Adrenal Issues & Surgery

Masha Livhits, MD, Endocrine Surgeon at UCLA School of Medicine, discussed detection and treatment of tumors of the adrenal gland. Pheochromocytomas occur inside the adrenal gland and paragangliomas occur outside. VHL patients are predisposed to develop these tumors which are often non-cancerous but produce too much adrenaline, the "fight or flight" hormone. Symptoms can be violent (panic attack), less obvious (elevated blood pressure), or non-existent.

Asymptomatic adrenal tumors are fairly common for VHL patients, so it is especially important to follow the screening recommendations. For example, under anesthesia for an unrelated surgery a "hidden" (undiagnosed / asymptomatic) adrenal tumor can create a life-threatening spike in blood-pressure. Patients who need anesthesia and know they have an adrenal tumor can receive pre-operative medicines (α-blockers and sometimes β-blockers) to help prevent this crisis. Emergency surgeries without the proper pre-operative medicines should be avoided. Screening for VHL patients can include a blood test, 24-hour urine test, and various types of scans.

Once a patient is diagnosed with a pheo or a paraganglioma, it should be surgically removed even if it is asymptomatic. Again, pre-operative medications, which are taken for 2-3 weeks, are vital! α-blockers block adrenaline hormone and control blood pressure. They can also make patients tired and thirsty, so taking patients should use this time to re-hydrate. β-blockers are sometimes added if a patient's heart rate needs to be lowered. To operate on the right adrenal gland, the surgeon will have to mobilize the liver; on the left adrenal gland, the spleen must be mobilized. In the 1950s open adrenalectomies were considered the gold standard. In the 1990s, laparoscopic (entering through small incisions in the front) and retroperitoneal approaches (entering through small incisions in the back, fewer surrounding organs to manipulate) became available which dramatically decreased healing time. Open adrenalectomies, however, are still used if the surgeon is concerned about malignancy or if it too large. The latest technique preserves some of the adrenal cortex so patients can hopefully avoid being on steroid supplementation for the rest of their lives. Although this is promising, there is an increased risk of recurrence because the only way to ensure that all the tumor tissue is removed is to remove the whole adrenal gland.

Adrenal Issues and Surgery

VHL Alliance Annual Family Meeting

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Saturday, September 24, 2016

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Outline

- How does VHL affect the adrenal gland?
- What are the unique features of pheochromocytoma in VHL?
- How do we detect and treat pheochromocytoma?
- Keys to successful surgery for VHL patients

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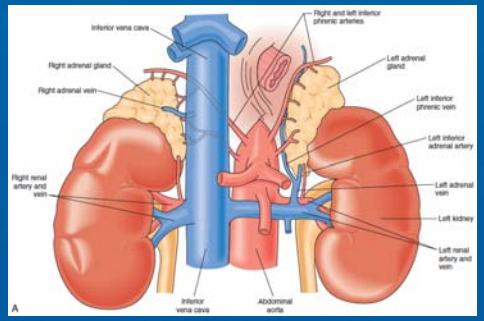
What are adrenal glands?

- Small organs that sit on top of each kidney
- Hormones essential for life (steroids, adrenaline)



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How does VHL affect the adrenal gland?

- **Pheochromocytoma**: tumor that produces too much adrenaline ("fight or flight" hormone)
- Usually in adrenal gland, but can also be outside of adrenal gland (paraganglioma)
- Occurs in 10 – 20% of patients with VHL (lifetime risk)
  - Type 1 VHL[a]: Risk of pheo <10%
  - Type 2 VHL[b]: Risk of pheo 50%

[a] Germline mutations predicting loss of function of VHL protein(s)
[b] Missense pathogenic variant, gain of function mutation

Zbar et al. J. Hum Mutat. 1996;8(4):348

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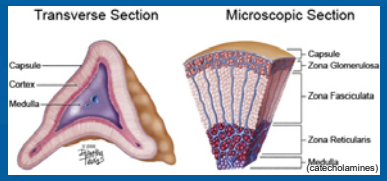
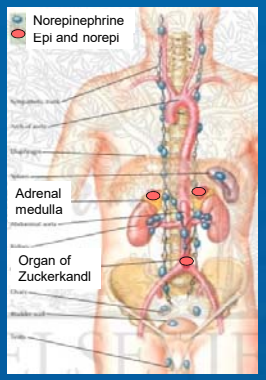
Location of pheochromocytoma

- Adrenal medulla
- Outside of adrenal gland:
  Abdomen (85%)
  Chest (12%)
  Head and neck (3%)





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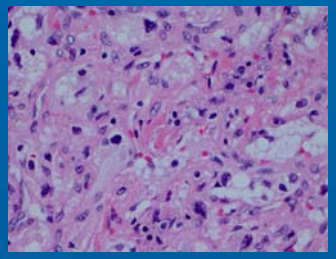
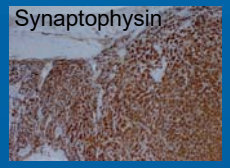
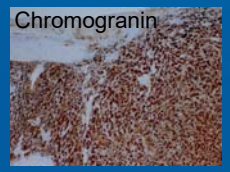
Under the microscope







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Symptoms of pheochromocytoma

- Episodes of headache, sweating, racing heartbeat (can mimic panic attack)
- High blood pressure (episodes or constant)
- Can occur at any time or be triggered by exercise, emotional stress, surgery, foods high in tyramine (red wine, chocolate, cheese)
- May have no symptoms
- Risks: heart attack, stroke, instability with anesthesia

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Pheochromocytoma in VHL

- Younger age at presentation (12 to 25 years)
- Often multiple
- May be outside of the adrenal gland
- Less likely to have symptoms
- Usually secrete normetanephrines, not metanephrines
- Usually benign

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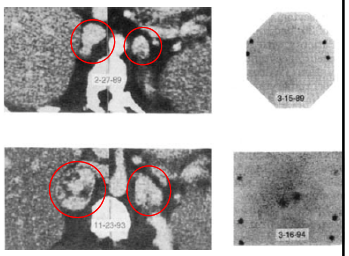
Pheochromocytoma in VHL

National Institutes of Health study: 64 patients with VHL and pheo (1999)

- Age at diagnosis: 30 yrs
- Bilateral adrenal: 47%
- Extra-adrenal: 12%
- No symptoms (normal BP and labs): 35%
- Metastatic disease: 1 patient (lung, liver)



M Walther et al. J. Urology 1999;162(3): 659-664

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How to detect pheochromocytoma

Laboratory test to check adrenaline levels

- Plasma free fractionated metanephrines (higher false-positive rate)
- 24-hr urine fractionated metanephrines
- Positive if 2-fold above upper limit of normal (lower threshold in VHL)
- Imaging: CT or MRI first; consider whole body scan with MIBG or 18F-DOPA

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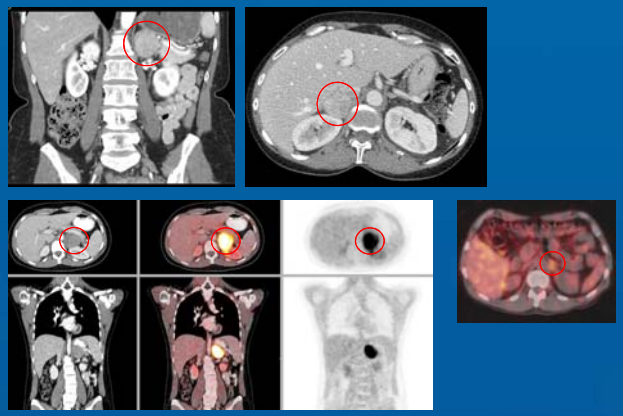
Imaging for pheochromocytoma



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Screening for pheochromocytoma in VHL

Tumors can occur even in childhood

Test	How often?	Age to start
Physical exam to include blood pressure check	Yearly	1 year
Plasma or 24-hr urine metanephrines	Yearly	5 years
Abdominal ultrasound*	Yearly	8 years
MRI abdomen*	1 – 2 years	16 years

*If earlier if indicated

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Preparation for surgery

Preoperative blockade is critical for safe surgery

- Alpha blocker: blocks adrenaline hormone and controls blood pressure
- Given for at least 2 weeks before surgery
- Allows time for patients to hydrate as blood vessels dilate (drink water, eat salty foods)
- Prevents dangerous blood pressure swings during surgery

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Preparation for surgery

Phenoxybenzamine most common (alternatives exist)

- Side effects: fatigue, stuffy nose (and cost)
- Beta blocker sometimes added AFTER alpha blocker to control heart rate

Date	Time	Sitting	Standing
9/22/16	11:19	160/85	162/83
	09:00		Phenoxybenzamine 20 mg at 09:00
	08:30	170/90	164/90
9/21/16	23:00	160/86	162/102
			(repeat 164/95)
	21:00		Phenoxybenzamine 20mg at 21:00
	18:00	158/86	168/78
			Phenoxybenzamine 20mg at 15:45

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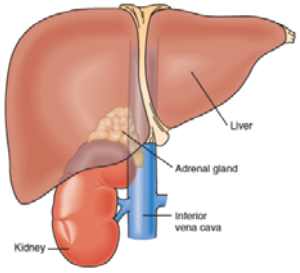
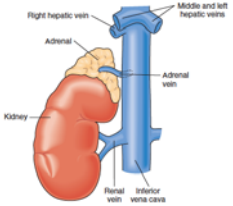
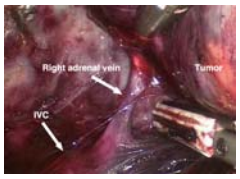
How do we remove the right adrenal gland?







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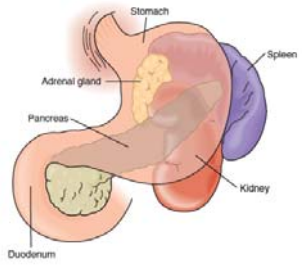
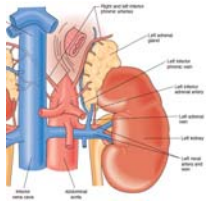
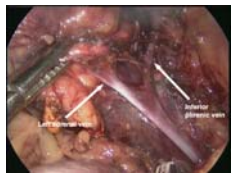
How do we remove the left adrenal gland?







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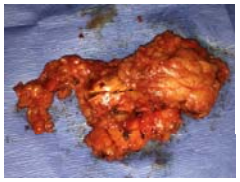
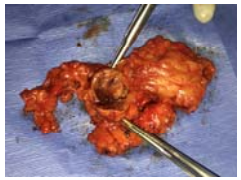
Keys to a successful surgery

Preoperative blood pressure control and experienced anesthesiologist are critical

- Avoid breaking capsule of tumor
- Control of adrenal vein

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History of adrenalectomy

- **1953:** Classical bilateral adrenalectomy for Cushing's syndrome. Open transperitoneal approach as the gold standard
- **1992:** Laparoscopic adrenalectomy
- **1993:** Initial bilateral adrenalectomy should not be systematic in metachronous hereditary PHEO
  First RET and VHL mutations identified
- **1996:** Open cortical sparing adrenalectomy
  Retroperitoneal approach for total adrenalectomy
- **1998:** Laparoscopic cortical sparing adrenalectomy
- **2014:** Only 300 patients with hereditary pheochromocytoma reported in the literature as treated by cortical sparing adrenalectomy

F Castinetti et al. Eur J Endocrinol 2016;174:R9-R18

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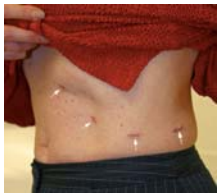
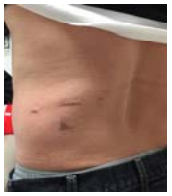
Surgical technique

Laparoscopic resection preferred for most patients (unless concern for malignancy or too large)

- Compared to open surgery, fewer post-op complications (bleeding, infection, pneumonia)
- Transabdominal or retroperitoneal (faster recovery)

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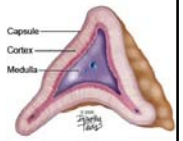
Role of cortical sparing adrenalectomy

Partial adrenalectomy to preserve cortex and potentially avoid need for steroids in bilateral cases



Appropriate if:

- Very low risk of malignancy
- Risk of recurrence not prohibitively high
- If recurrence develops, it is easy to diagnose, monitor, and treat
- High chance of maintaining normal cortical function (avoid steroids)

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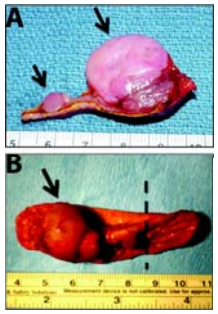
Role of cortical sparing adrenalectomy

Not possible to ensure that all medullary tissue is removed if part of adrenal gland is preserved

- Need at least 1/4 to 1/3 of adrenal gland to maintain normal cortical function
- If tumor >5cm, less likely to have enough normal adrenal gland left
- Depends on position of tumor



F Castinetti et al. Eur J Endocrinol 2016;174:R9-R18

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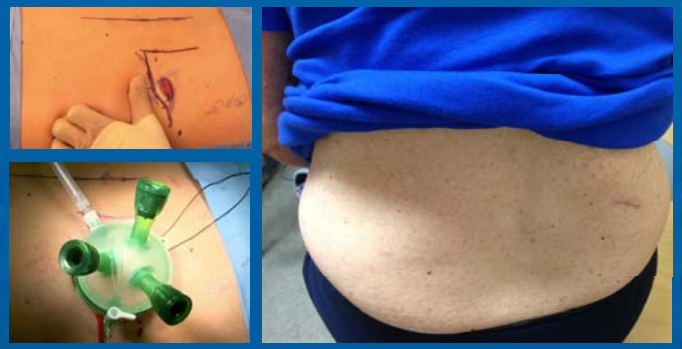
Advances in surgical technique: Single-Incision Retroperitoneoscopic Adrenalectom



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Advances in surgical technique: Simultaneous removal of bilateral tumors

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Case presentation

31 year old man with family history of VHL

- No symptoms, no medications
- Blood pressure 140/76
- VHL gene: (+) mutation
- Plasma normetanephrine: 23.0 nmol/L (nl <0.9)
- 24-hr urine norepinephrine: 1,517 mcg/24hr (nl 15-100)

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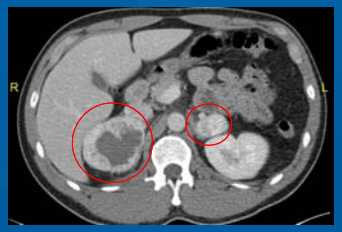
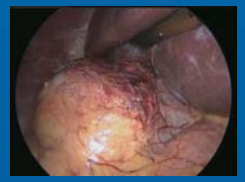
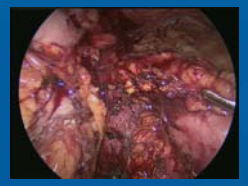
Bilateral laparoscopic adrenalectomy

- Cortical-sparing left side







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Case presentation

22 year old man with family history of VHL

- At age 13, cut knee and had sweating with hypertension and anxiety
- Resection of right pheochromocytoma at age 13
- At age 20, had elevated 24-hour urine normetanephrines at 1476 mcg/24hr (nl 82 to 500)

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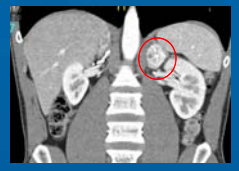
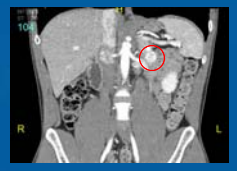
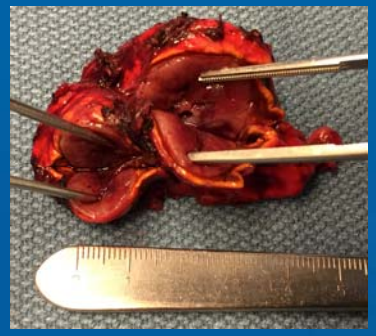
Left laparoscopic adrenalectomy

- Cortical-sparing not possible







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Take home points

- 10 – 20% of patients with VHL develop pheo
- May occur at younger age and be bilateral or outside of adrenal gland, but usually benign
- May have no symptoms, so screening important
- Preoperative medical preparation and experienced team (including anesthesiologist) critical for safe surgery
- Individualized approach to preserve adrenal function while considering risk of recurrence

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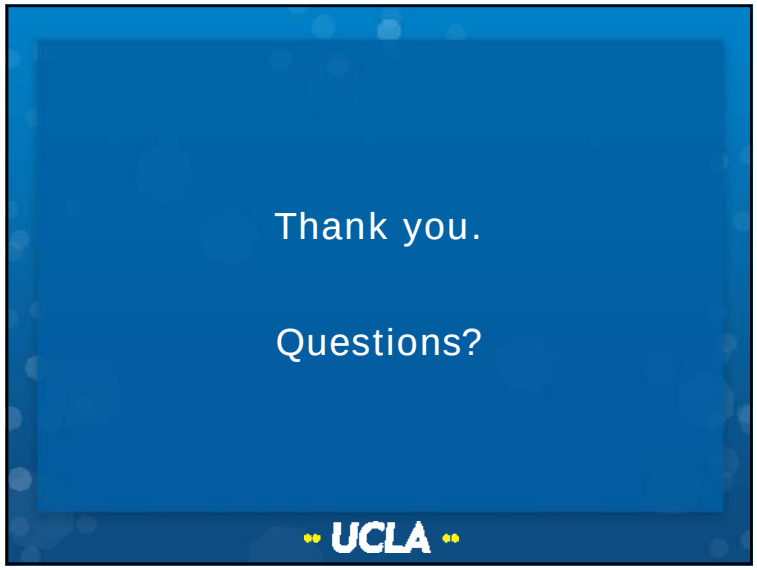
Thank you.
Questions?
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