Adrenocortical carcinoma (ACC) is a rare tumor with a poor prognosis. Overall incidence is about 0.5-2 / million inhabitants. ACC could be secreting (about 60% from all the cases) or non-secreting (diagnosed especially as an incidentaloma during an ultrasound or CT-scan exam). The paper discusses the difficulties of positive diagnosis for ACC, from a point of view of histological exam (Weiss criteria), biological markers (e.g. Ki67, p53), imagery techniques (CT-scan, MRI, scintigraphy). Treatment of the ACC is also challenging: radical surgery is possible in early stages. Large “en bloc” resections is also recommended in locally advanced 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 histological 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

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**ADRENOCORTICAL CARCINOMA**

- Incidence: 0.5-2 / million inhabitants /year
- Preoperative Diagnosis - “Difficult”
- Histological Diagnosis - “Difficult”: FOLLOW UP
- Surgery is “Radical”?: RECURRANCES
  \[\Rightarrow\]
  \[\rightarrow\]
  REINTERVENTIONS

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**THE SURGERY OF ADRENOCORTICAL CARCINOMA**

What had been changed?

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**NEW ISSUES**

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

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**ADRENOCORTICAL CARCINOMA**

- **SECRETING** (60%)
  - 35% HYPERCORTISOLISM
  - 22% VIRILITY
  - 10% FEMININITY
  - 3% HYPERALDOSTERONISM
  - 35% MIXED SECRETIONS
- **NON-SECRETING** (40%)
  - INCIDENTALOMA
ADRENOCORTICAL CARCINOMA

HISTOLOGICAL DIAGNOSIS

WEISS CRITERIA

1. HIGH DEGREE OF NUCLEATION
2. >5 MITOSIS PER 50 HPF
3. ATYPICAL MITOSIS
4. CYTOPLASMATIC EOSINOFILIA (>75% of tumor cells)
5. FIBROSIS AND TRABECULAR STRIPS
6. NECROSIS
7. VENOUS INVASION
8. SINUSOIDAL INVASION
9. CAPSULAR INFILTRATION

WEISS < 3

WEISS > 4

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

WEISS CRITERIA

- Ki-67
- p53

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

Correlation with Survival

Diagnosis criteria
Prognosis factor

ADRENOCORTICAL CARCINOMA

HISTOLOGICAL DIAGNOSIS

Insulin like Growth Factor II (IGF 2)

Growth factor (chromosome 11 p15)

- Higher in Carcinoma (90%) lower in Adenoma (0%)
- Correlation with survival

Diagnosis criteria
Prognosis factor

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

**VOLUMETRIC Criteria**

Malignant Tumor
- 90% > 6 cm
- 2% < 6 cm

BENIGN
- 85%
- 15%

**IMAGERY IMAGERY DIAGNOSIS**

**ADRENOCORTICAL CARCINOMA**

**SIZE**
- Regular form
- Clear-cut
- Homogeneous lesion

**DENSITY - HU**
- High lipidic content without contrast
- Low lipidic content

**ROLE of the CT-SCAN**

- Sensibility - 71%
- Specificity - 98%

**ROLE of the CT-SCAN**

- Density without contrast < 10 HU
- Benign vs Malign

**VOLUMETRIC Criteria**

- Diameter > 6 cm
- 85% BENIGN
- 15% MALIGNANT

**LIMITS of the CUT-OFF POINT**

- < 6 cm: 2-4% Carcinoma
- > 6 cm: 85% Benign tumor

**ROLE of the CT-SCAN**

- 25 HU: SMALL MALIGN TUMOR
- 2 HU: LARGE BENIGN MASS

**TABLE 5. Diagnostic power of different cut-off values for mean size (CT enhancement) is the differentiation of a patient's adrenocortical tumor from benign masses.**

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive PP (%)</th>
<th>Negative NP (%)</th>
</tr>
</thead>
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<td>10</td>
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<td>4</td>
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<td>98</td>
</tr>
</tbody>
</table>

Mantero, 2000

Mantero, 2000

Mantero, 2000

Boland 1998

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

ROLE of the IRM

HYPERINTENSITY in T2

The intensity in T2 is correlated with fluid content

ADENOMA
Low Fluid Content
CARCINOMA
High Fluid Content

Al-Hawary 2005

ROLE of the IRM

HYPERINTENSITY in T2

Chemical Shift

Diagnosis accuracy of 99%

Elsayes 2004

Surgery, 2000

ROLE of the SCINTIGRAPHY

Low level of radionuclid into the tumor.

PET (18FDG) marker of cell metabolism
TC morphological correlation

Advantage:
Accuracy in diagnosis (86-96%)

Limits:
High price
Low disponibility

Bergström 2000
Jana 2005

PET-CT

Endocrinosurgery PD (2003-2007)
n=20 cases

Sensibility: 75%; Specificity: 75%

RMN
PET (negative)

Articole Multimedia
Jurnalul de Chirurgie, Iaşi, 2008, Vol. 4, Nr. 4 [ISSN 1584 – 9341]
PATIENT: PET-TC positive ADRENOCORTICAL Carcinoma

**IMAGERY DIAGNOSIS**

**ROLE of the PET-CT**

PET-TC positive Carcinoma

**ADRENOCORTICAL CARCINOMA**

**SURGICAL TREATMENT**

* "RADICAL" SURGERY

- "En bloc" large resection

**Adrenal carcinoma - Left Adrenal Gland**

Adrenalectomy + Nephrectomy

**ADRENOCORTICAL CARCINOMA**

**SURGICAL TREATMENT**

- Adrenal carcinoma - Right Adrenal Gland

Open Adrenalectomy + resection and thrombectomy

Deckwe 2001

**ADRENOCORTICAL CARCINOMA**

**SURGICAL TREATMENT**

- "RADICAL" SURGERY

Survival: 40% at 5 years

- PALLIATIVE SURGERY

Survival: 5 months

Unsuccessful: BACKSLIDING (>60%)

"FOLLOW "The Backslides!!!

**ADRENOCORTICAL CARCINOMA**

**SURGICAL TREATMENT**

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, operation allows survival comparable to that observed in patients without recurrent disease. An aggressive strategy for recurrence, NAC, is advisable until prospective studies demonstrate a real effective role for chemotherapy (Surgery 1997;112:1126).

**ADRENOCORTICAL Carcinoma**

2-nd Reoperation - Hepatic Resection for liver MTS
Icard 2001

NO effects in survival (p=0.7) …but…


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)

Endocr Relat Cancer

ADRENCORTICAL CARCINOMA
ADJUVANT THERAPY
ROLE of the MITOTANE

NEJM 2007

Disease Free-Survival (p<0.01)

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

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)

Mortality per operative: 1 case (4-th Stage)

Survival after 1° intervention

Survival 12 months 24 months 36 months
Grad 1 e 2 96% 74% 32% 10%
Grad 3 e 4 71% 29% 6% 0%

University of Padova

1985 - 2008

489 ADRENALECTOMIES

The cases of ENDOCRINOSURGERY PD (1985- 2008)
CONCLUSIONS

Histological diagnosis
Criteria of Weiss

Biological Markers
(Ki67, P53, IGF2)

CONCLUSIONS

PREOPERATIVE DIAGNOSIS
Insufficiency of Volumetric Criteria

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

✓ Precocious Diagnosis
✓ Improvement of Prognosis

CONCLUSIONS

Surgery still remain today the only treatment even if we could not obtain the Radicality

Backslides

Reoperations could improve the survival

Adjuvant Therapy ??