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Adrenal Carcinoma

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Questions

- How many do adrenalectomy?
  - laparoscopic adrenalectomy?
- How many use laparoscopic adrenalectomy for malignancy?
  - Metastases?
- How many use percutaneous biopsy for work-up of adrenal masses?

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Adrenal cancer

- Biopsy of Adrenal Masses
- Laparoscopic adrenalectomy for Malignancy
- Systemic therapy for adrenal cancer

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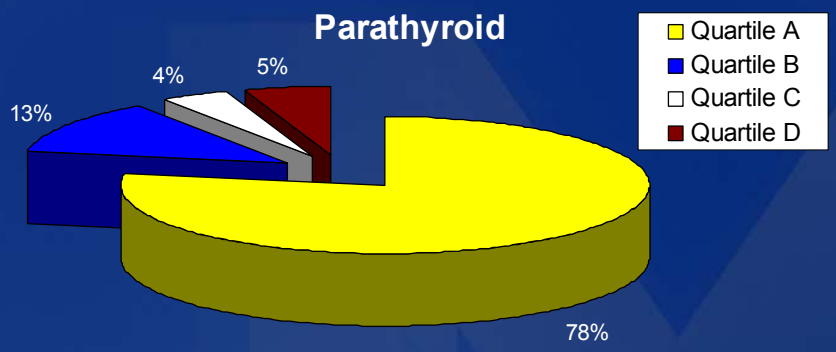
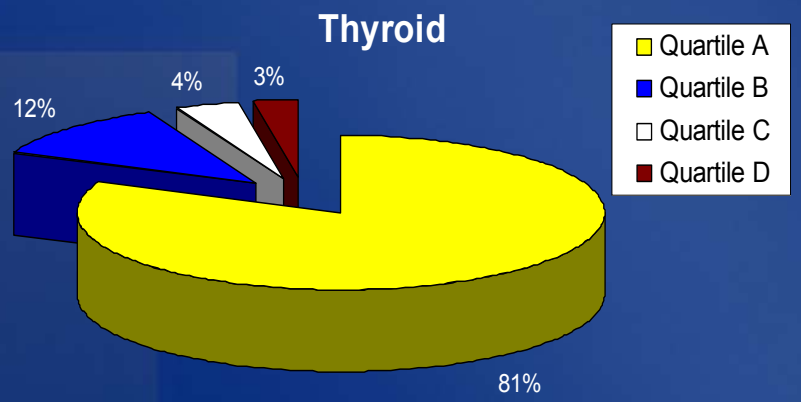
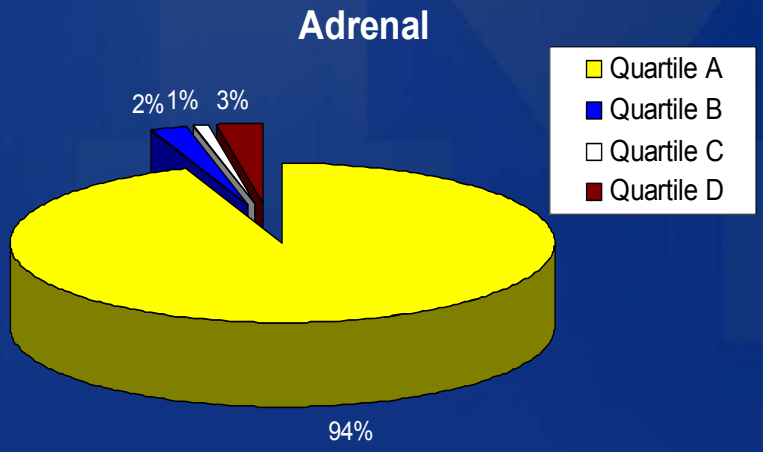
Fraction of Primary Surgeon Practice in Endocrine Surgery







A=0-25 %
B=26-50%
C=51-75%
D=76-100%

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Adrenocortical Carcinoma

- Signs/Symptoms:
  - 60% are functional and produce hormone excess related symptoms
    - Rapidly progressive Cushing syndrome
    - Mixed Cushing syndrome and an androgential disorder
  - 75% locally aggressive at time of diagnosis, median survival of 18 months following diagnosis. Tumor grade important for survival.
  - Non-functional tumors (or asymptomatic functioning tumors)
    - Abdominal pain/mass, weight loss, fatigue, nausea
- Diagnosis
  - Biochemical testing for hormone levels.
  - Contrast-enhanced CT of chest and abdomen, PET scan.
- Treatment
  - Surgical resection: minority are resectable with curative intent.
  - 38-85% recurrence rate after surgery.
  - Chemotherapy: no efficacy, adjuvant too toxic.

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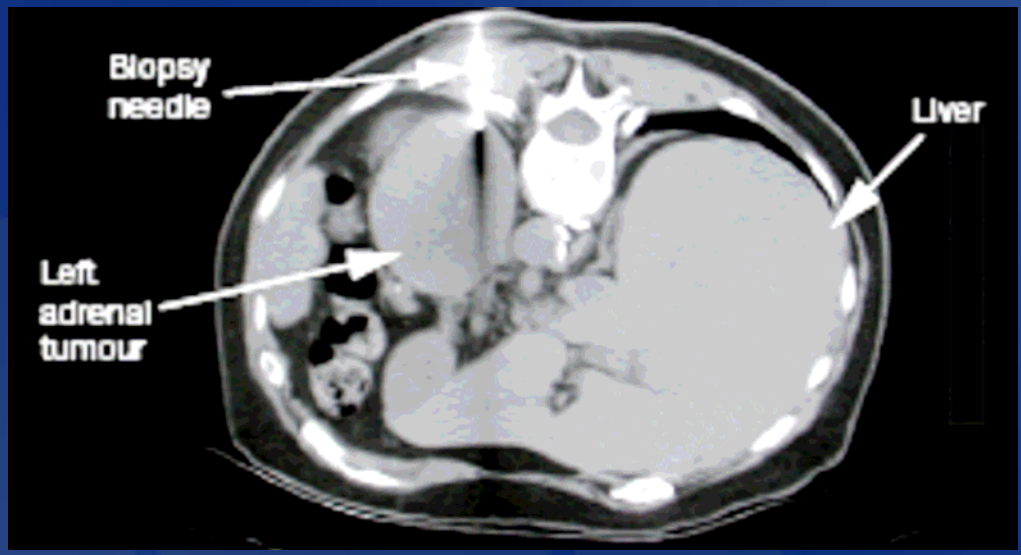
Biopsy of Adrenal Masses



- Don't Biopsy Adrenal Masses
  - Unless the patient has a known primary malignancy elsewhere
- Spread of Tumor
- Poor Information

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Adrenal cancer

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Collected series

Institution	N (patients)	Bilateral	Converted to open
Rush Medical College 1995	11	0	1
Univ. of Barcelona 1996	31	4	1
Greenslopes / Brisbane 1996	67	0	0
UCSF 1996	23	0	0
Washington University 1996	24	3	0
Hotel Dieu /Cleveland Clinic 1997	88	10	3
Vanderbilt 1997	19	0	0
Univ. Of Washington 1997	16	3	0
Mayo Clinics 1997	57	4	7
US NIH 1997	20	0	2
Belgium (multicenter) 1997	52	2	2
Univ.di Ancona 1998	50	1	0
Total	**459**	**27**	**16**

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Collected series: Morbidity and Mortality

- 41 complications and 1 death
- Death with multiorgan failure in an elderly man after adrenalectomy for Cushings adenoma
- 3 patients with perioperative bleeding requiring transfusion
- 2 patients required reoperation for bleeding
- 7 with documented deep venous thrombosis
- 3 with pulmonary emboli

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Laparoscopic adrenalectomy for malignancy?

- Safe?
- Effective?
  - Worry about recurrence - port site and intra-abdominal
  - Ability to do complete resection
- What if diagnosis is uncertain?

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Laparoscopy for primary malignancy

Table 1. Reported series of laparoscopic adrenalectomy for primary adrenal cancers

Adrenal disease	Patients	Tumour size (cm)	Conversions	Port site	Recurrences		Mean time to recurrence* (months)	Deaths	Ref
					Local	Distant			
Adrenocortical carcinoma	1	5·90	0	0	0	0	19·0	0	8
Adrenocortical carcinoma (n=6) Undifferentiated adrenal carcinoma (n=1)	7	6·60	1	0	2	1	39·6	NR	42
Adrenocortical carcinoma	1	5·00	0	0	1	1	21·0	1	44
Adrenocortical carcinoma (n=2) Sarcoma (n=1)	3	5·16	1	0	0	0	48·0	0	52
Adrenocortical carcinoma	6	7·70	2	0	0	1	6·0	1	53
Adrenocortical carcinoma	1	NR	NR	0	0	1	6·0	NR	54
Adrenocortical carcinoma	1	NR	NR	0	1	0	19·0	NR	55
Adrenocortical carcinoma	1	NR	NR	1	1	1	26·0	NR	56
Adrenocortical carcinoma	1	NR	NR	0	1	0	NR	NR	57
Adrenocortical carcinoma	4	NR	NR	0	1	0	16·0	NR	53†
Adrenocortical carcinoma	1	NR	NR	0	1	1	6·0	NR	58
Phechromocytoma	2	NR	NR	0	0	1	48·0	NR	59
Adrenocortical carcinoma	1	NR	NR	0	0	1	6·0	NR	60
Adrenocortical carcinoma	1	2·00	0	0	0	1	6·0	NR	61
Adrenocortical carcinoma	1	5·00	0	0	1	1	19·0	1	62

*Longest reported follow-up if no recurrence. †Abstract discussed in ref 53. NR, not recorded.

Adrenal Ca: N=26;
Recurrences: Port:1, Local:9, Distant: 9

Saunders B, Doherty GM. Lancet Oncol 2004

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Laparoscopy for Adrenal Metastases

Table 2. Reported series of laparoscopic adrenalectomy for adrenal-gland metastases

Patients	Tumour size (cm)	Conversions	Port site	Recurrences		Follow-up (months)	Deaths	Ref
				Local	Distant			
11	5·9	1	0	0	2	8·3	1	8
23	4·8	1	0	0	4	39·6	NR	42
2	5·5	1	0	0	1	8·0	1	62
41	4·5	0	0	NR	NR	21·0	NR	73
1	2·5	0	1	1	1	10·0	1	74
11	NR	NR	1	1	1	NR	NR	75

NR, not recorded.

- Adrenal metastases: N=89
- Recurrences: Port: 2, Local: 2, Distant 9
- Laparoscopy appears to be more safe and applicable for metastasectomy than for primary adrenal malignancy

Saunders B, Doherty GM. Lancet Oncol 2004

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Laparoscopic adrenalectomy for malignancy?

- Safe? Yes
- Effective? Not for primary disease
  - Worry about recurrence - port site and intra-abdominal
  - Ability to do complete resection
- What if diagnosis is uncertain? Probably can explore laparoscopically, and convert

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Adrenal cancer

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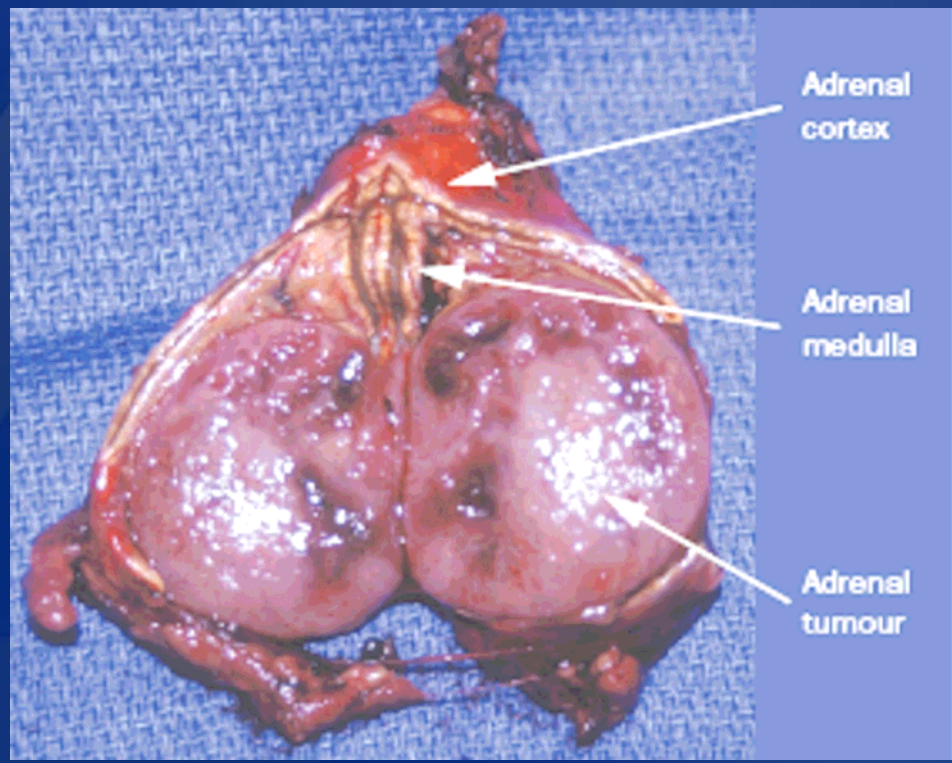
Systemic therapy for Adrenocortical Cancer

- Consensus meeting in Ann Arbor, USA in 2003.
- No clearly effective systemic regimens, and no informative trials
- Decision to study two regimens with activity



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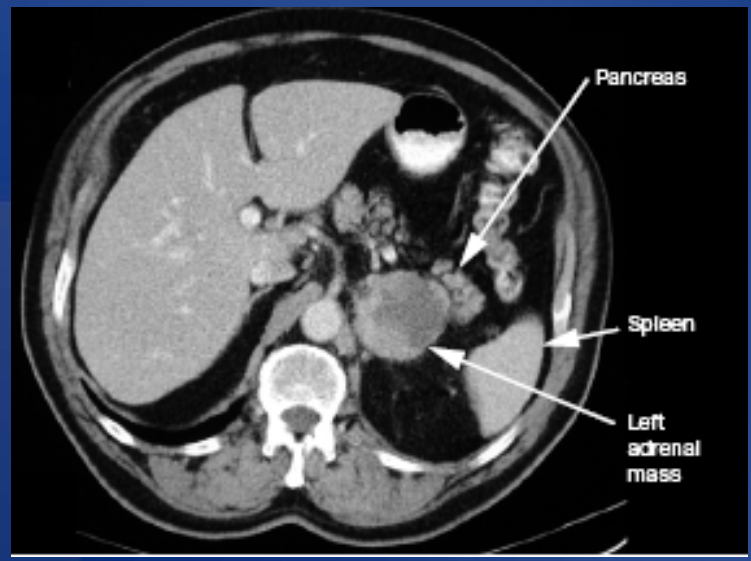
FIRM-ACT Trial: Collaborative Group for Adrenocortical Carcinoma Treatment*



- Patients with locally advanced or metastatic adrenocortical cancer not amenable to resection
- Randomizes EDP-M [etoposide, doxorubicin, cis-platinum, mitotane] versus Sz-M [streptozotocin, mitotane]
- Expected Total Enrollment: 300
- Study start: June 2004; Expected completion: December 2011
  Last follow-up: December 2010; Data entry closure: March 2011

*FIRM-ACT: First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment

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FIRM-ACT Trial: Collaborative Group for Adrenocortical Carcinoma Treatment

- Primary Outcomes: Overall survival
- Secondary Outcomes:
  - Time to progression;
  - Quality of life as measured by QLQ-C30;
  - Best overall response rate and duration of response;
  - Number of disease-free patients;
  - Impact of reaching mitotane blood levels between 14-20 mg/l in both arms on survival and overall response rate;
  - TTP of both regimens as second line treatment in case of failure of the other initial regime

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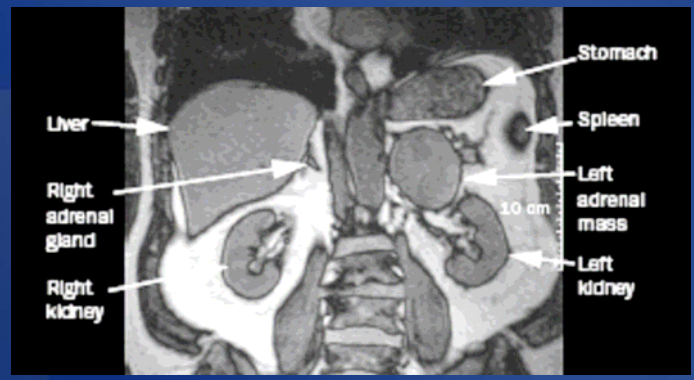
FIRM-ACT: Inclusion Criteria

- Inclusion Criteria:
- Histologically confirmed diagnosis of adrenocortical carcinoma
- Locally advanced or metastatic disease not amenable to radical surgery resection (Stage III-IV)
- Radiologically monitorable disease
- ECOG performance status 0-2
- Life expectancy > 3 months
- Age ≥18 years
- Adequate bone marrow reserve (neutrophils > 1500/mm3 and platelets > 100,000/mm3)
- Effective contraception in pre-menopausal female and male patients
- Patient's written informed consent
- Ability to comply with the protocol procedures (including availability for follow-up visits)
- Previous palliative surgery, radiotherapy or radiofrequency ablation is acceptable as long as radiologically monitorable disease is verifiable afterwards.



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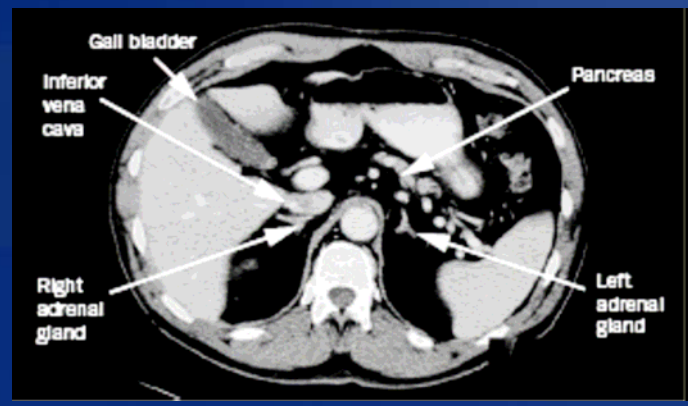
FIRM-ACT Exclusion Criteria

- History of prior malignancy, except for cured non-melanoma skin cancer, curatively in situ cervical carcinoma, or other cancers treated with no evidence of disease for at least five years.
- Previous cytotoxic chemotherapy for adrenocortical carcinoma
- Renal insufficiency (serum creatinine ≥2 mg/dl or creatinine clearance ≤ 50 ml/min)
- Hepatic insufficiency (serum bilirubin ≥2 x the institutional upper limit of normal range and/or serum transaminases ≥ 3 x the institutional upper limit of normal range; exception: in patients on mitotane, transaminase levels up to 5 x the institutional upper limit of normal range are acceptable)
- Pregnancy or breast feeding
- Known hypersensitivity to any drug included in the treatment protocol
- Presence of active infection
- Any other severe clinical condition that in the judgment of the local investigator would place the patient at undue risk or interfere with the study completion
- Decompensated heart failure (ejection fraction <50%), myocardial infarction or revascularization procedure during the last 6 months, unstable angina pectoris, and uncontrolled cardiac arrhythmia
- Current treatment with other experimental drugs and/or previous participation in clinical trials with other experimental agents for adrenocortical carcinoma
- Prisoners



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FIRM-ACT Participating Institutions
Study chair:Britt Skogseid Uppsala University

http://clinicaltrials.gov/

- **France**
  - Institut Gustave Roussy, Eric Baudin
  - Clinique Marc Linquette, Lille, J Wemeau
  - Centre Leon Berard, Lyon, Jean Piere Droz
  - Cochin Hospital, Paris, Francois Goldwasser
  - Hospital de Marseille la timone, Patricia Niccoli Sire
  - Hospital Bordeaux , Pessac, Antoine Tabarin
- **Germany**
  - University of Wuerzburg, Bruno Allolio
  - University of Duesseldorf, Matthias Schott
  - University of Munich, Martin Reincke
  - Otto-von-Guericke University; Hendrik Lehnert
  - Charité-University, Campus Benjamin Franklin, Matthias Moehlig
  - Charité-Universitätsmedizin Berlin - Campus Mitte, Marcus Quinckler
  - Zentrum für Innere Medizin – Endokrinologie des Universitätsklinikum Essen, Stephan Petersenn
  - Endokrinologie Medizinische Hochschule Hannover, Georg Brabant
  - Dept. of Medicine III, Dresden, Stefan Bornstein
  - Dept of Medicine I, Mainz, Matthias M Weber
- **Michigan**
  - University of Michigan, David Schteingart
- **Australia**
  - Royal Adelaide Hospital, David Torpy
- **Italy**
  - University of Turin, Massimo Terzolo
  - Clinica Endocrinologica, Università di Padova, Azienda Ospedaliera di Padova, Franco Mantero
- **Netherlands**
  - Maxima Medisch Centrum; Eindhoven, Harm Haak
  - Academisch Medisch Centrum; Amsterdam, Hans de Vries
  - Leiden University Medical Center, Hans Romijn
  - University Hospital Groningen; Bruce Wolffenbuttel
  - Vrije Universiteit Medisch Centrum, Amsterdam, Mareliese Eekhoff
- **Sweden**
  - Uppsala University Hospital, Britt Skogseid
  - The Jubileum Institute, Lund University, Michael Garkavij
  - Sahlgrenska University Hospital, Gothenburg, Monica Sender
  - Linköping University Hospital, Najme Wall
  - Karolinska Hospital, Stockholm, Goran Wallin

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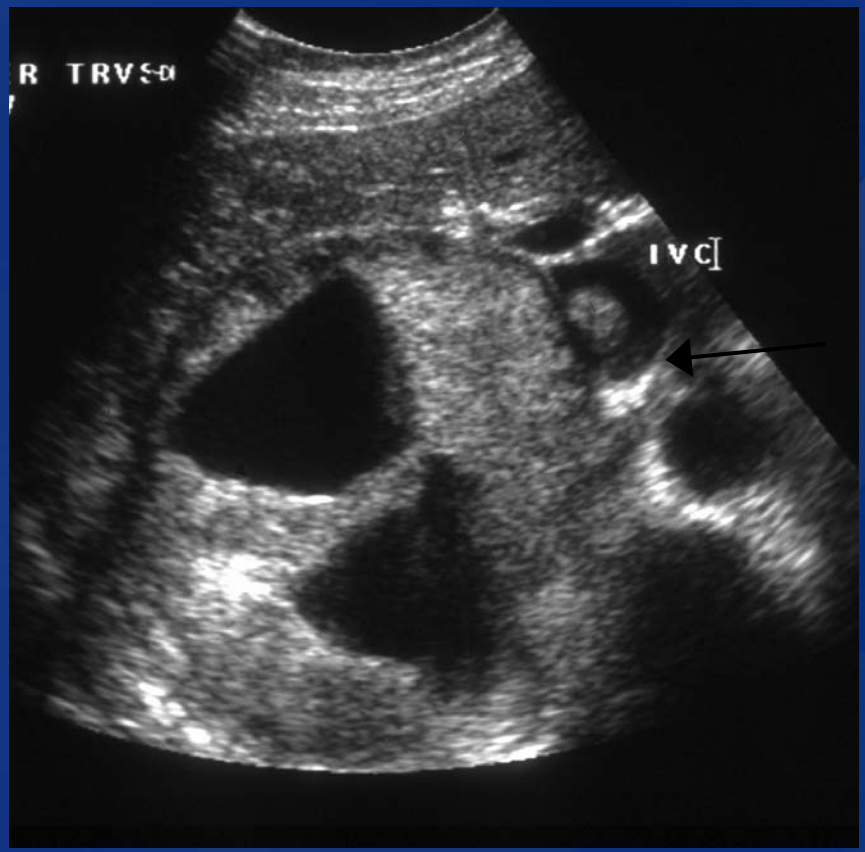
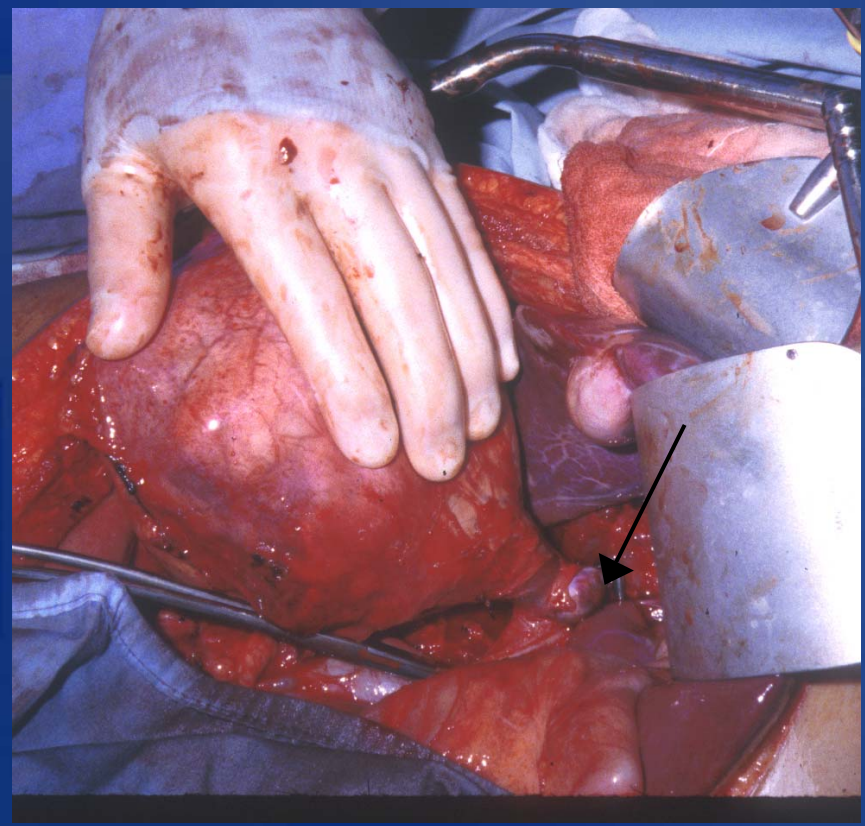
Imaging: Ultrasound





- Useful for specific questions in operative planning

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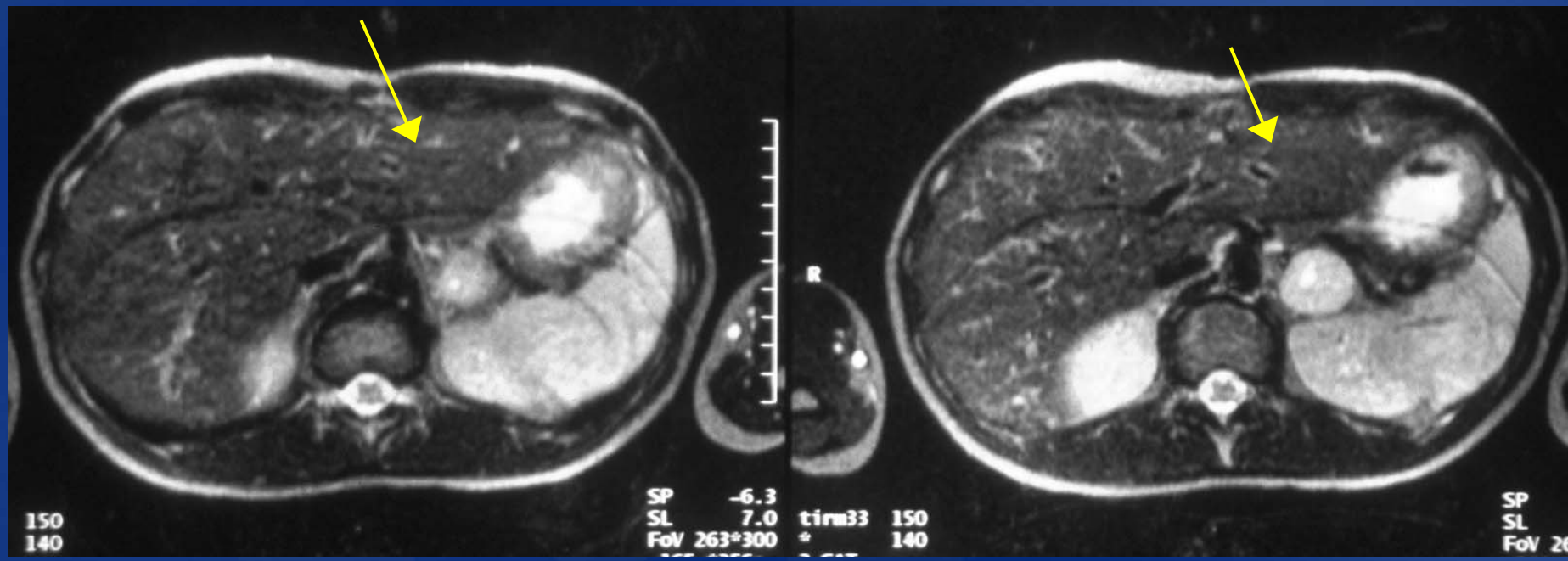
Imaging: MR



- Pheochromocytomas typically brighter than liver on T2 images

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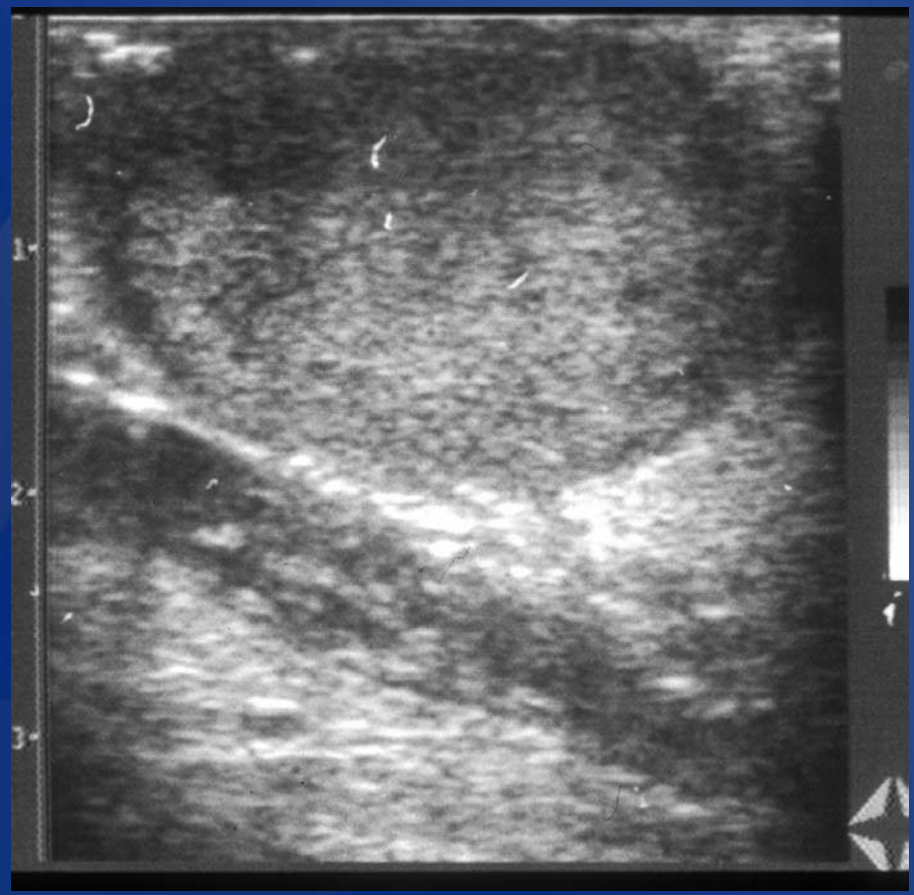
Intraoperative imaging

- Intraoperative ultrasound useful for identifying the adrenal location, tumor extent and relationship to surrounding structures



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Collected series: Demographics

Institution	Age (y)	Gender	Tumor Size (cm)
Rush Medical College 1995	50 (37-71)	M:7 F:3	4.8 (3 - 8)
Univ. of Barcelona 1996	46 (25-74)	M:10 F:21	4 (1.2 - 8)
Greenslopes / Brisbane 1996	54 ± 1.3	M:37 F:30	NR
UCSF 1996	NR	NR	3.5 (1 - 13)
Washington University 1996	50 (19-77)	M:10 F:14	2.7 (1 - 5.5)
Hotel Dieu /Cleveland Clinic 1997	46 (17-84)	NR	5 (0.7 - 14)
Vanderbilt 1997	46 (25-73)	M:6 F:13	2.5 (1 - 5)
Univ. Of Washington 1997	52 (29-71)	M:7 F:9	NR
Mayo Clinics 1997	50	M:18 F:32	2.9
US NIH 1997	47	M:10 F:10	NR
Belgium (multicenter) 1997	44 (12-74)	M:18 F:34	4 (1.5 - 12)
Univ.di Ancona 1998	49 (19-75)	M:17 F:33	4.8 (1.5 - 10)
Total	**12 y - 84 y**	**M:140 F:199**	**7 mm - 14 cm**

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Collected series: Indications

Institution	Pheo	Cushing's	APA	Nonfunctional	Other
Rush Medical College 1995	4	2	0	3	1
Univ. of Barcelona 1996	8	6	11	3	3
Greenslopes / Brisbane 1996	6	1	52	8	0
UCSF 1996	3	2	10	5	3
Washington University 1996	11	3	6	2	2
Hotel Dieu /Cleveland Clinic 1997	20	13	21	19	15
Vanderbilt 1997	3	4	9	3	0
Univ. Of Washington 1997	4	12 total		0	0
Mayo Clinics 1997	10	10	24	6	0
US NIH 1997	6	2	11	0	1
Belgium (multicenter) 1997	17	8	15	7	5
Univ.di Ancona 1998	8	13	13	14	3
Total	**100**	**76**	**172**	**70**	**33**