virilizing and feminizing tumors

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take home message

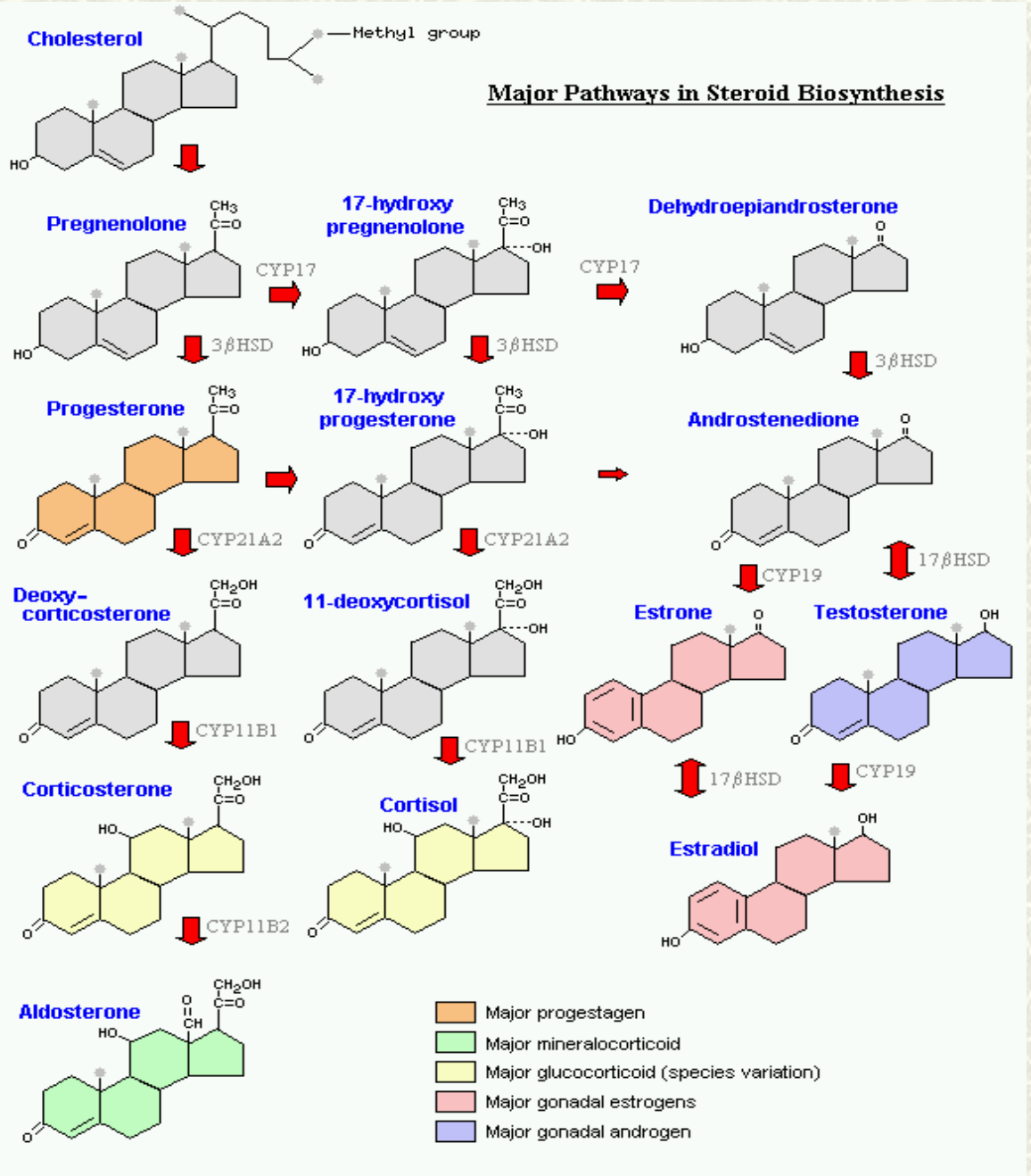
- these are rare tumors that require careful work-up to exclude other conditions – surgical excision is only definitive treatment

presentation

- virilizing and feminizing tumors of the adrenal gland are rare: virilizing tumors have an estimated incidence of 1 per 1.7 million, with feminizing tumors being even rarer.
- looked at another way however, such symptoms are a common feature of adrenocortical carcinoma,
  - pure virilization is present in 20% of cancers
  - a combined hormone excess manifestation (ie virilization with symptoms of Cushing's syndrome) is present in 35% of cancers

steroidogenesis

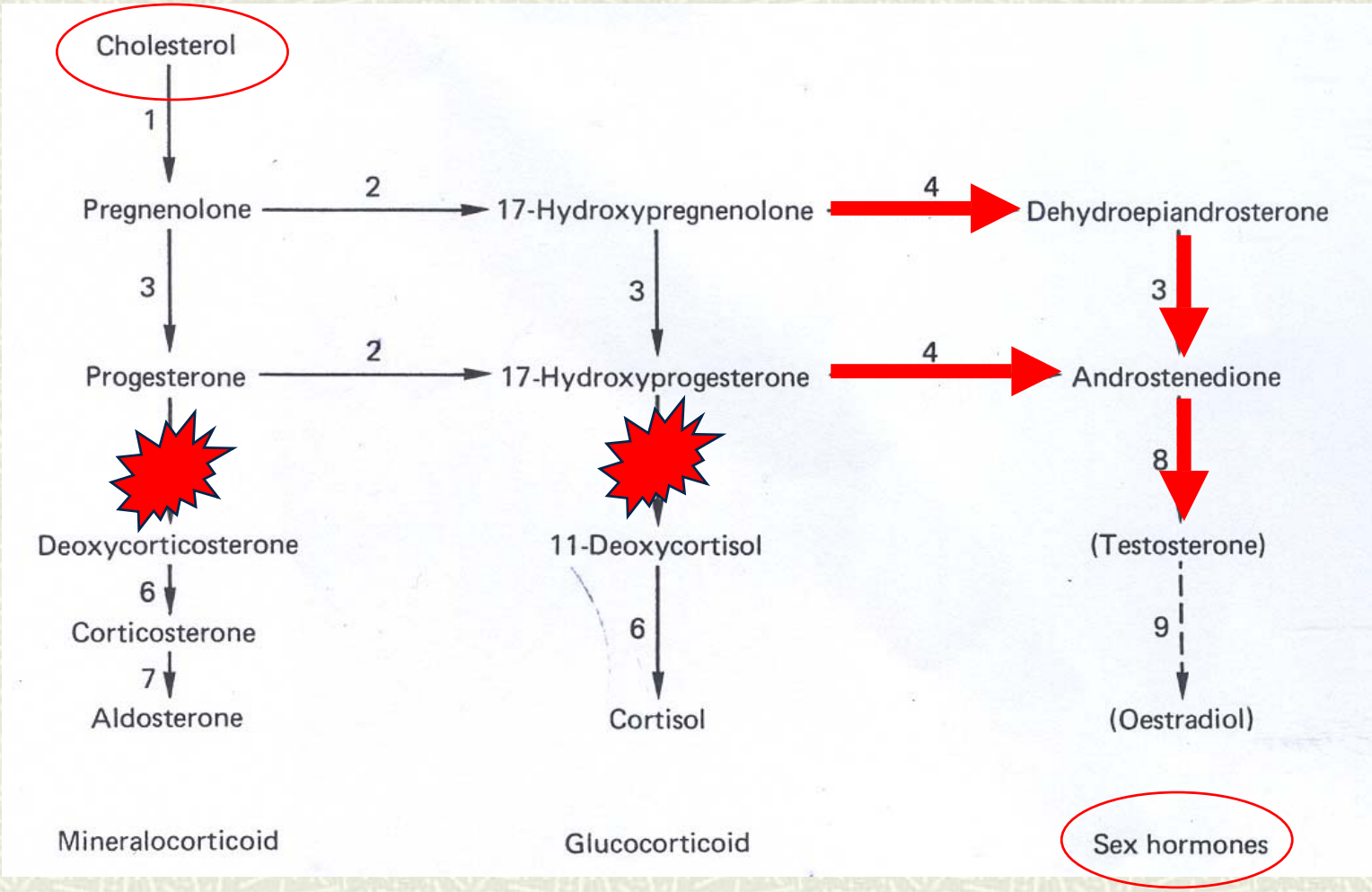
- steroid hormones from the adrenal cortex share cholesterol as a common precursor



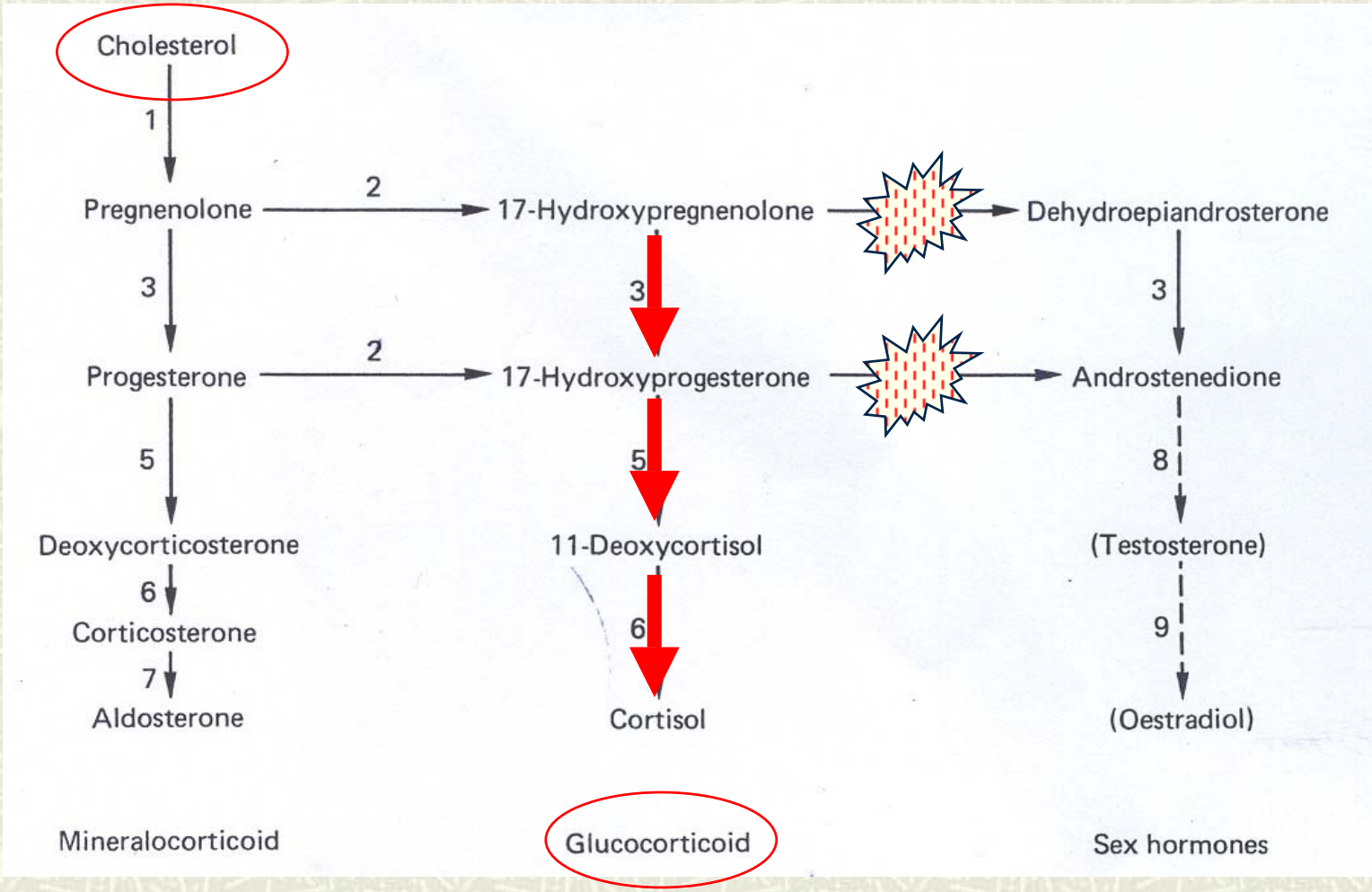
androgen secretion

- pattern of androgen secretion related to pathology, eg CAH (congenital adrenal hyperplasia)
- adenomas often deficient in 17,20 lyase resulting in increased secretion of cortisol compared to androgens
- carcinomas often deficient in 3-hydroxysteroid dehydrogenase leading to decreased cortisol and mineralocorticoid secretion hence increased incidence of virilization and feminization or mixed secretion in adrenocortical cancers

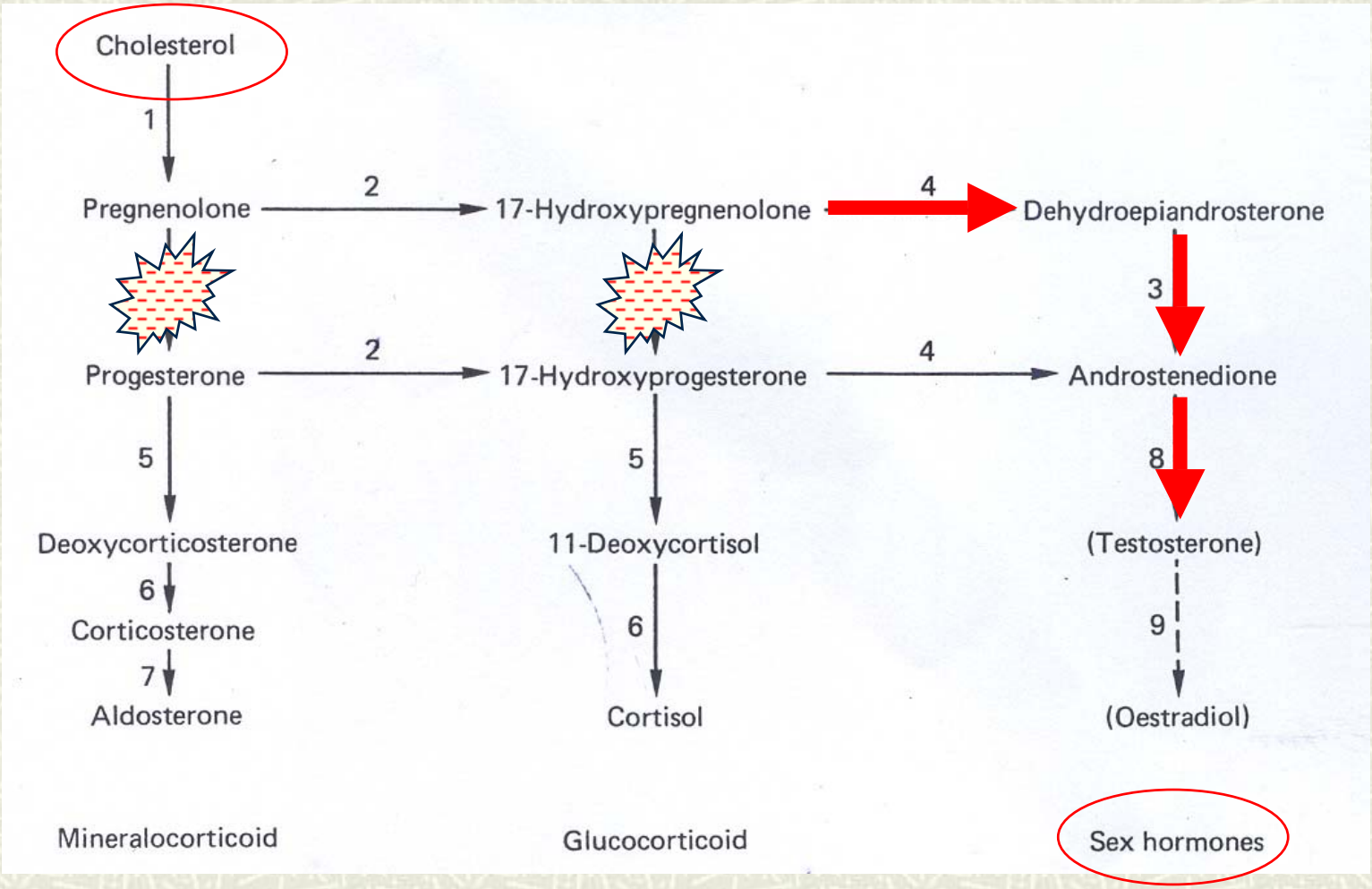
CAH (21-hydroxylase)



adrenal adenomas (17,20 lyase)



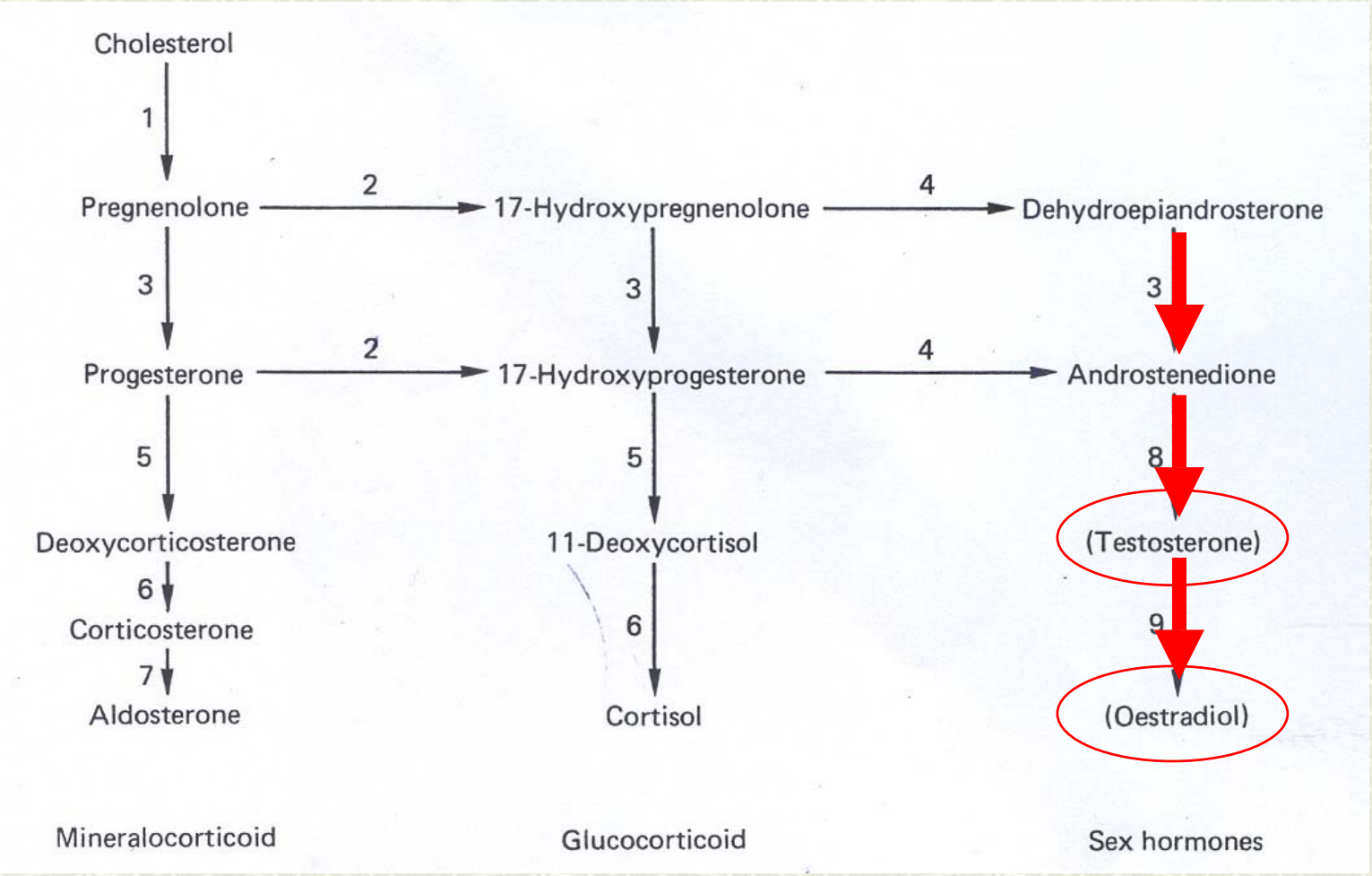
carcinoma (3-OH dehydrogenase)



clinical presentation

- there is a bimodal peak in the age of incidence of such adrenal tumors in the first and then in the fourth to fifth decades of life.
- virilizing tumors are more common and patients usually present with symptoms of androgen excess ie hirsutism (excess facial and body hair) plus virilization ie, severe acne in the face and back areas, male pattern baldness, increased muscle mass, oligo/amenorrhea, increased libido, and cliteromegaly
- feminizing tumors are exceedingly uncommon
- patients may also present with metastatic disease

virilization vs feminization (aromatase)



with unregulated tumor hormone production, testosterone will always exceed oestradiol such that symptoms more common in females

investigation of androgen excess

- high awareness is needed to avoid inappropriate surgical excision: the co-existence of two common conditions such as polycystic ovarian syndrome (PCOS) and an adrenal incidentaloma means that such a female with some degree of androgenization and a benign adrenal tumor will be encountered more frequently than a virilizing adrenocortical carcinoma
- other causes in addition to PCOS include late onset CAH, Cushing's Disease, ovarian tumors, drugs (phenytoin, diazoxide)

investigations

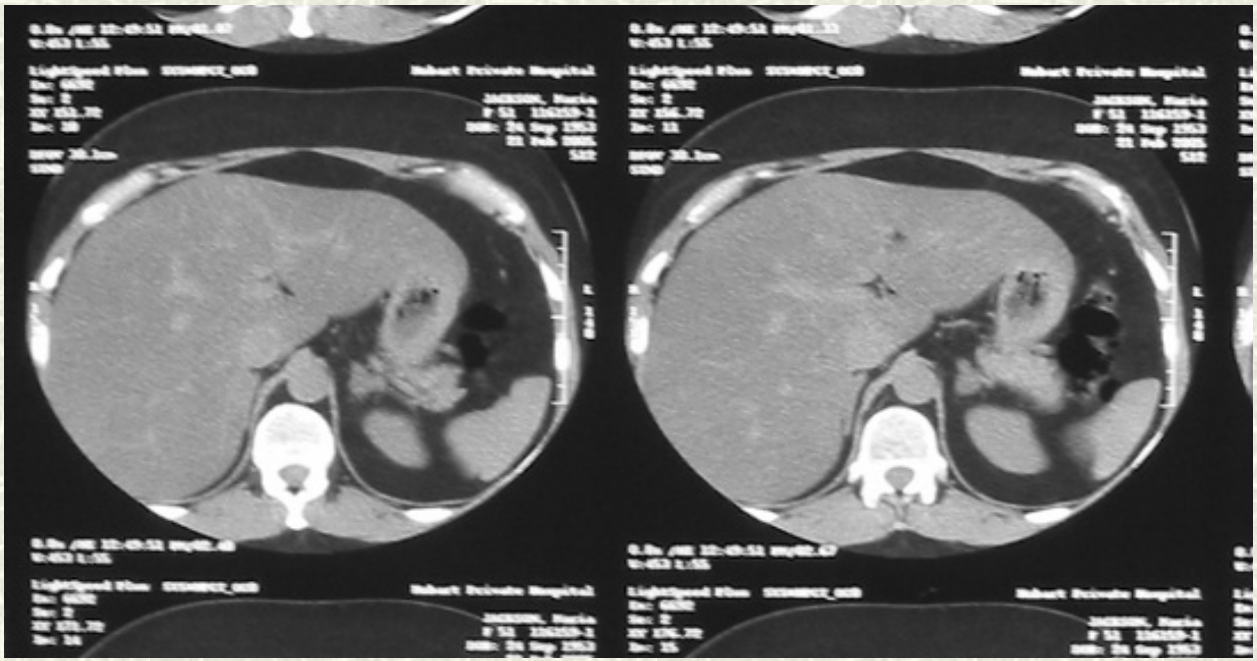
- clinical – hirsutism vs virilization
- cortisol, testosterone, DHEA-S, androstendione
  - compare testosterone (ovarian) to DHEA (adrenal) levels
- low dose dexamethasone suppression test
  - if not suppressed think adrenal pathology

case #1

- 51 yr female
- presented with longstanding facial hirsutism which had increased over past few months
- laparoscopic cholecystectomy 6 months prior
- total testosterone 9.8nmol/L (0.5-3.7)
- further investigations ?

case #1

- CT abdomen:
  - 1.8x1.3cm left adrenal lesion
  - fatty liver
- surgical referral
  - ? adrenalectomy



concerns

- pure androgen-secreting adenomas are unusual
- a carcinoma is rarely this size
- co-existence of an adrenal incidentaloma and androgenization of some other origin is much more likely

case #1

- further history:

  - postmenopausal

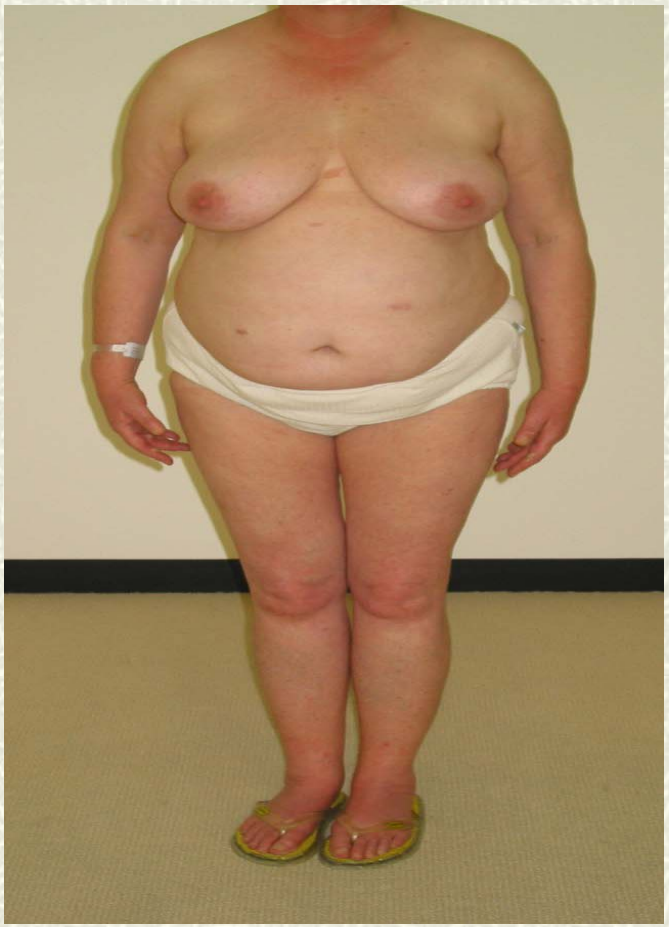
  - metabolic syndrome (hypertension, dyslipidemia, increasing visceral obesity)

  - lethargy

  - “moody”, agitated, “dizzy” (CT brain 12 months previously was normal)

case #1

- physical examination
  - marked hirsutism with plethoric facies
  - centripetal obesity
  - supraclavicular fat pads
  - pigmented abdominal scars
  - no proximal weakness, acne, bruising or striae



case #1 – further investigations

- DHEAS 20.2 umol/L (1-12)
- repeat testosterone 4.2 (0.5-3.7)
- dexamethasone suppression test - 8am cortisol post 1mg dexamethasone was 710nmol/L (<50)

- Cushing's syndrome (ACTH-independent, 2^0 to adrenocortical adenoma?)
  - adrenalectomy?
  - more investigations?

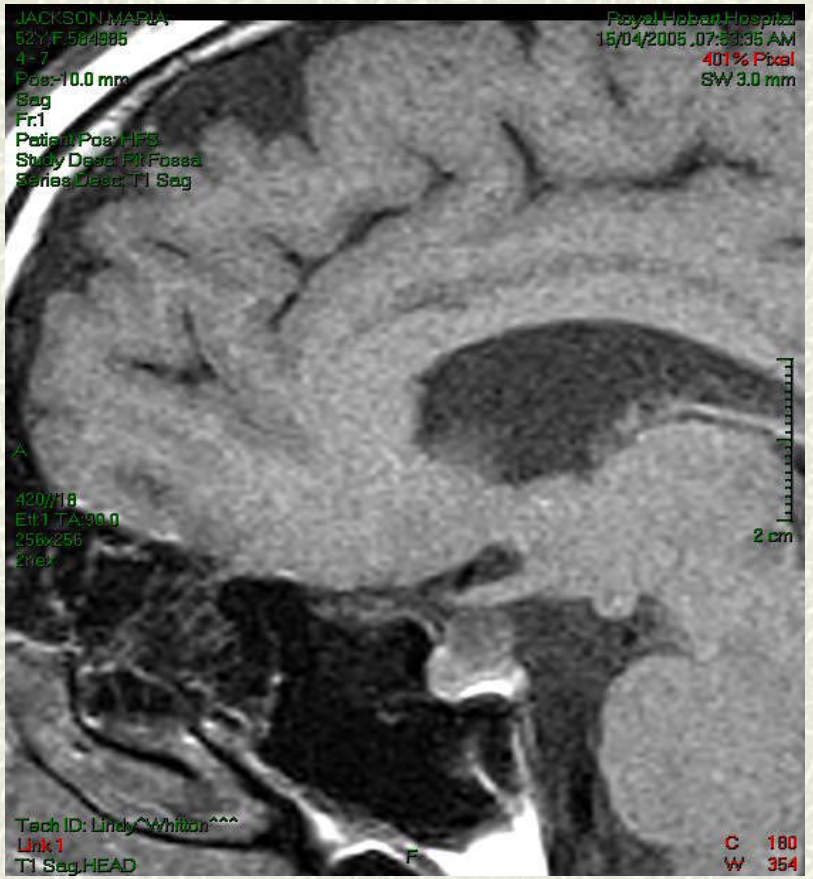
case #1 - further investigations

high dose Dexamethasone suppression test

Time (h)	Cortisol (nmol/L)	ACTH (ng/mL)
-1	631	31.1
+3	461	22.6
+4	237	15.1
+5	188	10.1
+23	592	28.7

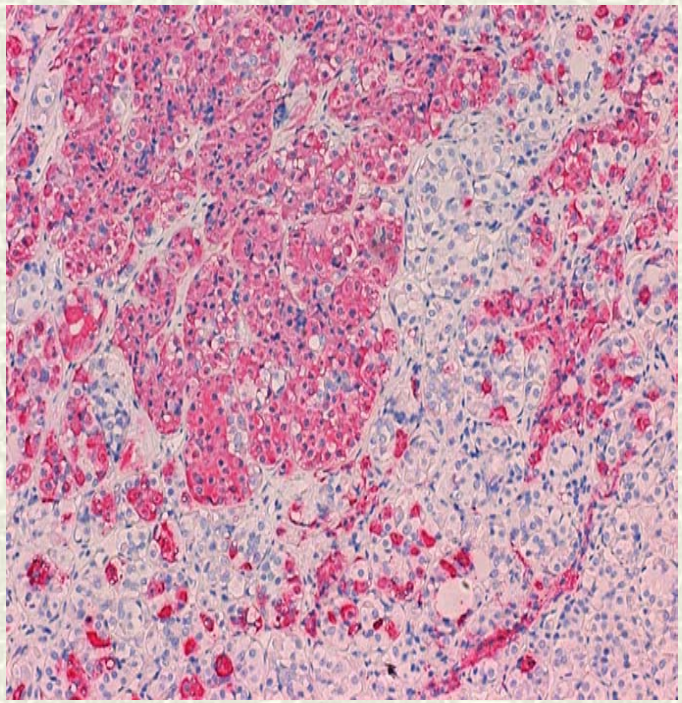
case #1 - further investigations

- suppressible cortisol on high dose dexamethasone suppression test
- persistently elevated ACTH
- pituitary MRI



case #1 - management

- Cushings Disease + adrenal incidentaloma
- transpehenoidal hypophysectomy
- discharged home cured
- ACTH < 10 ng/ml



management

- surgery is the only logical treatment choice for treating virilizing or feminizing adrenal tumors since, once removed, the adrenal steroid pattern reverts to normal in the absence of metastatic disease.
- total resection remains the management modality of choice and offers the only hope of cure for adrenocortical carcinoma.

open ***vs*** laparoscopic

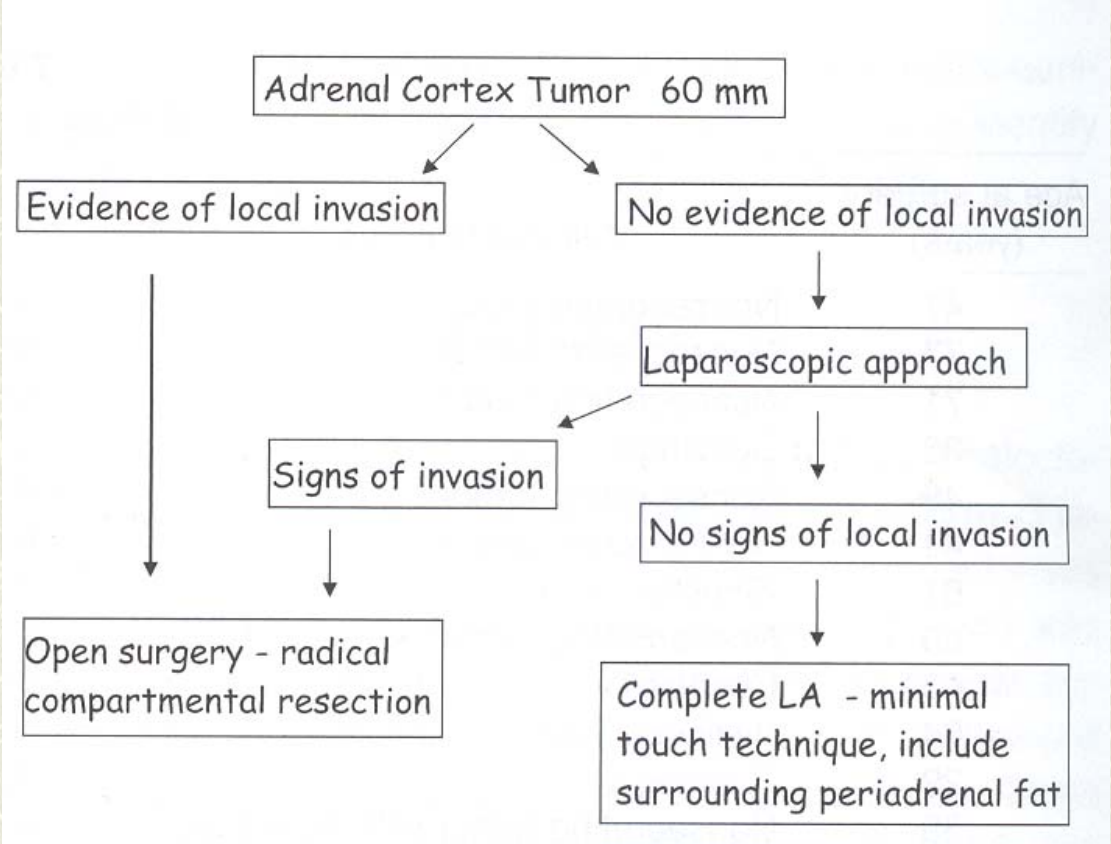
- the indications for a laparoscopic approach should be the same as for all other adrenal tumors with malignant potential, ie if intact removal of the tumor can be achieved safely then a laparoscopic approach is appropriate, however ready conversion should be considered if required to achieve complete tumor resection.

recommendations

- no data that, when performed correctly, laparoscopic adrenalectomy is oncologically inferior to open adrenalectomy
- recommendations:
  - adrenal tumors with imaging findings of local invasion, regional lymphadenopathy, or metastases should have open adrenalectomy
  - large tumor with apparent local disease should have initial diagnostic laparoscopy with readiness to convert if intraoperative suspicion of malignancy, difficulty in dissection because of tumor adhesions, technical difficulty because of tumor size
  - *Sturgeon C, Shen WT, Clark O, Duh Q. J AM Coll Surg 2006;202:423-30*

recommendations

- long term outcome from laparoscopic adrenalectomy for tumors > 6cm (19/391)
- 1 virilizing tumor
- 2 tumors causing pure Cushings syndome with virilization
  - *Palazzo FF, Sebag F ... Henry JF. World J Surg 2006;30:893-8*



University of Sydney data

- last 10 years 1995-2005
  - 177 adrenalectomies (173 with size measured)
  - 28/173 (16%) greater than 6 cm

	<6cm	>6cm
mean age	50	52
mean size (range)	2.8 (2.5-5.8)	87 (60-220)
mean op time (min)	153	165

clinical presentation

	<6 cm	> 6cm
Conn's syndrome	59 (41%)	3 (11%)
Cushing's syndrome	22 (15%)	4 (14%)
phaeochromocytoma	33 (23%)	6 (22%)
virilizing/feminizing tumour	0 (0%)	1 (4%)*
refractory hypertension	1 (1%)	1 (4%)
incidentaloma	30 (21%)	13 (46%)

* 13.5 cm adrenocortical cancer in 35 yr male presenting with feminizing syndrome

surgical approach

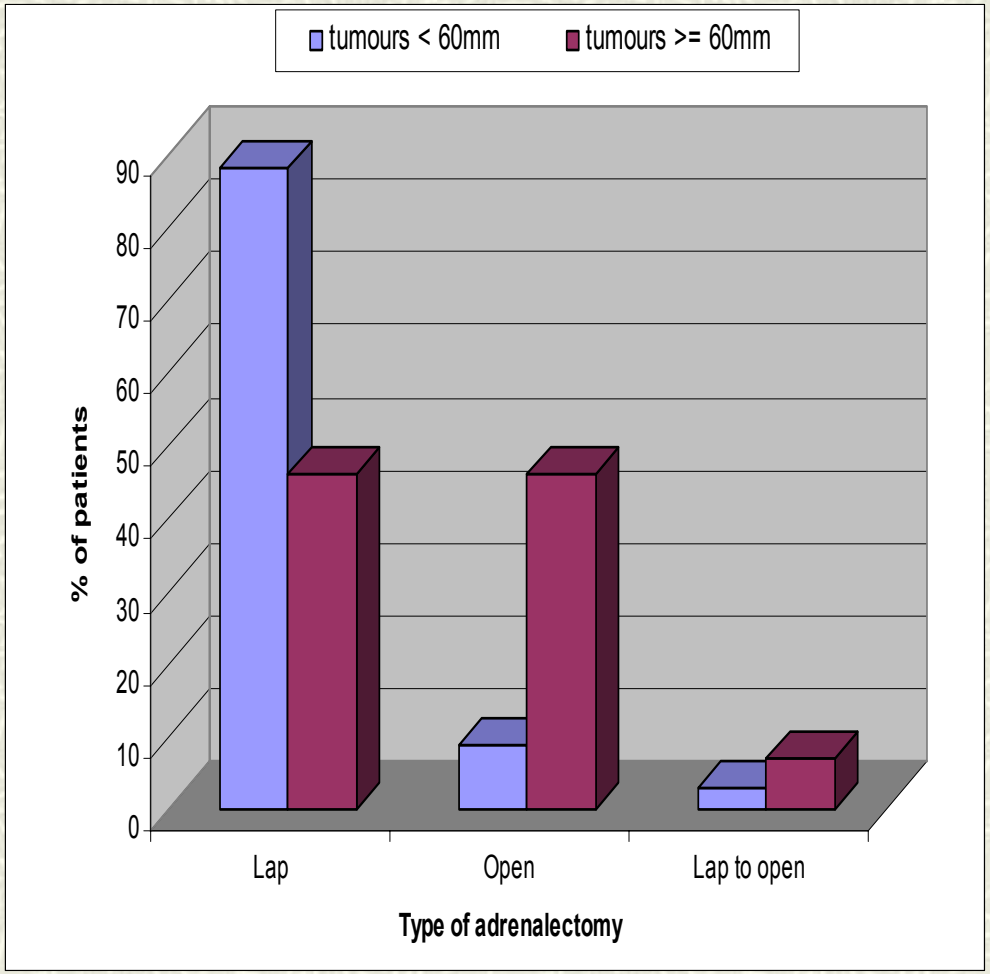
open adrenalectomy(46%)

laparoscopic(46%)*

laparoscopic converted(7%)*

* 53% large tumors initial laparoscopic approach

compares to 91% of tumors < 6cm initial laparoscopic adrenalectomy



however !!

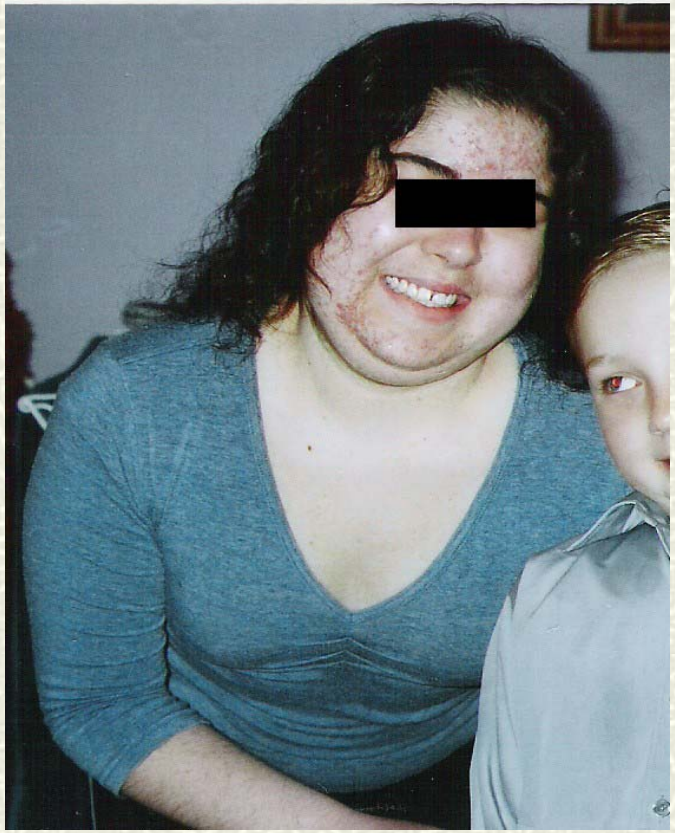
- laparoscopic adrenalectomy requires:
  - advanced laparoscopic skills
  - understanding of vagaries if adrenal anatomy and pathology
  - an appreciation of the issues in relation to hormonal oversecretion
  - readiness to convert to open adrenalectomy if appropriate

- ie requires an experienced laparoscopic endocrine surgeon

case #2

- 17 yr female with known PCOS
- presented March 2005 with 6 month history of increasing:
  - plethora
  - truncal obesity
  - acne
  - amenorrhoea
  - virilization
  - hypertension

  on background of obesity and hirsutism attributed to PCOS

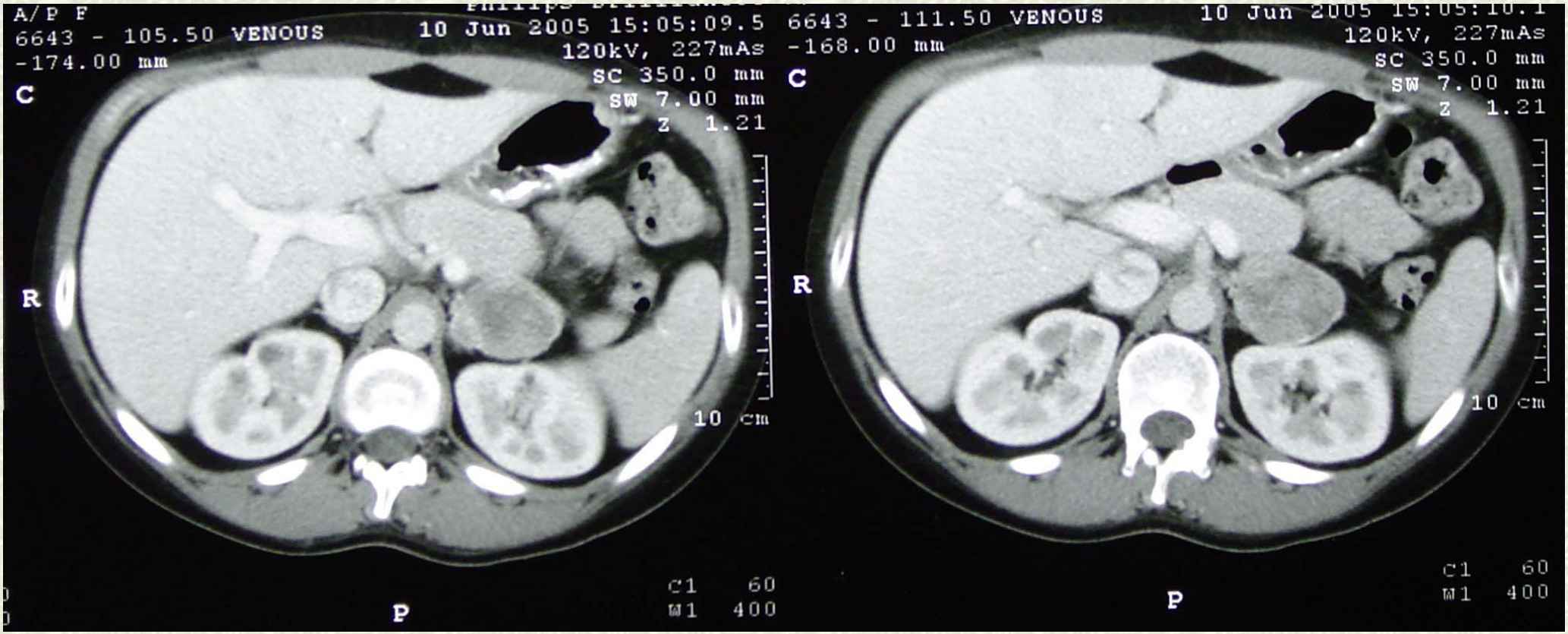


case #2 - investigations

- labs
  - 24hr urinary free cortisol >1493 nmol/d (25-180 nmol/d)
  - ACTH <1.1 pmol/L (0 – 12 pmol/L)
  - testosterone 5.5 nmol/L (1.0 – 4.5 nmol/L)
  - DHEA-S 15.1 umol/L (< 11.7 umol/L)
  - androstenedione 8.9 nmol/L (1.4 - 8.1)
  - non suppressible cortisol and androgens on low dose dexamethasone suppression test

case #2

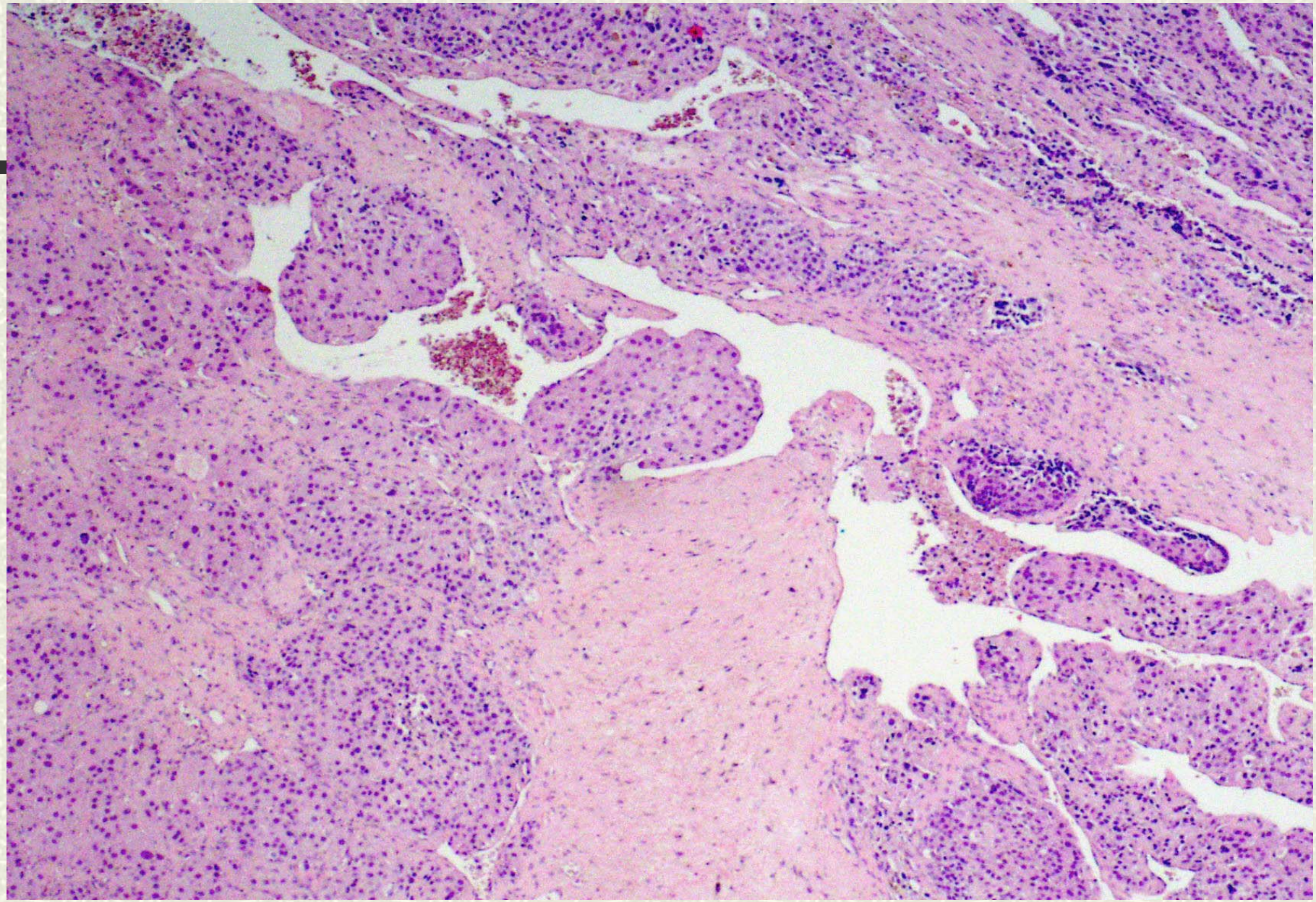
4.2 cm bilobed left adrenal mass, normal right adrenal



case #2 - initial surgery

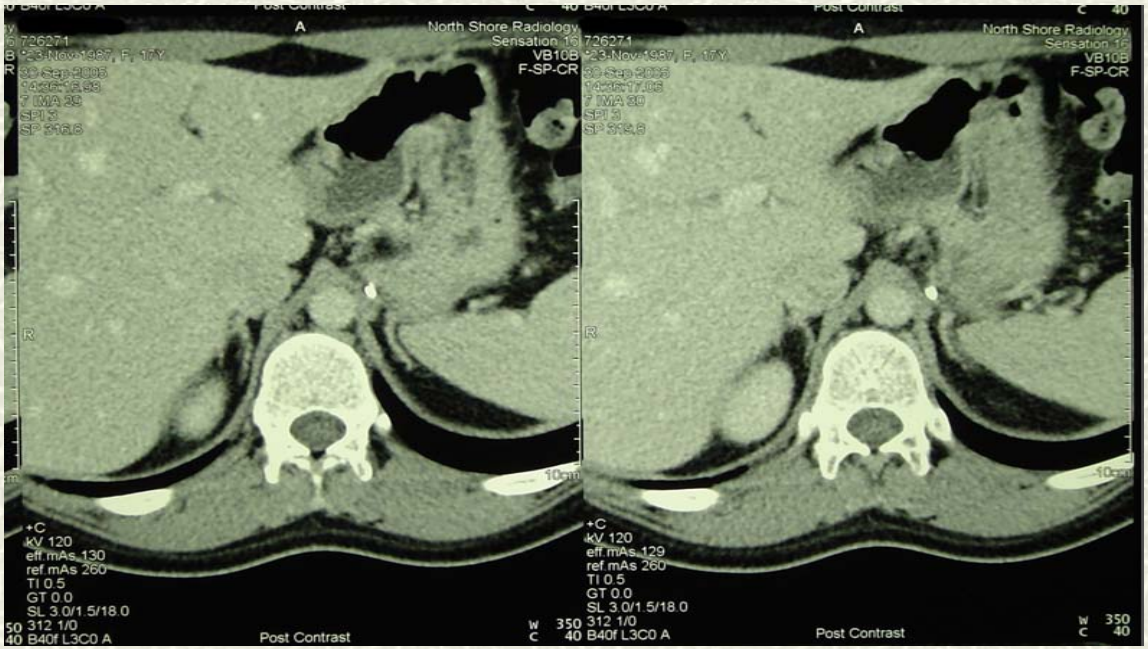
- laparosocopic adrenalectomy (elswehere) with tumor disruption during procedure

- pathology – adrenocortical carcinoma
  - ‘disrupted’ 6cm mass with non-intact capsule
  - areas of severe pleomorphism, numerous mitoses, necrosis
  - disrupted fibrous capsule, tumor infiltration in focal areas
  - resection margin focally involved by tumour cells
  - scanty remnant non-neoplastic adrenal tissue present at the periphery of the tumour



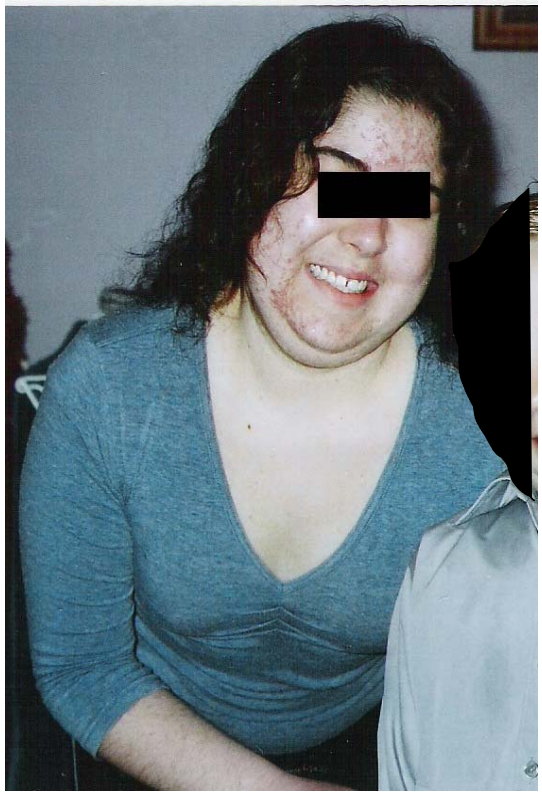
case #2 - progress

- normalization of all hormone studies
- CT
  - 10 x 3mm density above the left renal vein with residual left adrenal still present
  - right adrenal gland appeared normal



case #2 - subsequent surgery

- left open adrenalectomy and retro peritoneal dissection
- pathology: residual adrenal gland and periadrenal scar tissue but no evidence of residual adrenocortical cancer



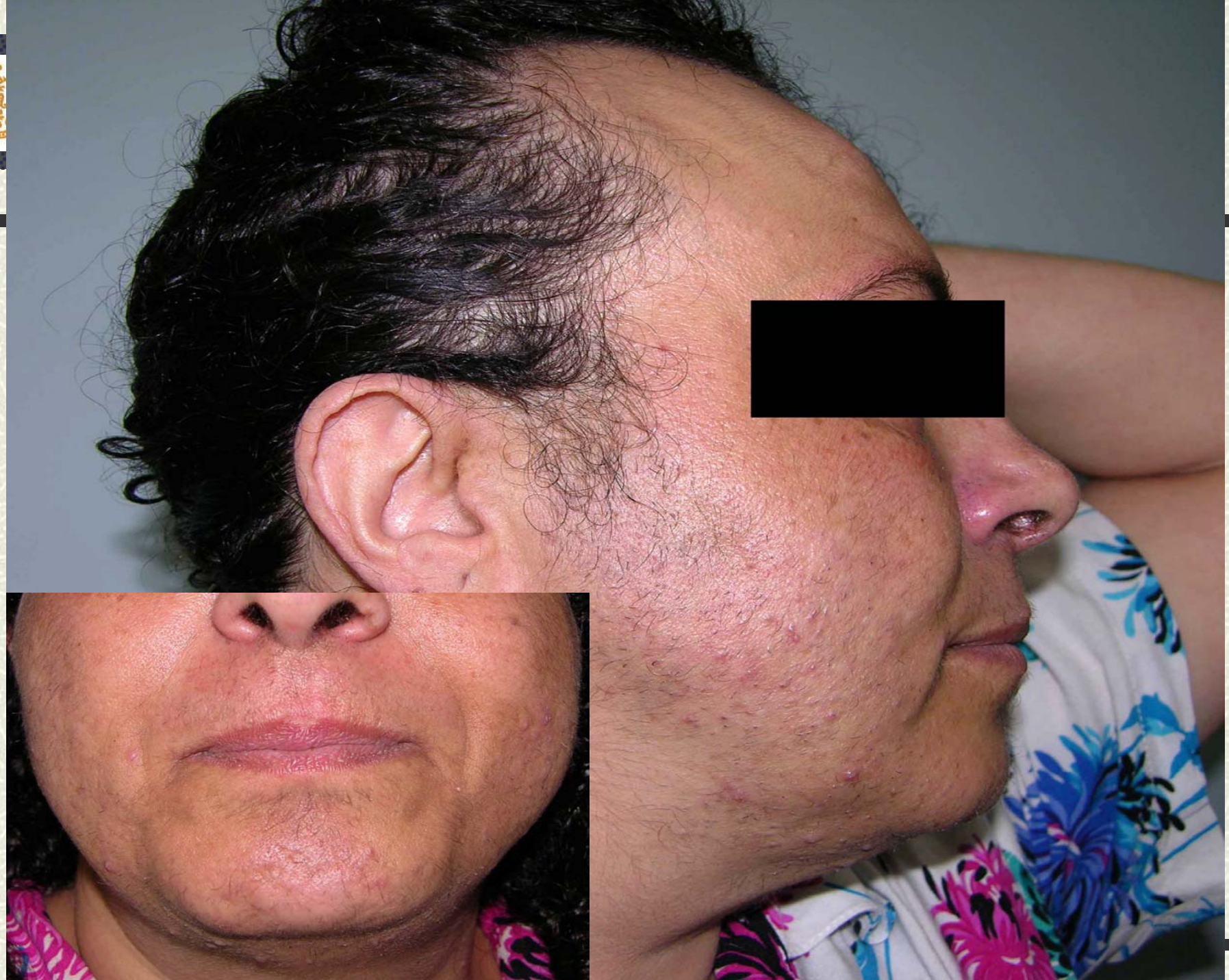
extensive tumors

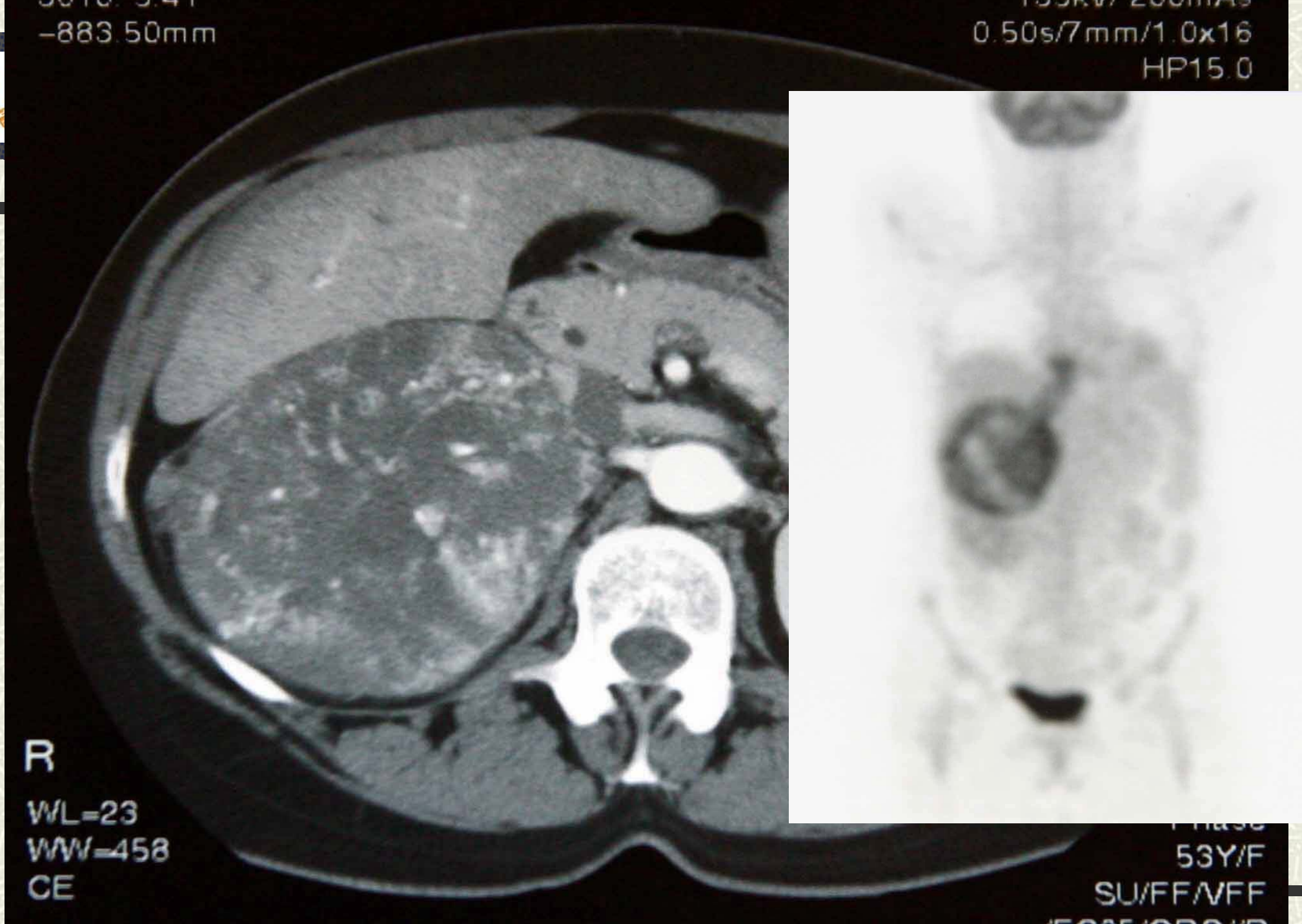
- surgery is the only form of management
- hormone excess (hence symptoms of virilization) disappear with removal of tumor)
- surgical excision still indicated for very large tumors
- ACC has propensity to extend into adrenal vein, IVC an right atrium – still amenable to surgical extension

case #3

- 53 yr old female
- hirsutism, temporal balding, weight gain, acne and obesity
- labs:

testosterone	14.3 nmol/L	(1.0-4.5)
DHEA-S	25 umol/L	(<5.2)
androstenedione	90 nmol/L	(<3.0)
cortisol	616 nmol/L	(138-650)

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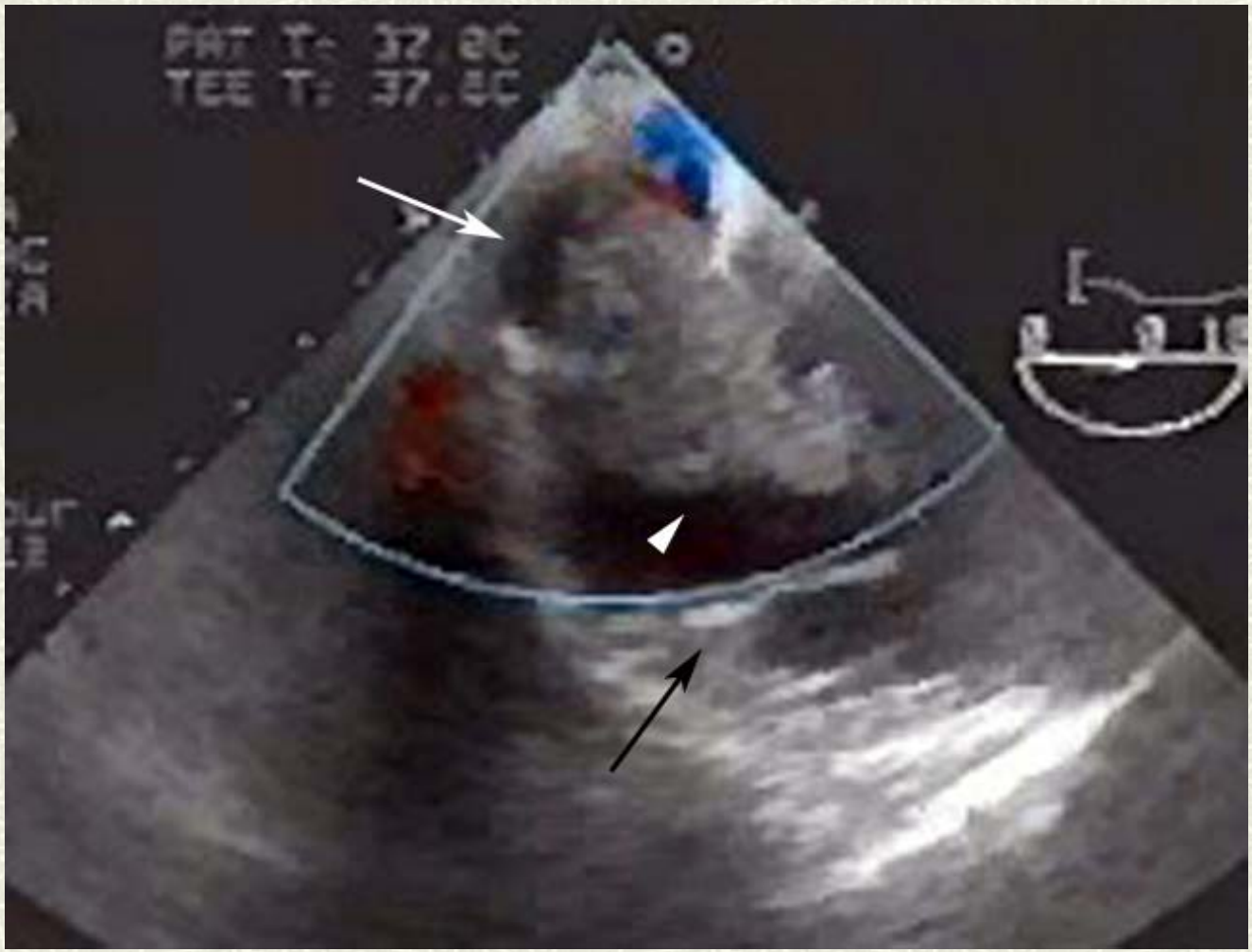
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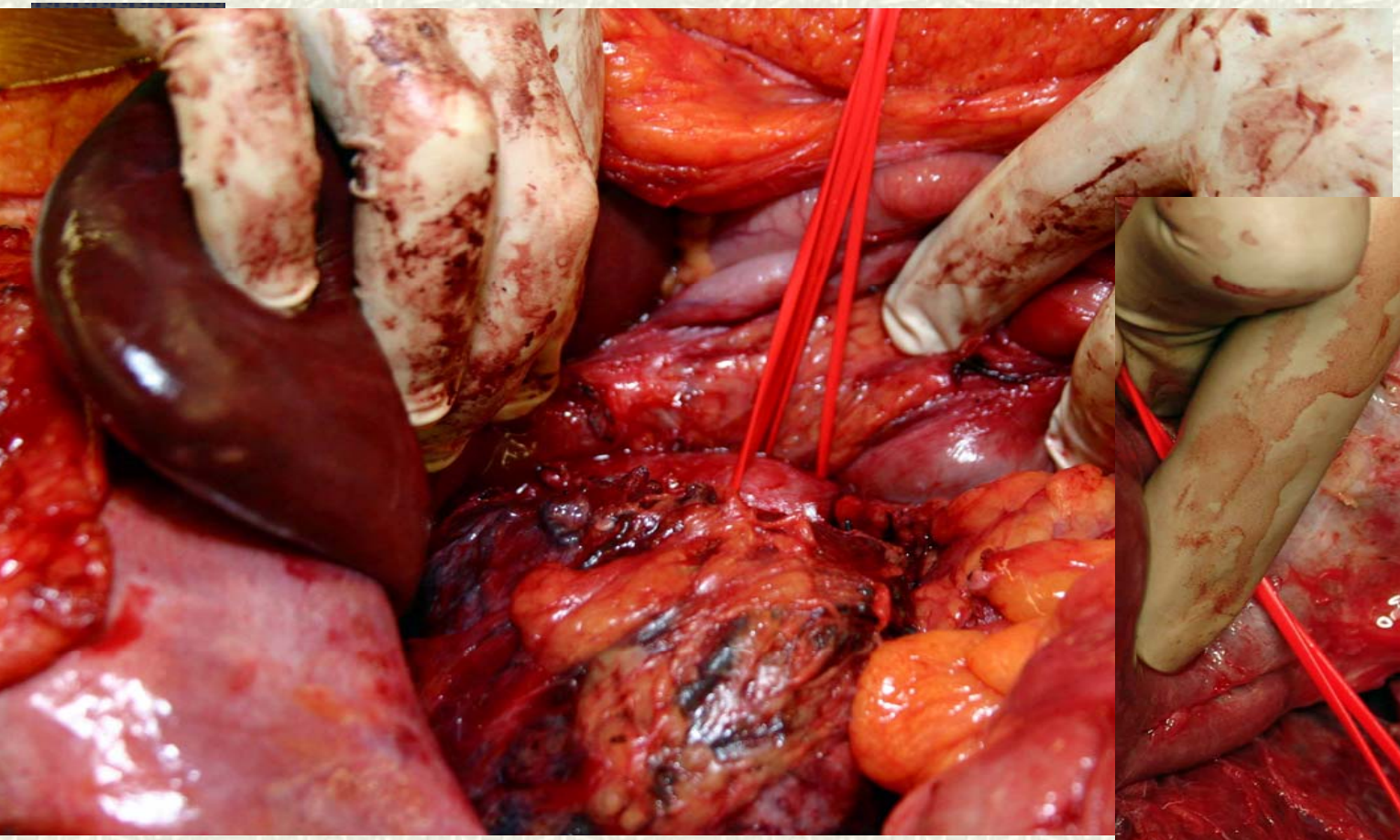
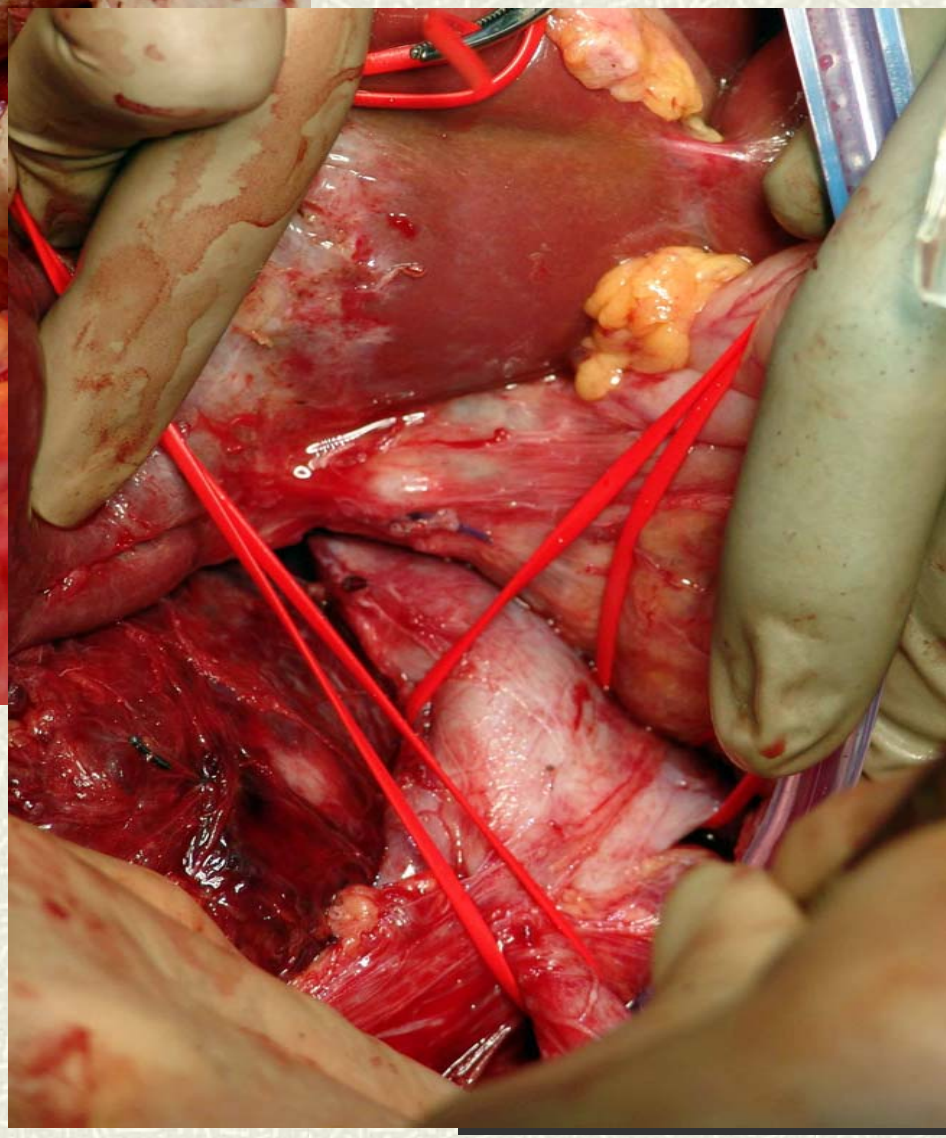
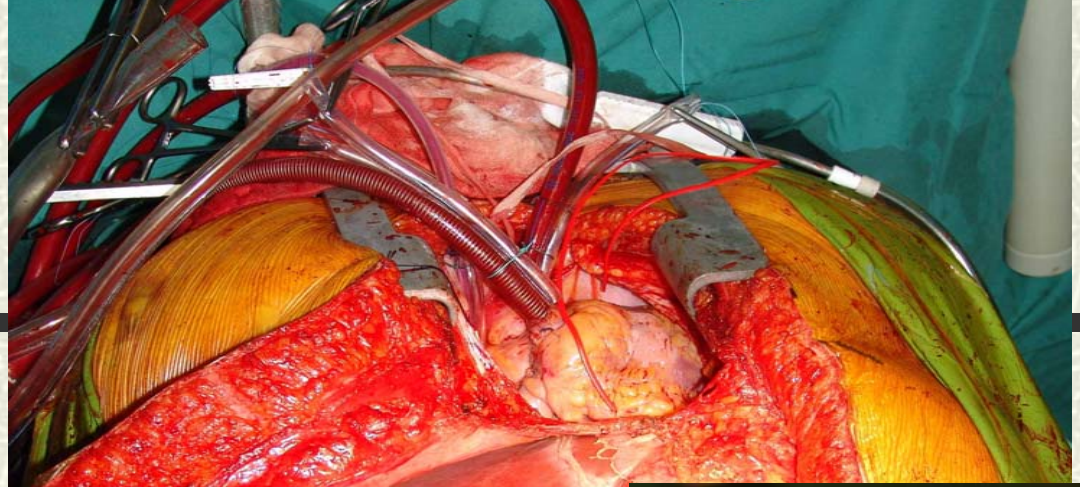
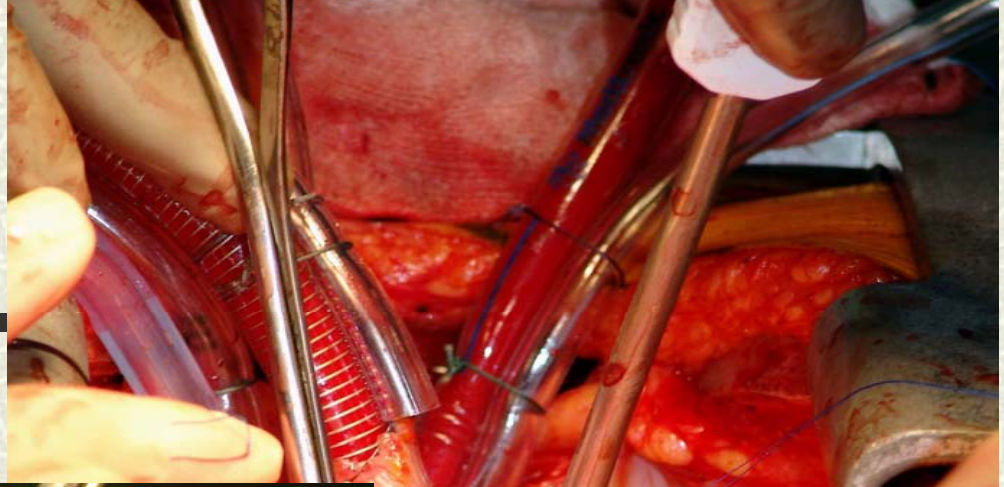
case #3 - surgical management

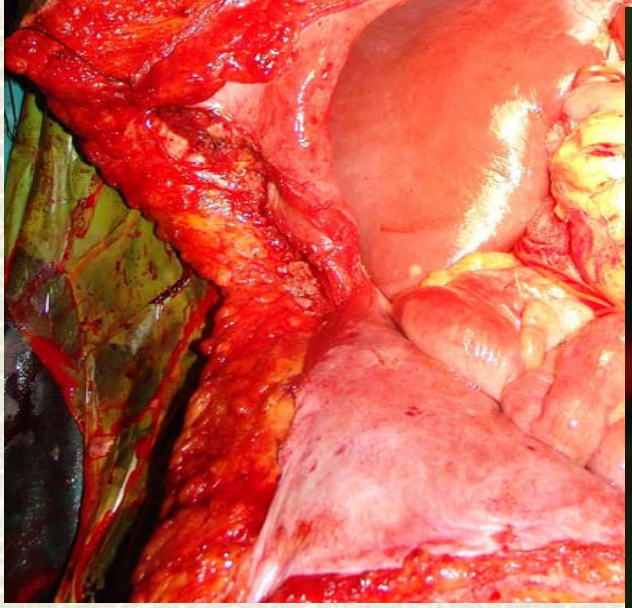
- laparotomy
- mobilization of tumour
- extracorporeal bypass
- opening of atrium and delivery of tumor thrombosis
- uncomplicated recovery

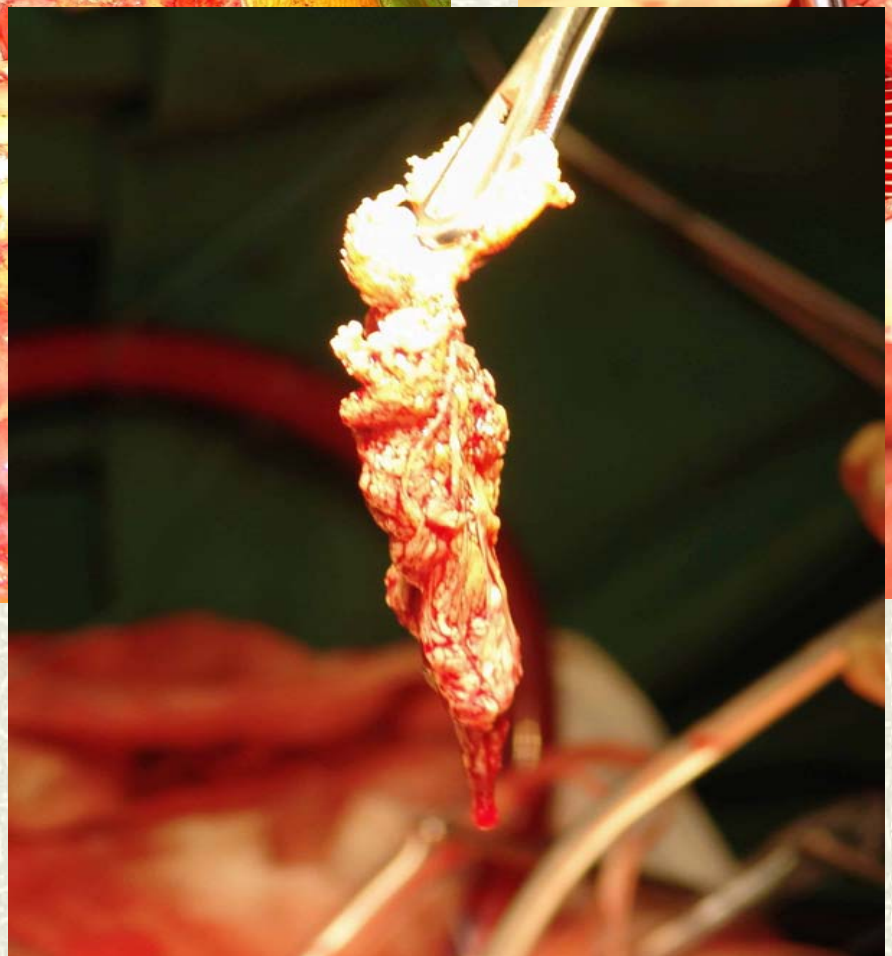


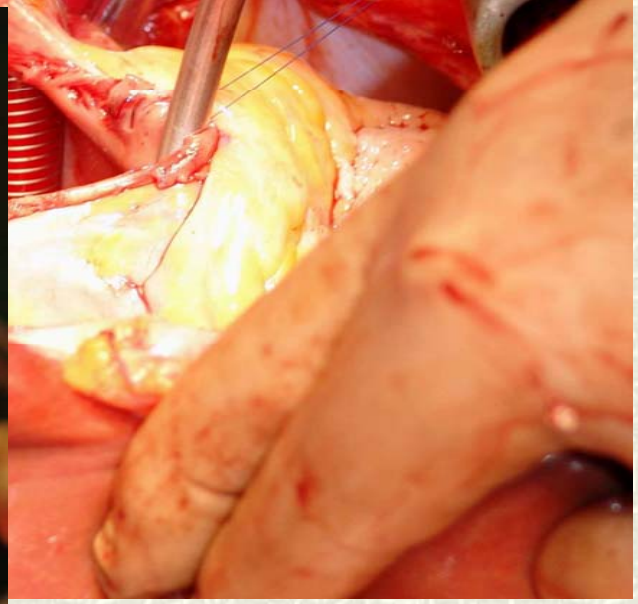


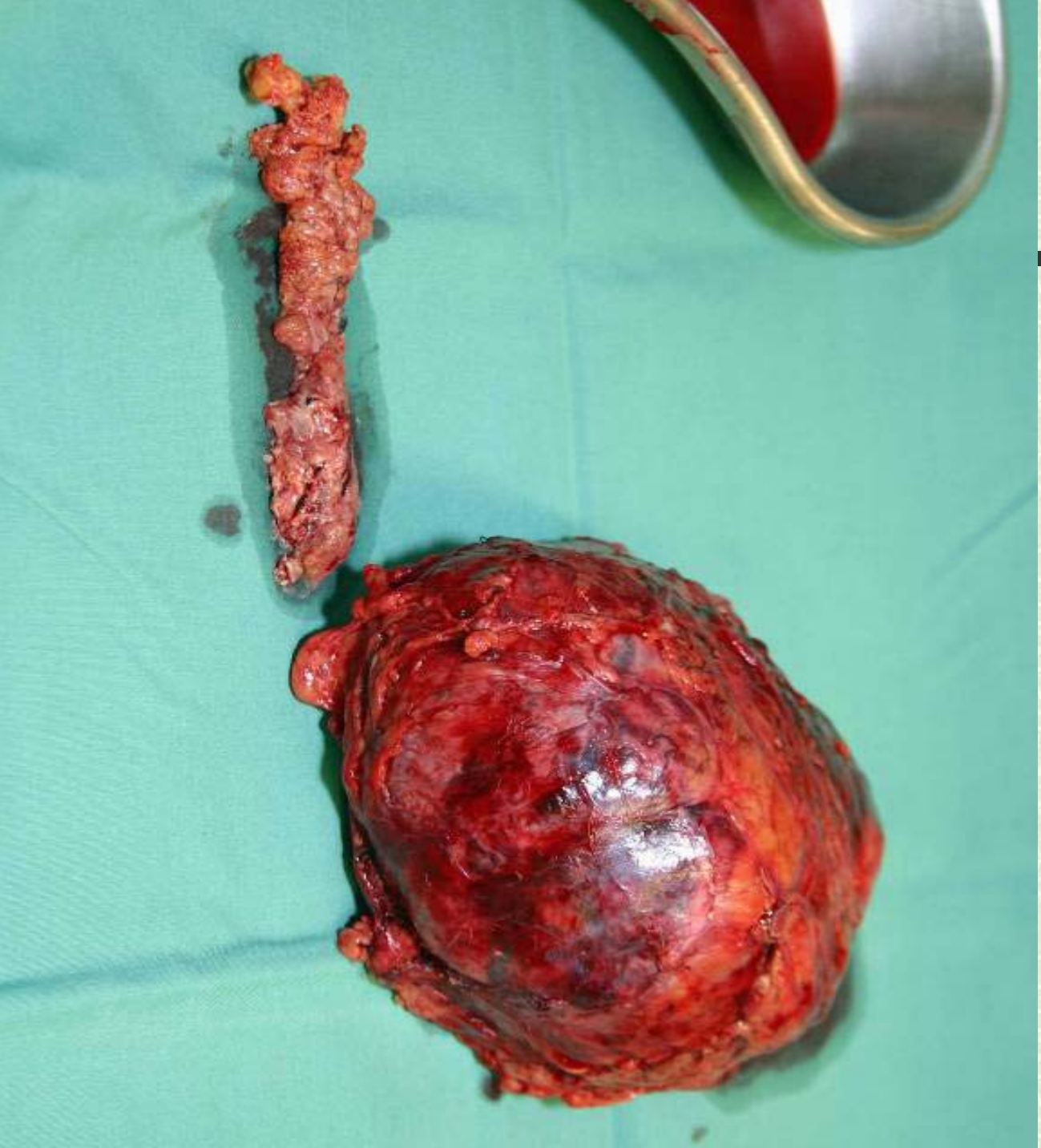


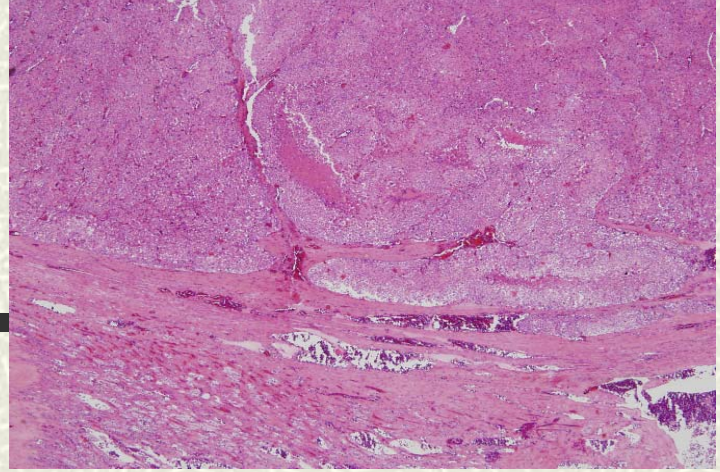


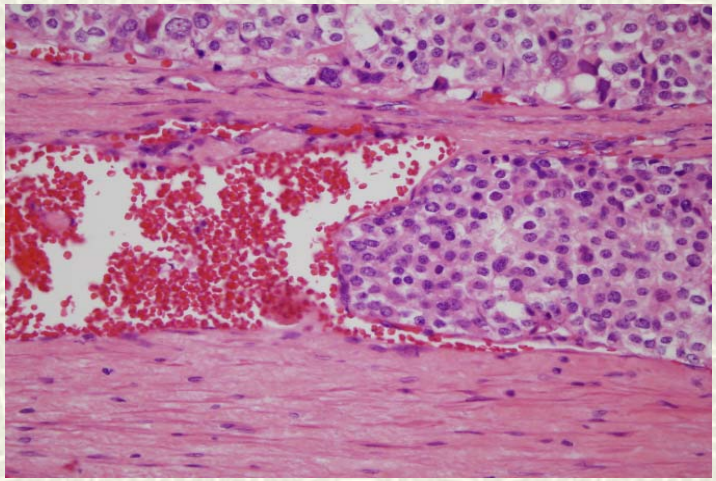


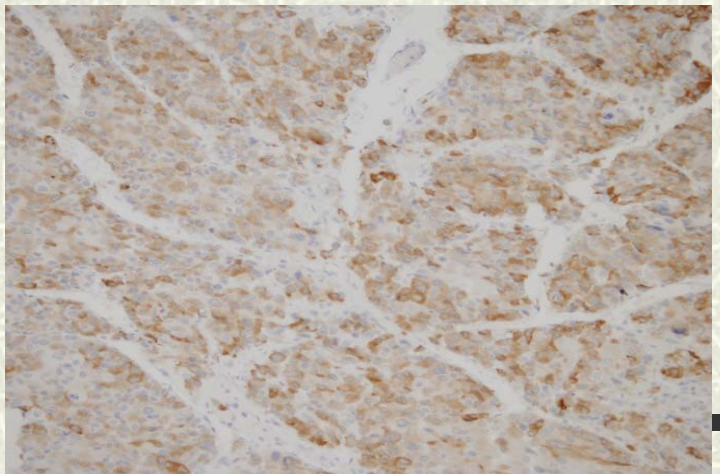












adjuvant therapy

- adrenocortical carcinoma is resistant to standard cytotoxic therapy as such tumors express high levels of the multidrug resistance protein MDR1 (P-glycoprotein).
- for patients with metastatic disease, mitotane, a specific adrenocortical cytotoxin which inhibits cholesterol side-chain cleavage, remains the treatment of choice in doses increasing up to 2-16 g/day as tolerated . However mitotane may take up to 3 months to demonstrate an effect, only 25% respond, and side-effects are common.

other therapies

- some newer targeted therapies, such as with tyrosine kinase inhibitors, and gene therapy are all currently being evaluated in trials.
- specific management of the functional endocrine syndromes such as hyperandrogenism may also be of some benefit.

hyperandrogenism management

- cyproterone acetate (progestative agent) and flutamide (non-steroidal)
- both inhibit binding of dihydrotestosteone to the androgen receptor
- lead to reduction of virilization without change in hormonal profile
- cyproterone also has an antiproliferative effect and there are reports of tumour shrinkage
  - *Lasco A, Morini E ... Benvenga S. Endocrine-related cancer 2005;12:939-44*

summary

- these are rare tumors that require careful work-up to exclude other conditions – surgical excision is only definitive treatment
- complete surgical resection is required and can be achieved laparoscopically or open