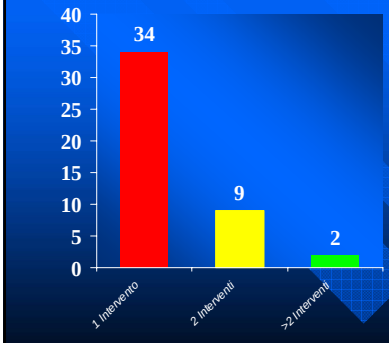
1985 - 2008

489 ADRENALECTOMIES



The cases of ENDOCRINOSURGERY PD (1985– 2008)

Patients with ACC = 45



TOTAL NUMBER 59 OPERATIONS

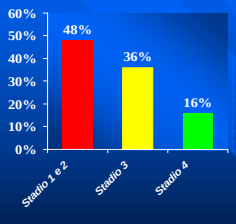
Median Age: 50 years (range 25-75)

Sex Ratio W/M: 2

Median Size: 11 cm (range 4-19)

The cases of ENDOCRINOSURGERY PD (1985– 2008)

Statistics of First Intervention



Mortality perioperatory: 1 case (4-th Stage)

Survival after 1° Intervention

Survival	12 month	24 months	36 months	p
Grad 1 e 2	90%	74%	32%	<0,01
Grad 3 e 4	71%	29%	6%	

CONCLUSIONS

Histological diagnosis
Criteria of Weiss

⇩

Biological Markers
(Ki67, P53, IGF2)

CONCLUSIONS

PREOPERATIVE DIAGNOSIS
Insufficience of Volumetric Criteria

TC	RMN	PET - TC
(Density)	(T2 e Chemical Shift)	

✓Precocious Diagnosis

✓Improvement of Prognosis

CONCLUSIONS