Challenges in Phaeochromocytoma

Dr Elbert Lee

Pamela Youde Nethersole Eastern Hospital

1/6/2023

Mr Yiu SK, 68/M

Past Medical History: hypertension, diabetes

4/2022 admitted to medical for loss of consciousness

- 2 episodes of unwitnessed blackout for few seconds, precipitated by dizziness
- No limb weakness/numbness, no slurring of speech, no seizure, no headache
- No shortness of breath, central retrosternal chest discomfort

- GCS 15/15, 4 limbs power 5/5, no cerebellar signs
- Chest, heart, abdominal exam normal

Blood tests

- CBC normal, Cr 150
- Serial TnI static at ~200
- TSH normal

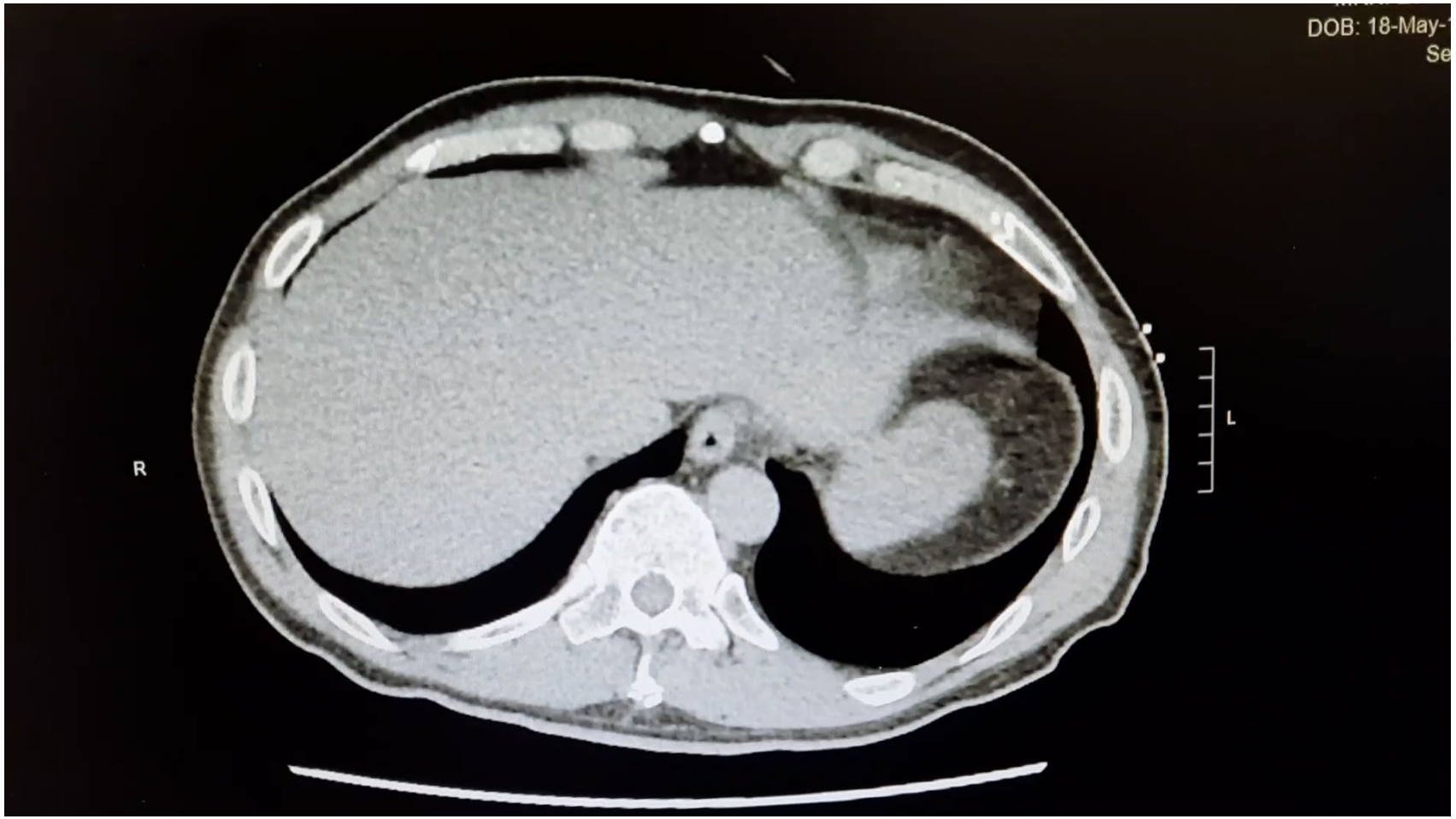
Further workup

- CT brain unremarkable
- ECG- normal sinus rhythm
- Echocardiogram: concentric LVH with preserved LV systolic function LVEF 60%

Episode of dizziness, hypotension and fall during admission

- Elevated WCC 18 and AKI with Cr ~400

Non-contrast CT scan of abdomen and pelvis 7/4/2022



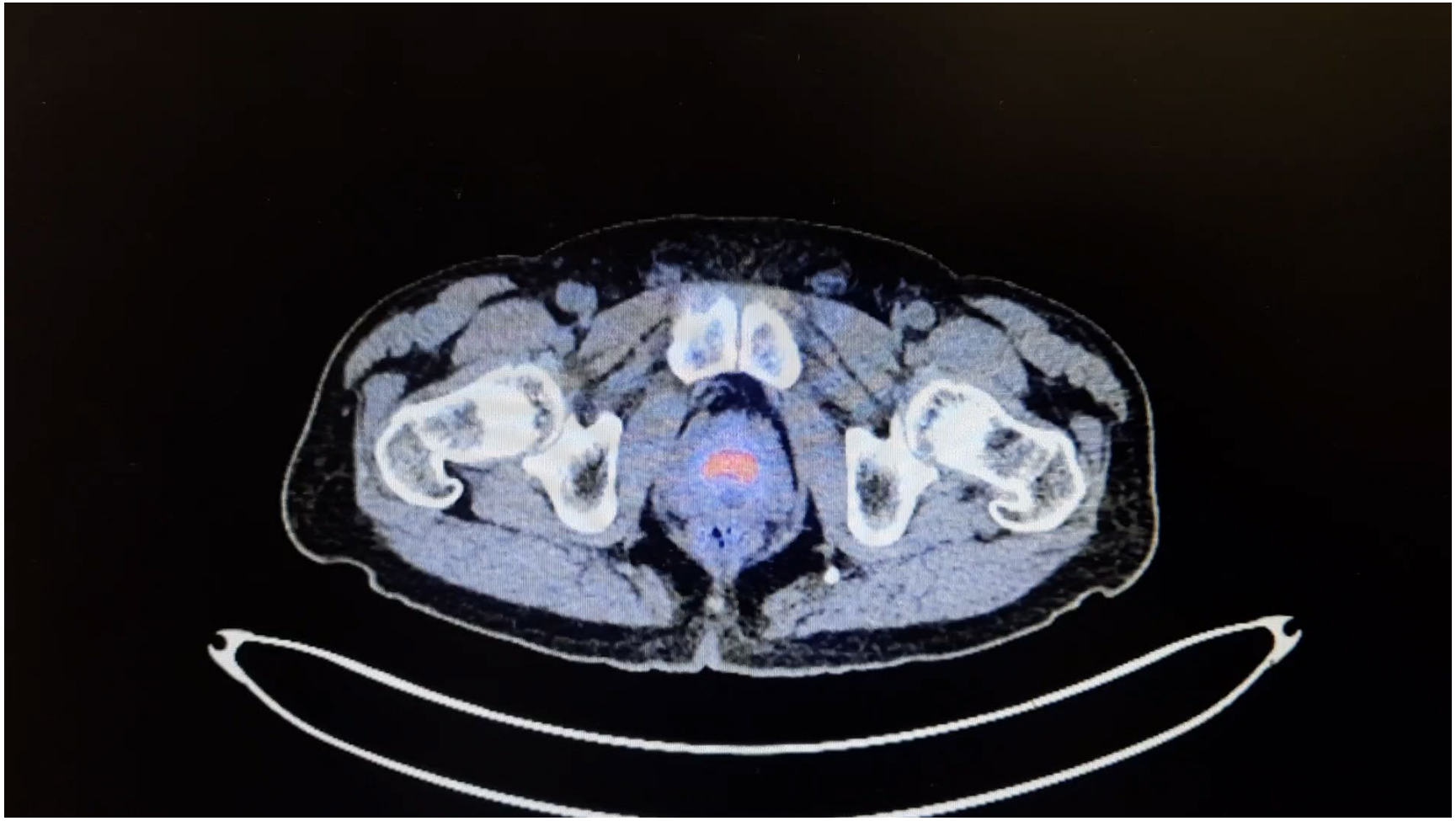
Left JJ stent was inserted 8/4/2022

Blood tests

- LDH 382
- AFP/ PSA normal, CEA 5.5, β-hCG <1.2

Hospital Code	PYN	PYN	
Collect Date	11/05/22 15:30	02/05/22 06:00	
Type, Specimen	---	---	
Adrenaline, Urine, 24 hr	952 ↑	1039 ↑	(<86)
Noradrenaline, Urine, 24 hr	1053 ↑	909 ↑	(<627)
Dopamine, Urine, 24 hr	1600	1393	(<2469)
Metanephrine, 24 hr Urine	5161 ↑	4652 ↑	(<271)
Normetanephrine, 24hr Urine	3531 ↑	2778 ↑	(<320)

68-Ga DOTATATE + FDG PET scan 18/5/2022



Seen by endocrine team

- Started on phenoxybenzamine and titrated to 10mg BD
- Then added propranolol 10mg BD

Initially scheduled operation in June

- On admission noted high BP
- Takeover to endocrine bed for further pre-op optimization
- Titrated phenoxybenzamine to 20mg TDS, added Norvasc 7.5mg daily

Surgical plan & approach?

Open

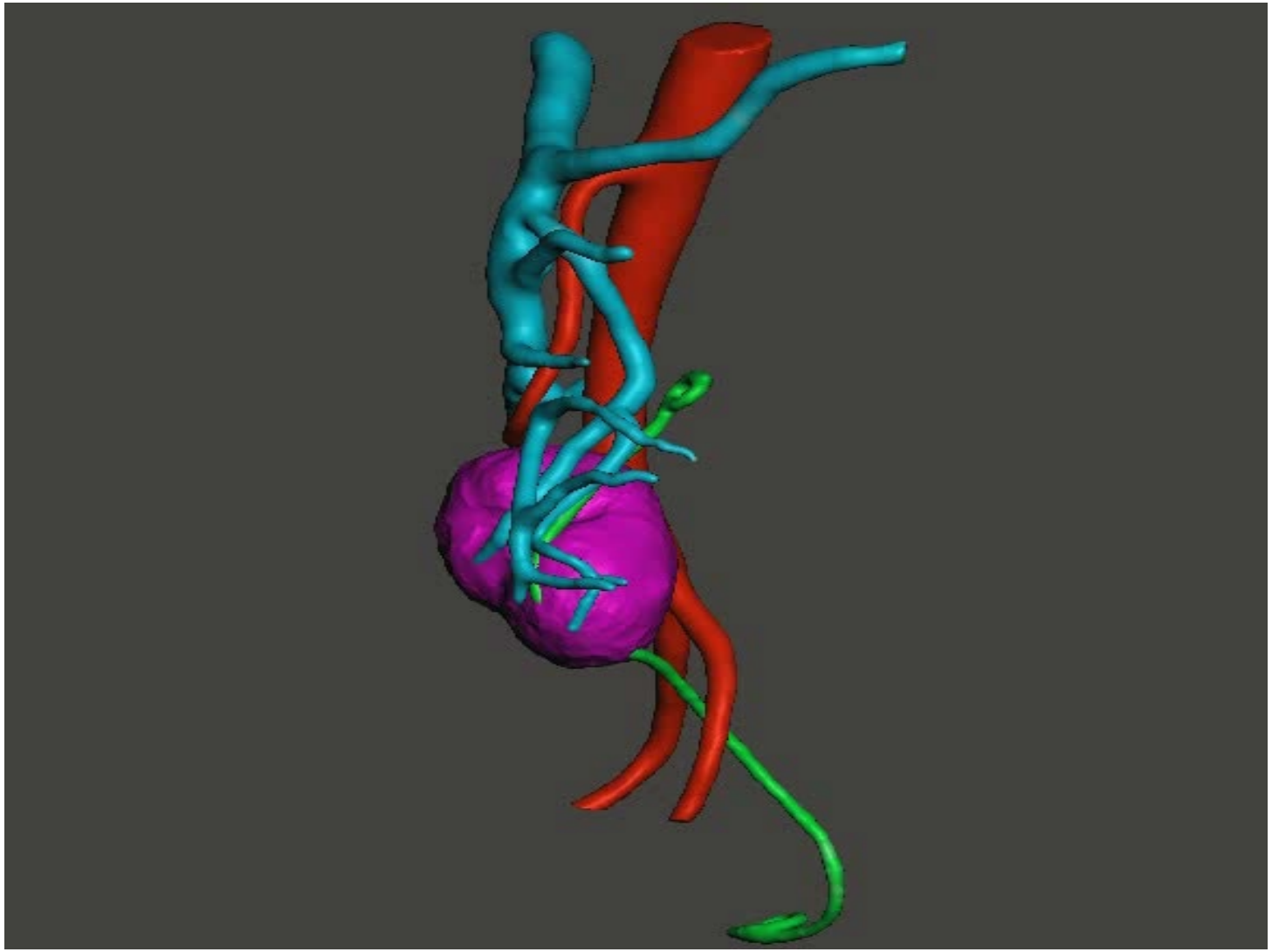
- Complete tumor resection
- Prevent tumor rupture
- Avoid local recurrence

- Large tumor
- Locally advanced tumor
- Ureteric involvement

Minimally invasive (transperitoneal/ retroperitoneal)

- Lower postoperative pain
- Earlier ambulation
- Faster recovery
- Cost-effective

- Finer and precise dissection
- Magnified view
- Stable retraction
- Good hemostatic properties



Robotic-assisted resection of retroperitoneal paraganglioma 14/7/2022

- Four 8mm ports at right abdominal wall. Robot dock in
- Mobilization of tumor from aorta and iliac vessels
- IMA root and IMV branches ligated with hemoloks and divided
- Open conversion. Midline incision
- 4cm mid-ureter excised en-bloc with retroperitoneal tumor
- uretero-ureterostomy performed with 4/O vicryl continuous manner over 6Fr 24 cm JJ stent
- Silicone drain inserted to pelvis

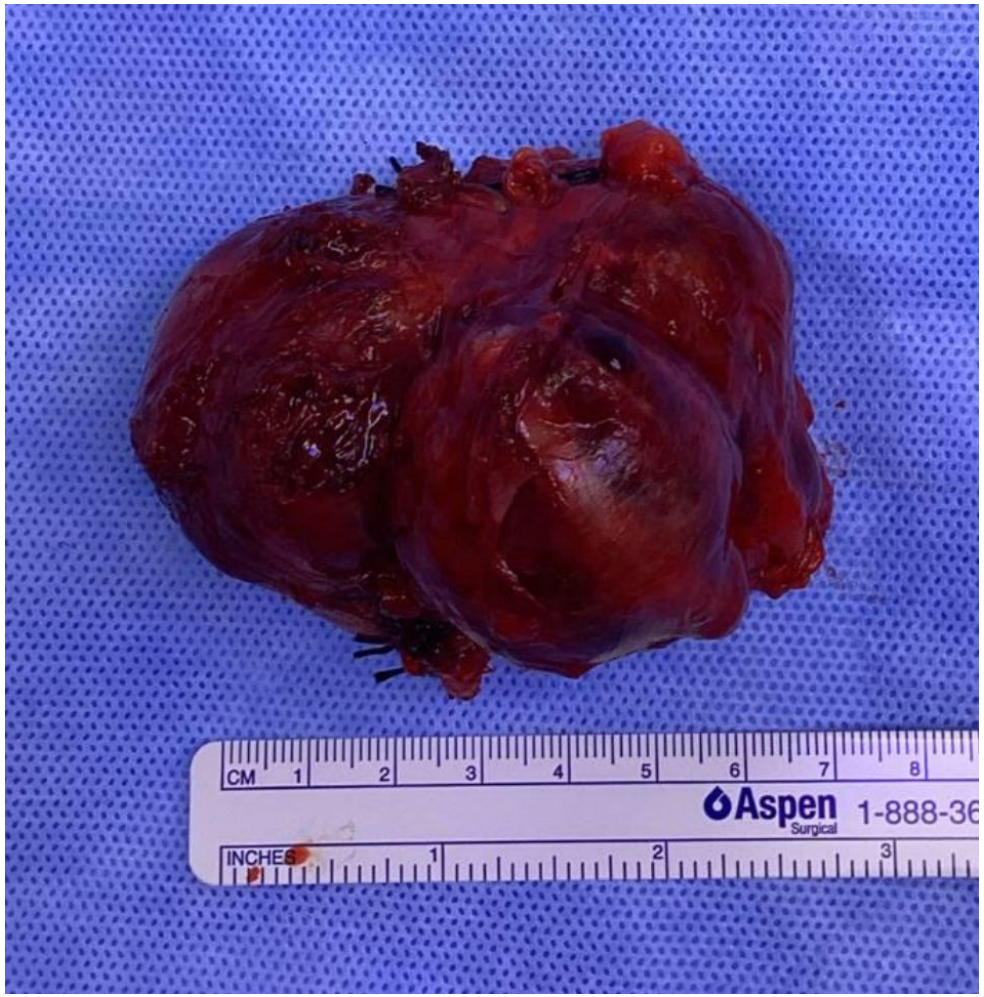
Blood loss 150ml; given 3L fluids intra-op

OT time: 3 hr 9 mins

Post operative progress

- Extubated and transferred to ICU
- Put on 3ml single strength NA, later weaned at ICU
- Pain control well on regular IV panadol & PCA
- Stopped alpha and beta blockage with stable BP

- Transient ileus requiring NG tube decompression, spontaneously resolved and tolerated diet
- Abdominal drain removed and discharged on postop day 8



Pathology: PARAGANGLIOMA

Hospital Code	PYN	PYN
Collect Date	15/07/22 16:00	11/05/22 15:30
Type, Specimen	---	---
Adrenaline, Urine, 24 hr	59	952 ↑
Noradrenaline, Urine, 24 hr	657 ↑	1053 ↑
Dopamine, Urine, 24 hr	877	1600
Metanephrine, 24 hr Urine	297 ↑	5161 ↑
Normetanephrine, 24hr Urine	537 ↑	3531 ↑

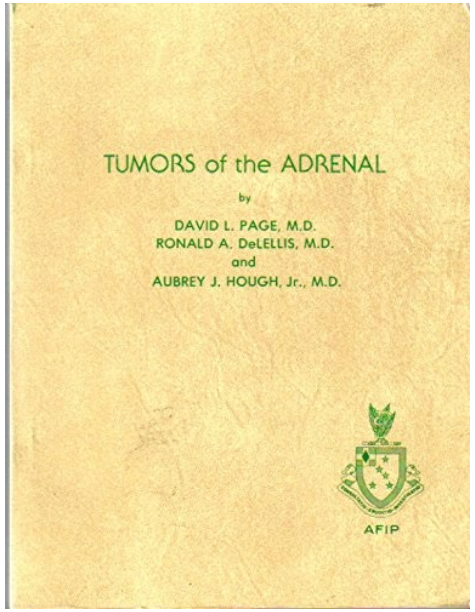
68-Ga DOTATATE + FDG PET scan 10/2022:
no residual or recurrent tumor

Phaeocheomocytoma & Paraganglioma

Nomenclature

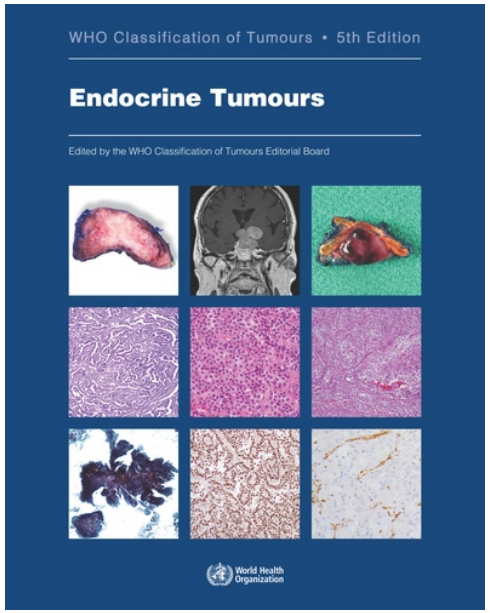
1950 Atlas of Tumor Pathology, Tumors of the Adrenal first series

Phaeochromocytoma:
tumors “in or near the adrenal”



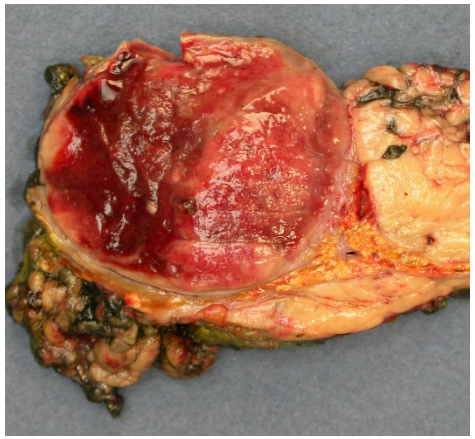
1985 Atlas of Tumor Pathology, Tumors of the Adrenal second series

Phaeochromocytoma:
only intra-adrenal neoplasms

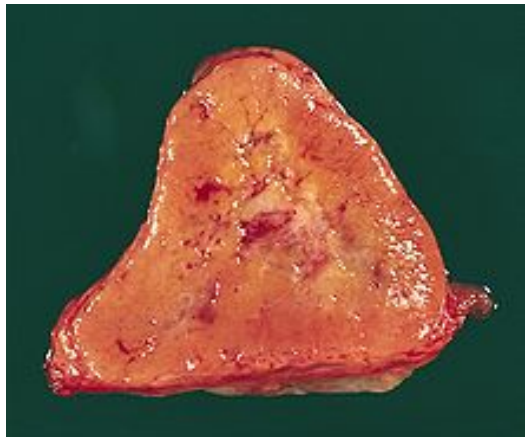


2004 WHO Classification of Tumors

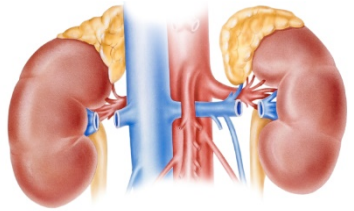
- Phaeochromocytoma: in the adrenal medulla, chromaffin cells of neural crest origin
- Paraganglioma: chromaffin cells in sympathetic and parasympathetic paraganglioma



Phaeochromocytoma



Paraganglioma



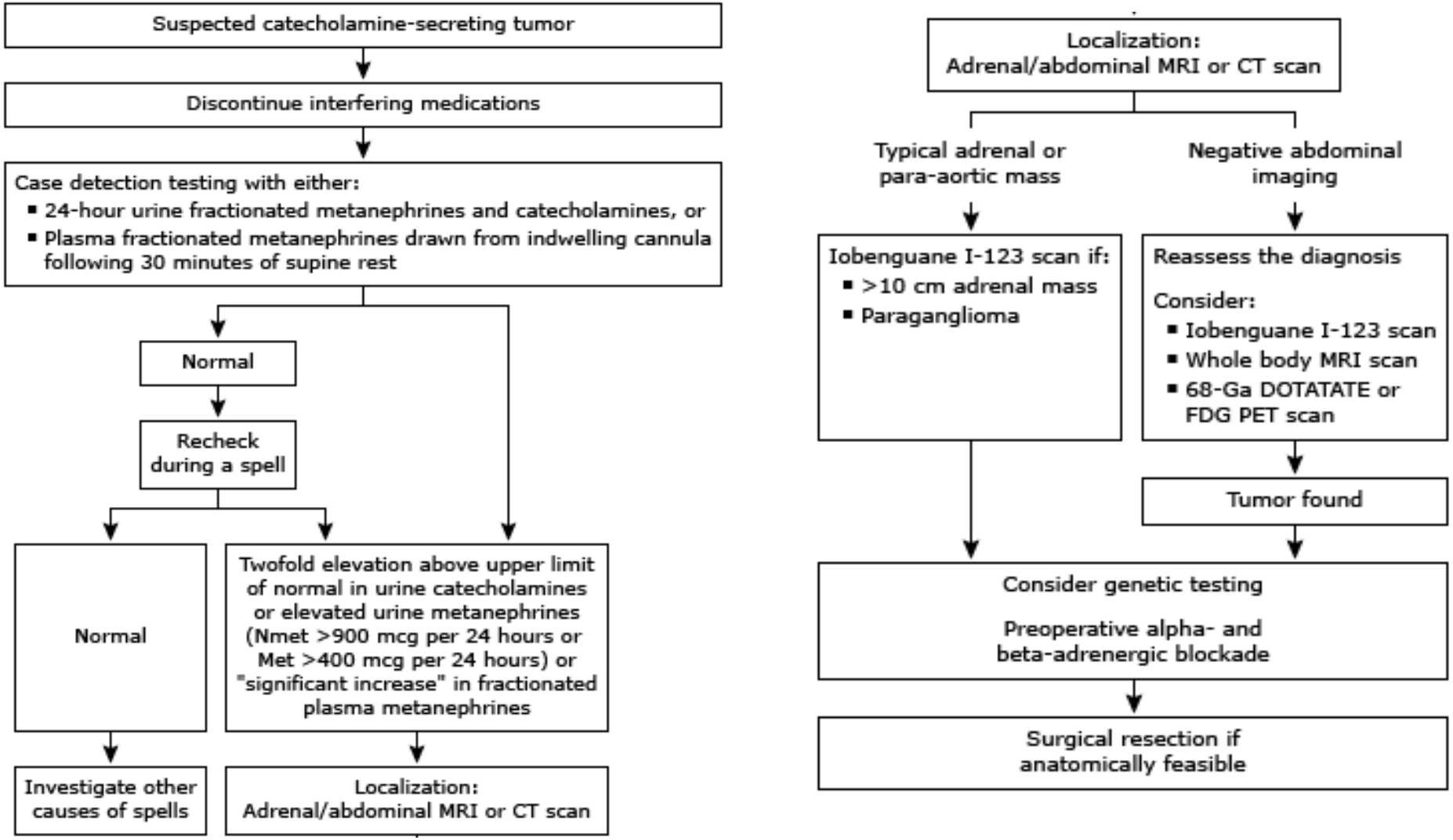
Similarities

- Mostly identical presentation
- Similar or identical morphology
- Sometimes share the same genetic predisposition

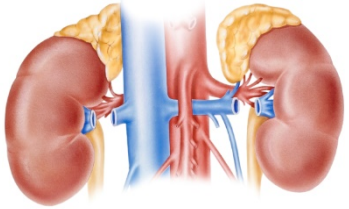
Differences

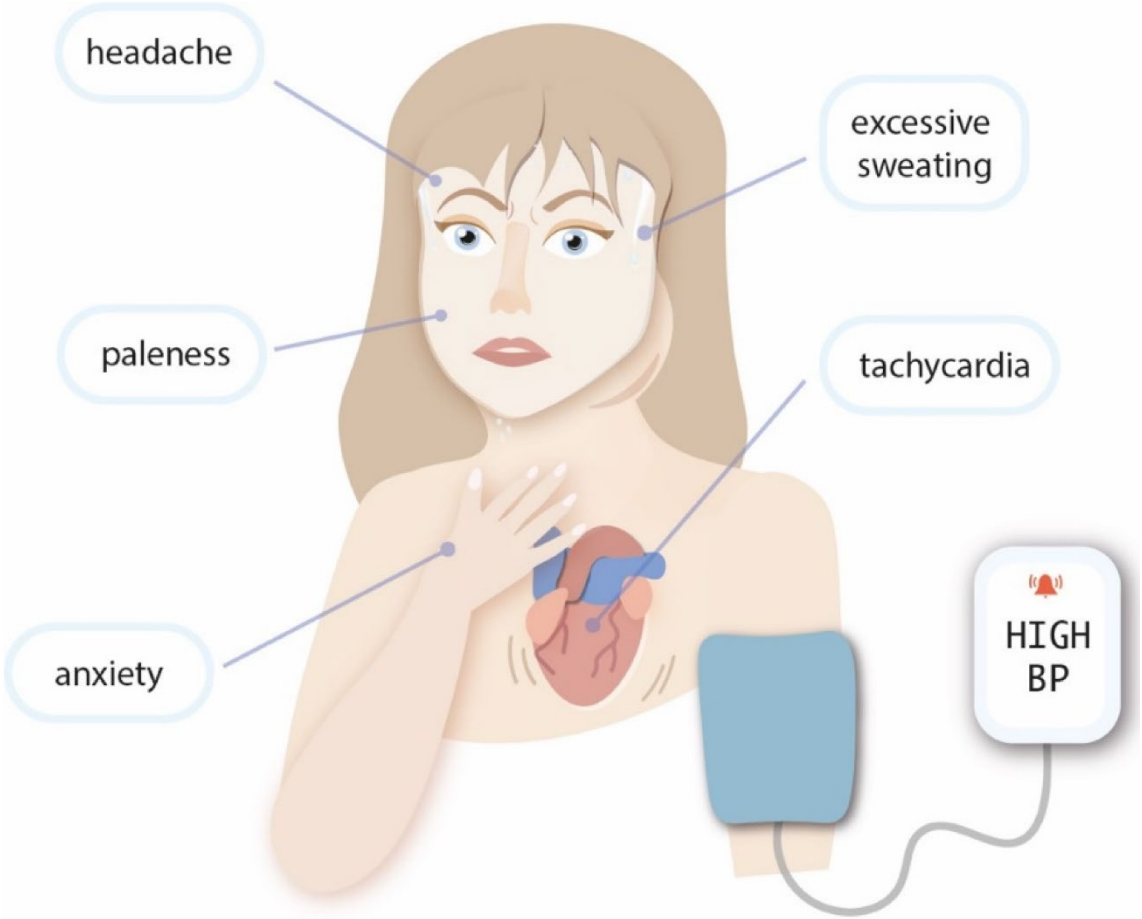
- Adrenergic/ Noradrenergic
- Lower rate of malignancy
- Association with genetic disorders

Diagnostic algorithm

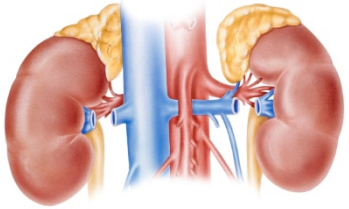


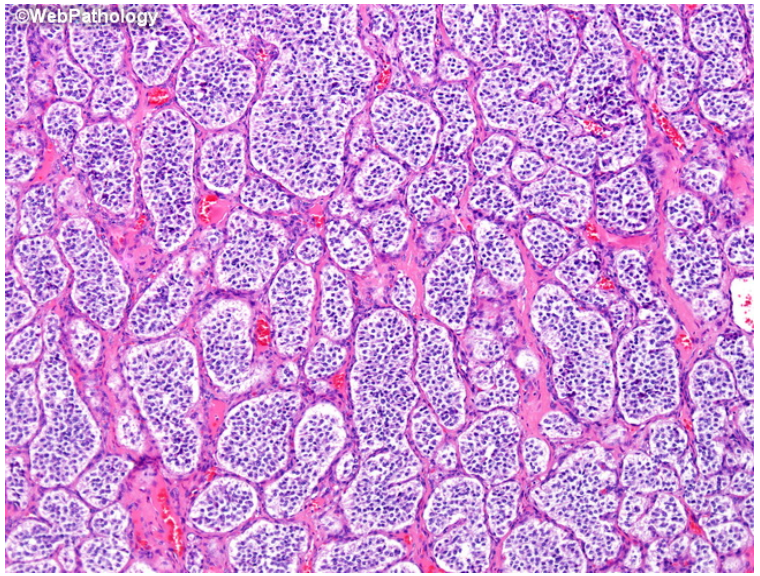
Diagnostic challenge 1 Clinical Presentation





Diagnostic challenge 2 Malignant potential



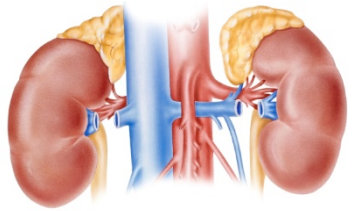


“Zellballen”

Tumors of higher grade

- a progressive loss in the relationship between chief cells and sustentacular cells
- a decrease in the overall number of sustentacular cells

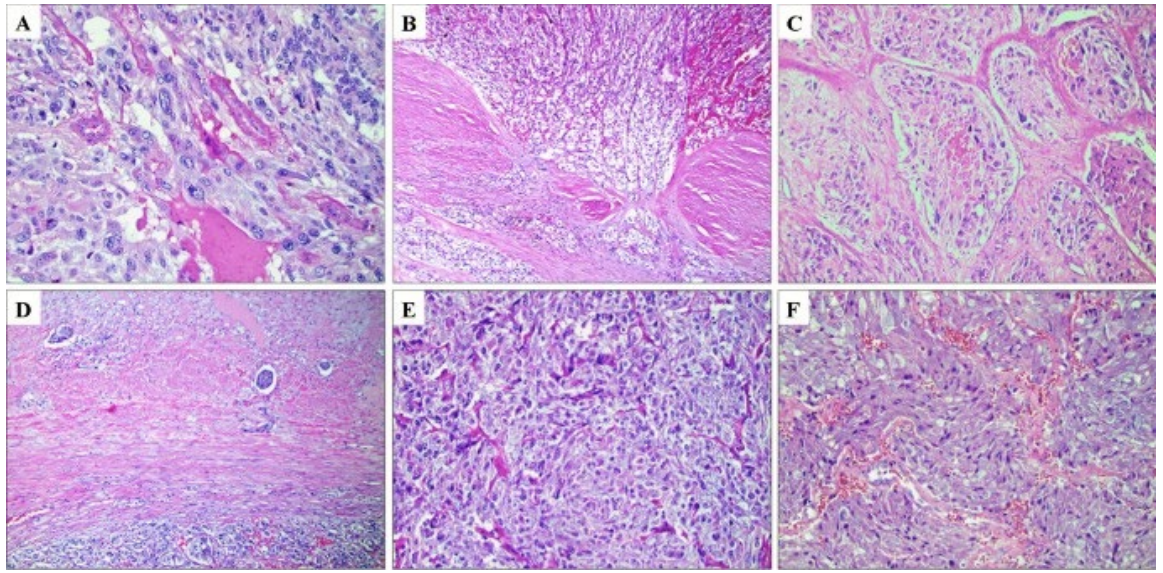
Diagnostic challenge 2 Malignant potential



Difficult to assess malignant potential on the basis of histologic findings

- No basement membrane penetration
- Malignant features/ Soft tissue invasion ≠ malignant
- Low incidence of metastasis and with a long latency

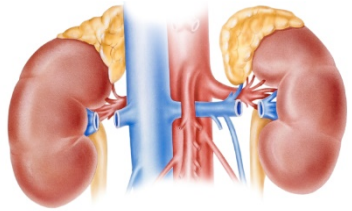
Pleomorphic | Capsular invasion | Comedo necrosis



Vascular invasion | Tumor cell spindling | Large nests

Recurrence-free
20 years

Diagnostic challenge 2 Malignant potential

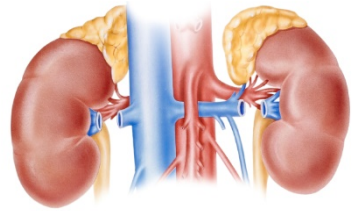


2004 World Health Organization criteria

- the only true indicator of malignant behavior is metastatic spread

"malignant" pheochromocytoma or paragangliomas ⟶ "metastatic" pheochromocytoma or paragangliomas

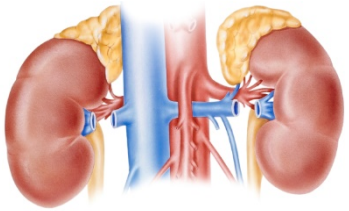
Diagnostic challenge 2 Malignant potential

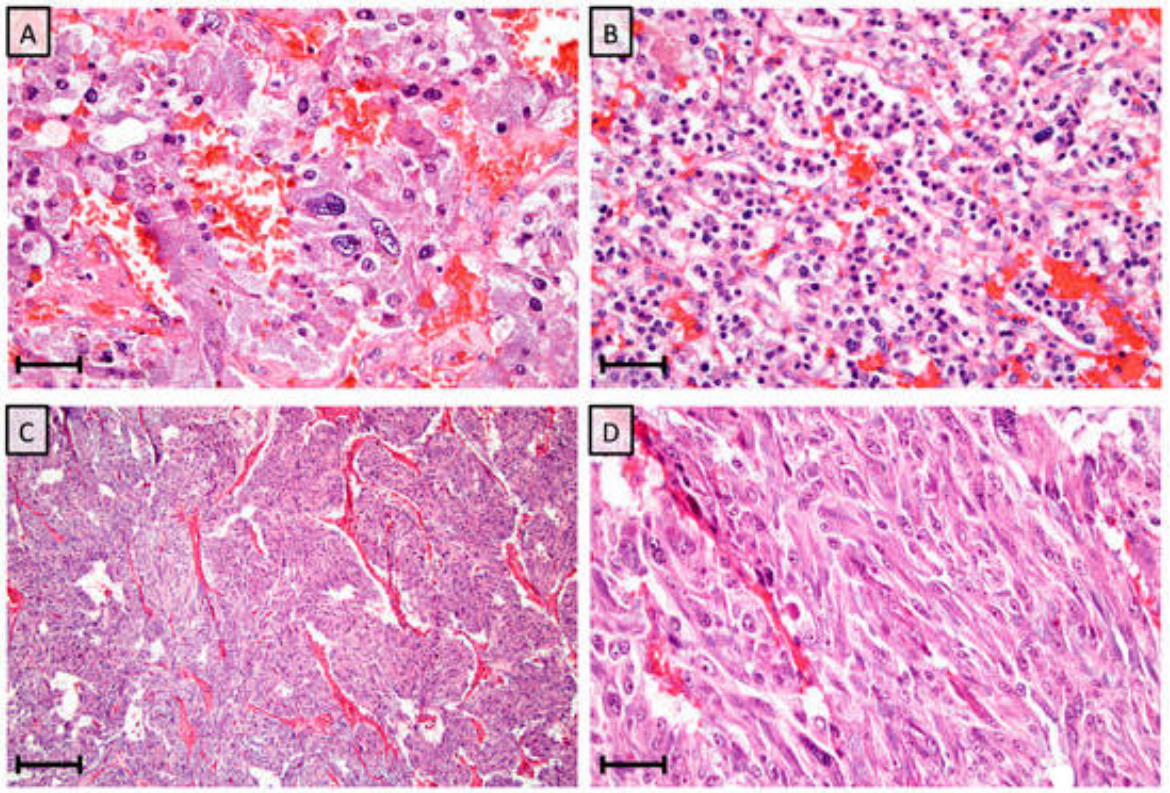


- Histologic scoring systems
  - PASS system (Pheochromocytoma of the Adrenal gland Scales Score)

Items	Value
Nuclear hyperchromasia	1
Profound nuclear pleomorphism	1
Capsular invasion	1
Vascular invasion	1
Extension into adipose tissue	2
Atypical mitotic figures	2
Greater than 3 of 10 mitotic figures high-power field	2
Tumor cell spindling	2
Cellular monotony	2
High cellularity	2
Central or confluent tumor necrosis	2
Large nests or diffuse growth (>10% of tumor volume)	2
Total	20

Diagnostic challenge 2 Malignant potential





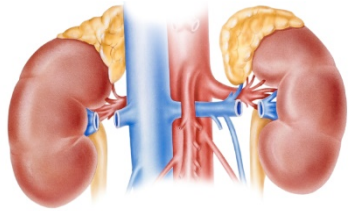
PASS score 8

→ metastasis

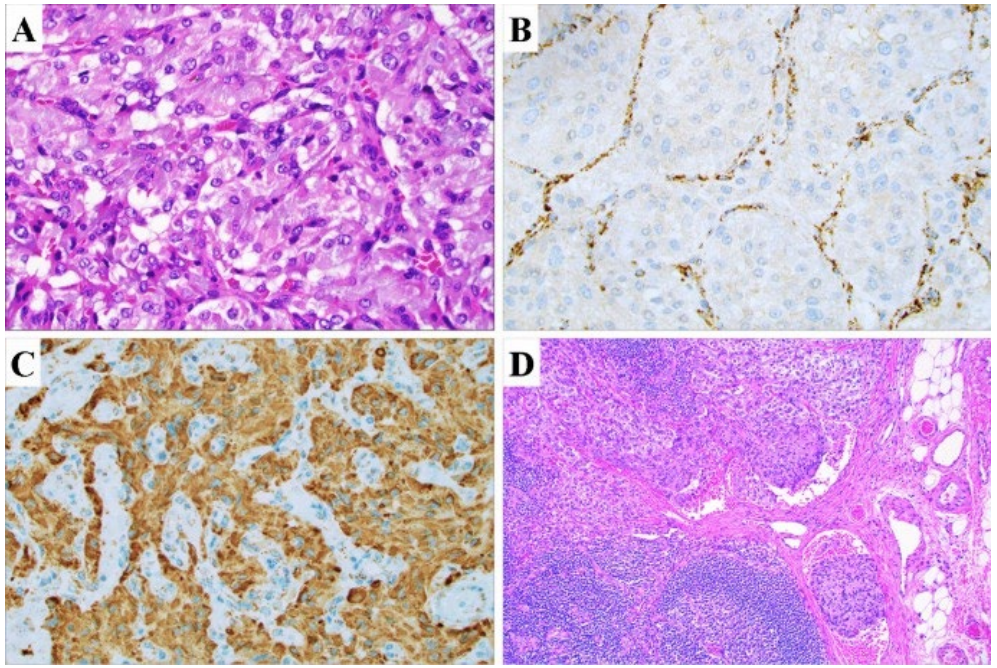
PASS score 7

→ no metastasis

Diagnostic challenge 2 Malignant potential



- Immunohistochemical Analyses
  - Ki-67 proliferative index
  - SDHB immunohistochemistry

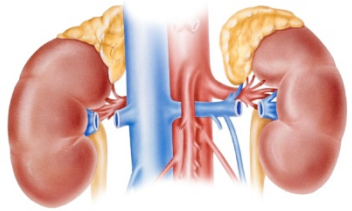


Absent SDHB staining

Positive SDHB staining

→ metastatic regional LN

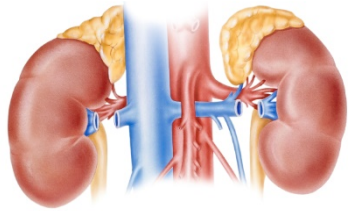
Diagnostic challenge 2 Malignant potential



- GAPP score (Grading System for Adrenal Phaeochromocytoma and Paraganglioma)

Parameters	Points scored
Histological pattern	
Zellballen	0
Large and irregular cell nest	1
Pseudorosette (even focal)	1
Cellularity	
Low (<150 cells/U)	0
Moderate (150–250 cells/U)	1
High (more than 250 cells/U)	2
Comedo necrosis	
Absence	0
Presence	2
Vascular or capsular invasion	
Absence	0
Presence	1
Ki67 labelling index (%)	
<1	0
1–3	1
>3	2
Catecholamine type	
Epinephrine type (E or E+NE)	0
Norepinephrine type (NE or NE+DA)	1
Non-functioning type	0
Total maximum score	10

Diagnostic challenge 3 Genetic testing

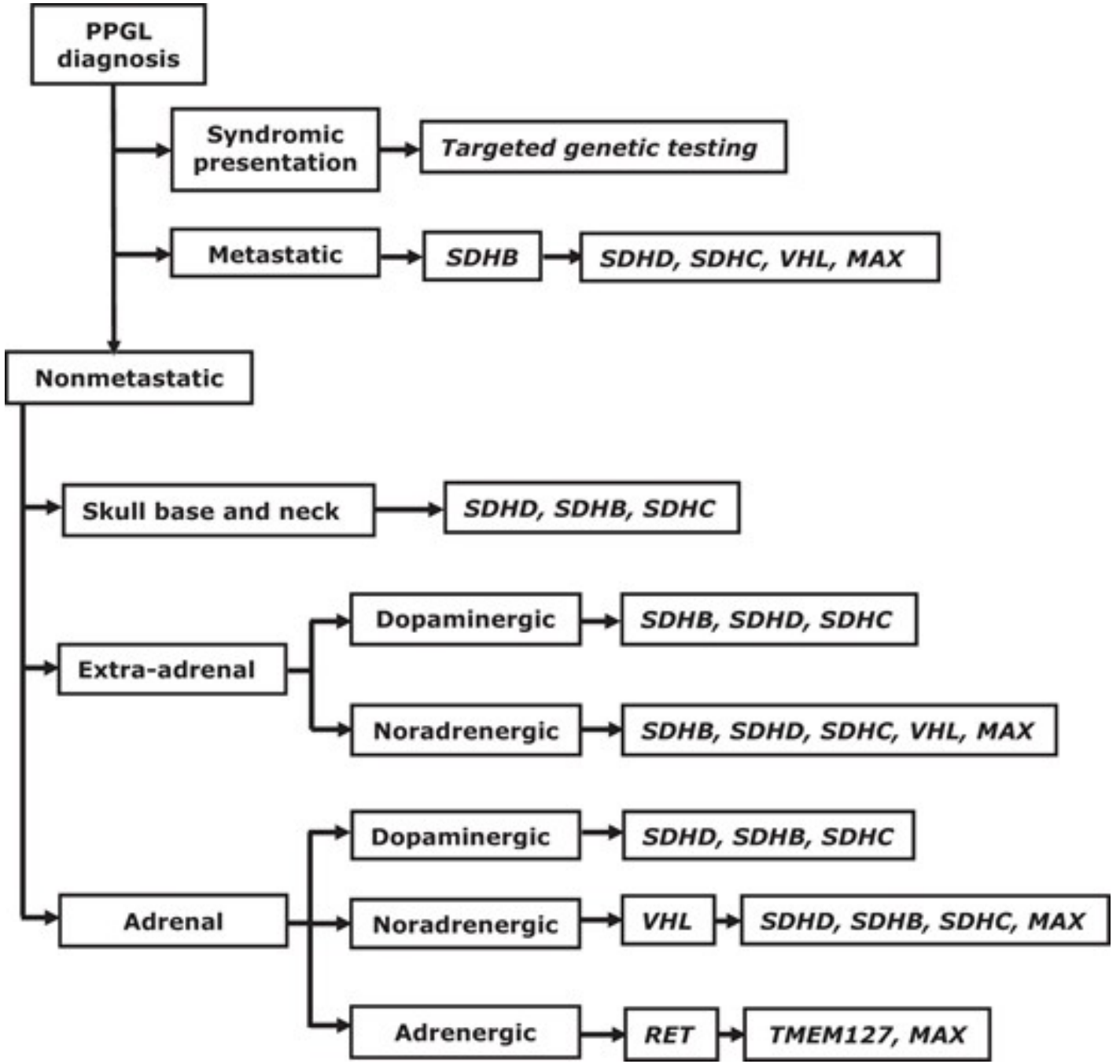


- Paraganglioma has the highest heritability among endocrine tumor
- Germline genetic testing for all patients with paraganglioma
- Genetic testing
  - Estimating the chance of recurrence, either metachronous or malignant
    - *SDHB* pathogenic variants had an increased frequency of malignant disease
    - *SDHD* carriers had a higher incidence of skull base and neck paragangliomas and multifocality
  - Determining follow-up algorithm for associated syndromic manifestations

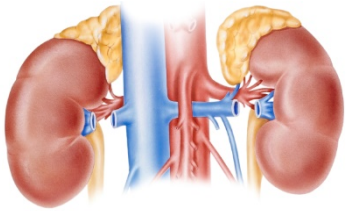
Endocrine Society Clinical Practice Guideline

Syndromic PPGL	Associated clinical findings
MEN 2	- medullary thyroid carcinoma - parathyroid hyperplasia - mucocutaneous neuromas
VHL disease	- cerebellar hemangioblastoma, - retinal angiomas - clear cell renal cell carcinoma - pancreatic neuroendocrine tumors
NF1	- café au lait spot - axillary freckling - subcutaneous neurofibroma - Lisch nodules

Genetic testing panel:
RET, VHL, NF-1, SDHD, SDHC, SDHB, SDHA, SDHAF2, TMEM127, MAX



Treatment



Pre-operative

- Alpha blockade
- Beta blockade

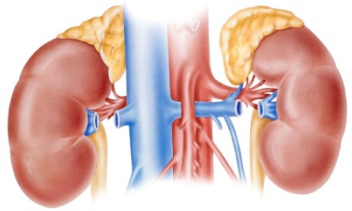
Intra-operative

- Close liaison with anesthetists
- IV catheter, CVC, A-line, foley
- Close BP monitoring
- Fluid replacement
- Minimize tumor manipulation
- Control vascular drainage

Post-operative

- ICU support
- Watch out for complications

Treatment challenge 1 BP control

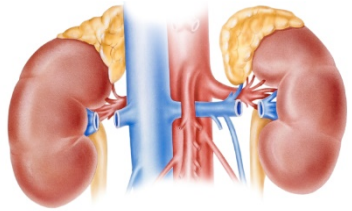


Roizen criteria

1. No in-hospital blood pressure >160/90 mmHg for 24 h prior to surgery;
2. No orthostatic hypotension with blood pressure <80/45 mmHg;
3. No ST or T wave changes for 1-week prior to surgery;
4. No more than 5 premature ventricular contractions per minute.

- Indicators of adequate pharmacological preparation
- Reduced episode of intraoperative hemodynamic instability, thus decreased surgical complications and mortality

Treatment challenge 1 BP control

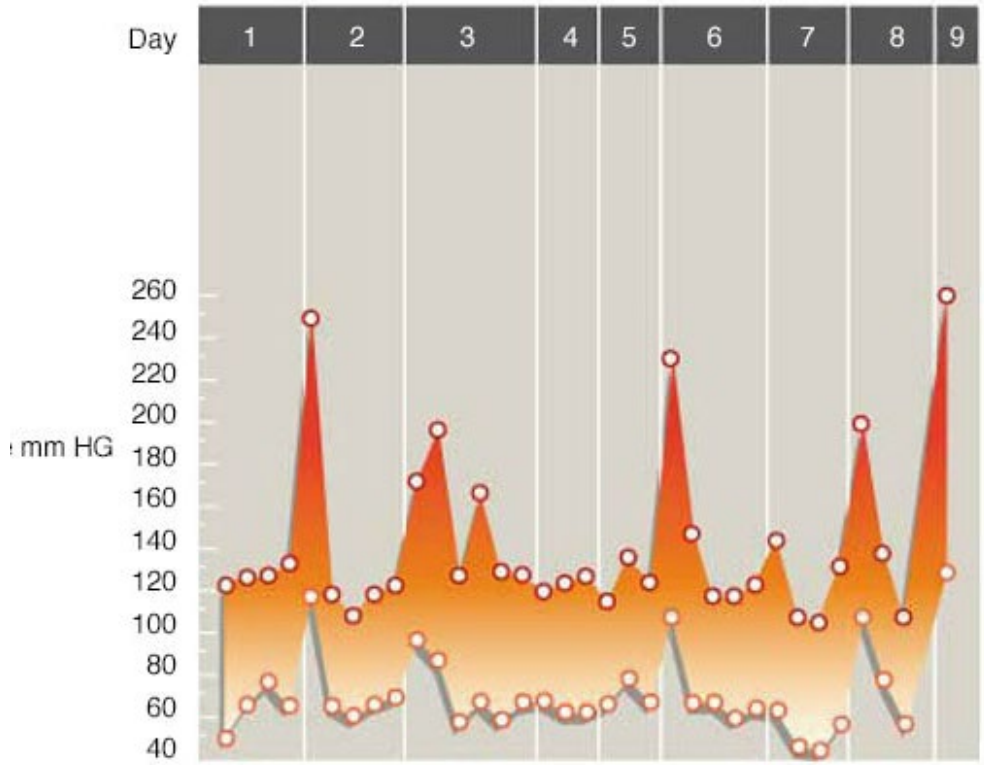


? Blood pressure goal

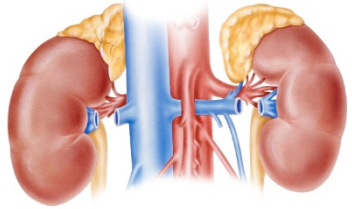
? Intraoperative hemodynamic instability definition

? Association

? Hypotensive phases

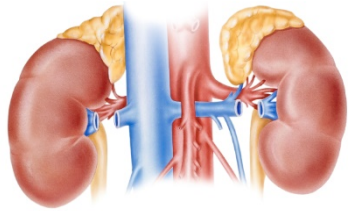


Treatment Challenge 2 Surgical Complexity



- Technical challenges
  - Vascularity
  - Tumor size
  - Tumor location
- Approach
  - Minimally invasive vs Open resection

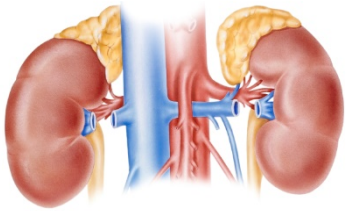
Treatment Challenge 3 Follow up



- Benign vs Malignant
- Risk of local recurrence

NCCN guidelines on surveillance	
Resectable	Blood pressure and biochemical markers every 6-12 months for the first three years, then annually to year 10
Locally unresectable/ metastatic	Blood pressure and biochemical markers every 3-4 months
All	Imaging as clinically indicated

Conclusion



Clinical presentation
Non-specific episodic symptoms
Lack of awareness

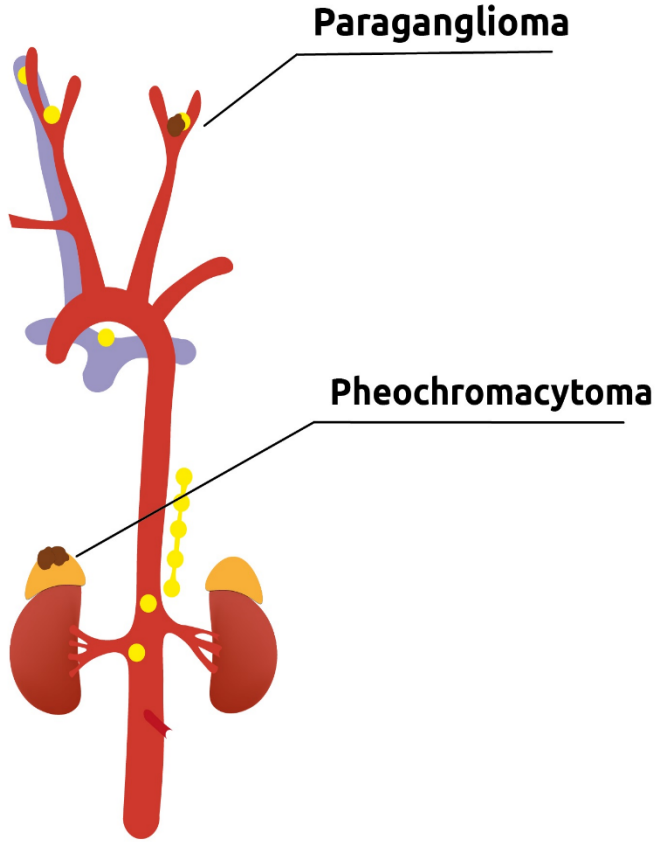
01

Malignant potential
Histological, Immunohistochemistry
PASS score, GAPP score

02

Genetic testing
European Society Guidelines
? Optimal genetic testing algorithm

03



04

Blood pressure control
? Target hemodynamic goals
? Association with intraoperative

05

Surgical complexity
Vascularity, tumor size and location
Surgical approach

06

Follow-up
NCCN guidelines
? Optimal surveillance protocol