Pheochromocytoma/ Paraganglioma

Work-up and management

February 25th, 2022

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UT Health San Antonio

University Health System

Mays Cancer Center
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No disclosures

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Overview

- Work-up
- Perioperative management
- Surgical interventions

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- Work-up
- Perioperative management
- Surgical interventions

What are pheochromocytoma/ paraganglioma (PPGL)?

- Catecholamine-secreting tumor
- Adrenal
- Extra-adrenal

- Classic triad: episodic headache, sweating, and tachycardia
- Rule of 10s: 10% familial, 10%, malignant, 10% extra-adrenal

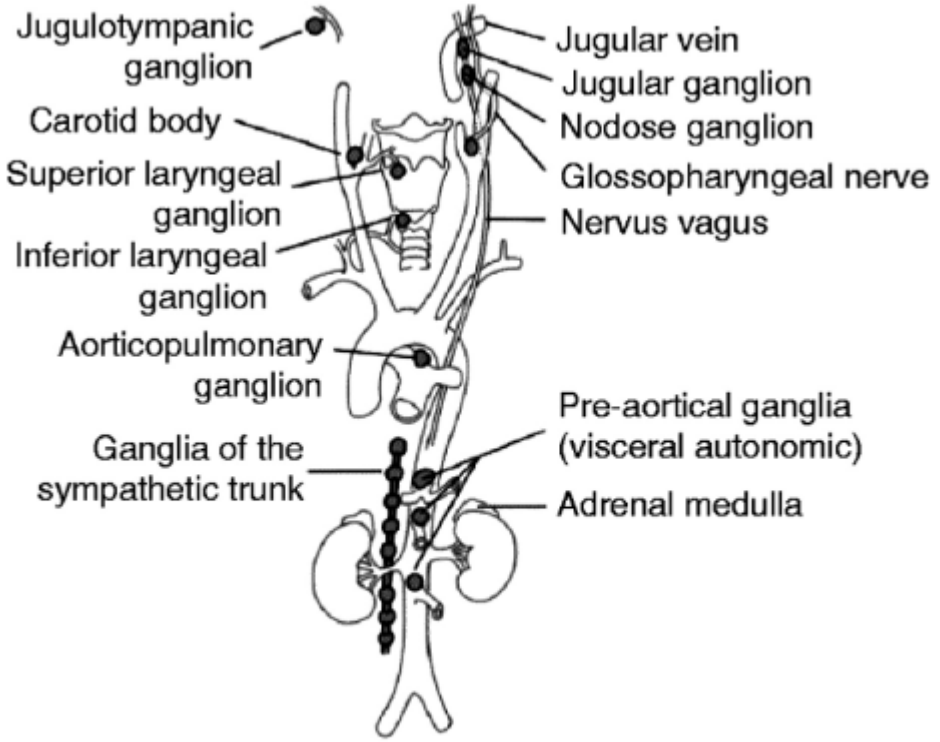


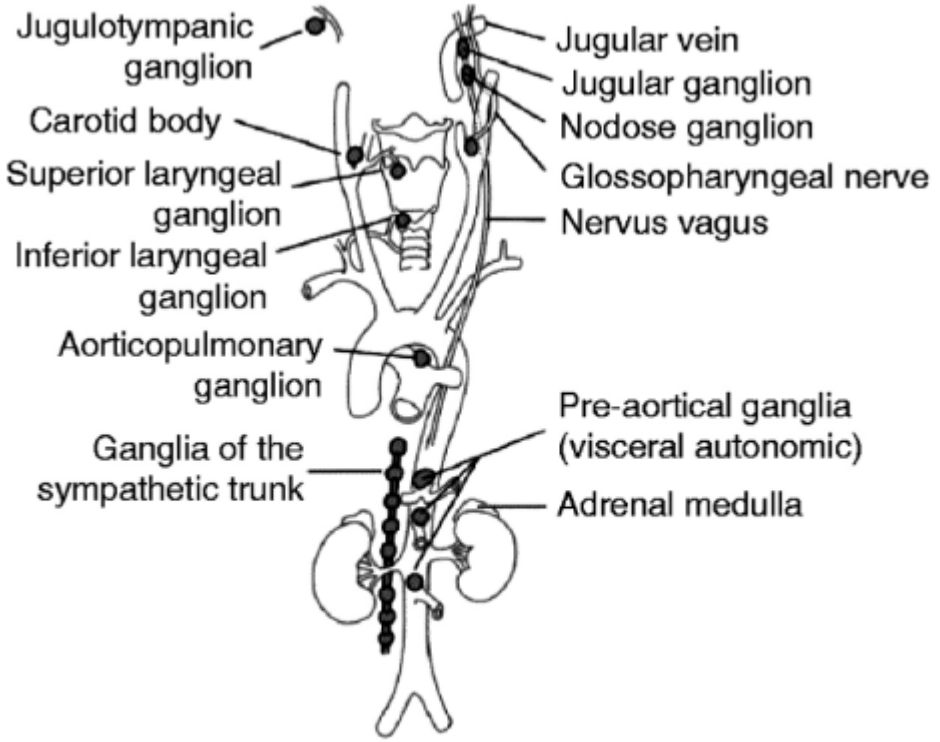
Fig. 1 *Common localizations of PPGL ((Welander* et al. *2011), modified with permission from (Lips* et al. *2006)).*

J Intern Med. 2019 Feb;285(2):187-204. doi: 10.1111/joim.12869. Epub 2019 Jan 15.

What are pheochromocytoma/ paraganglioma (PPGL)?

- Catecholamine-secreting tumor
- Adrenal
- Extra-adrenal

- Classic triad: episodic headache, sweating, and tachycardia
- Rule of 10s: 40% familial, 10%, malignant, 10% extra-adrenal



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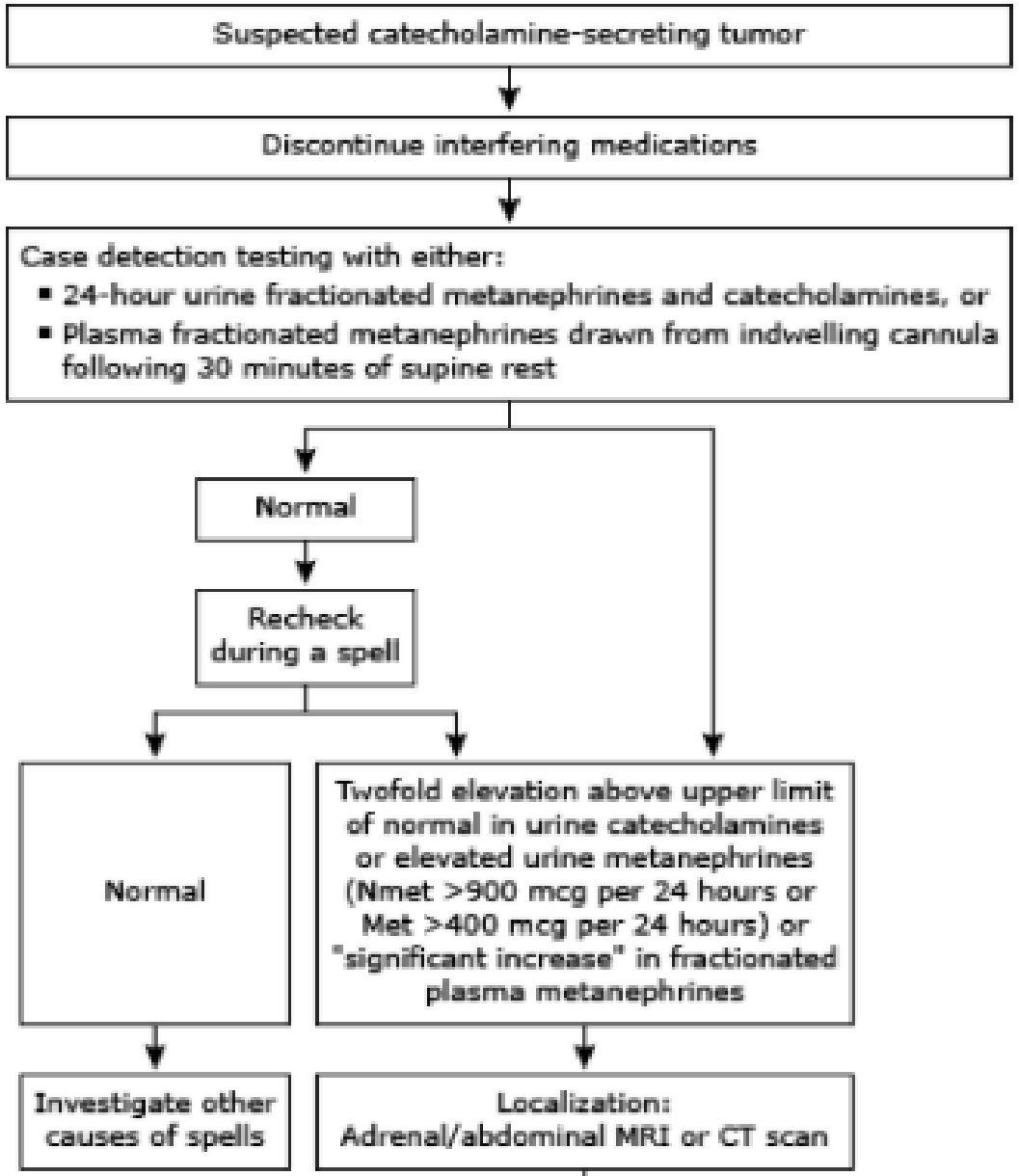
Work-up

- 37 yo F with uncontrolled hypertension for 4 years, presented to the ED with complaint of epigastric and LUQ abdominal pain.
- BP 250/117, HR 68
- PMHx: HTN, pre-eclampsia with the last pregnancy

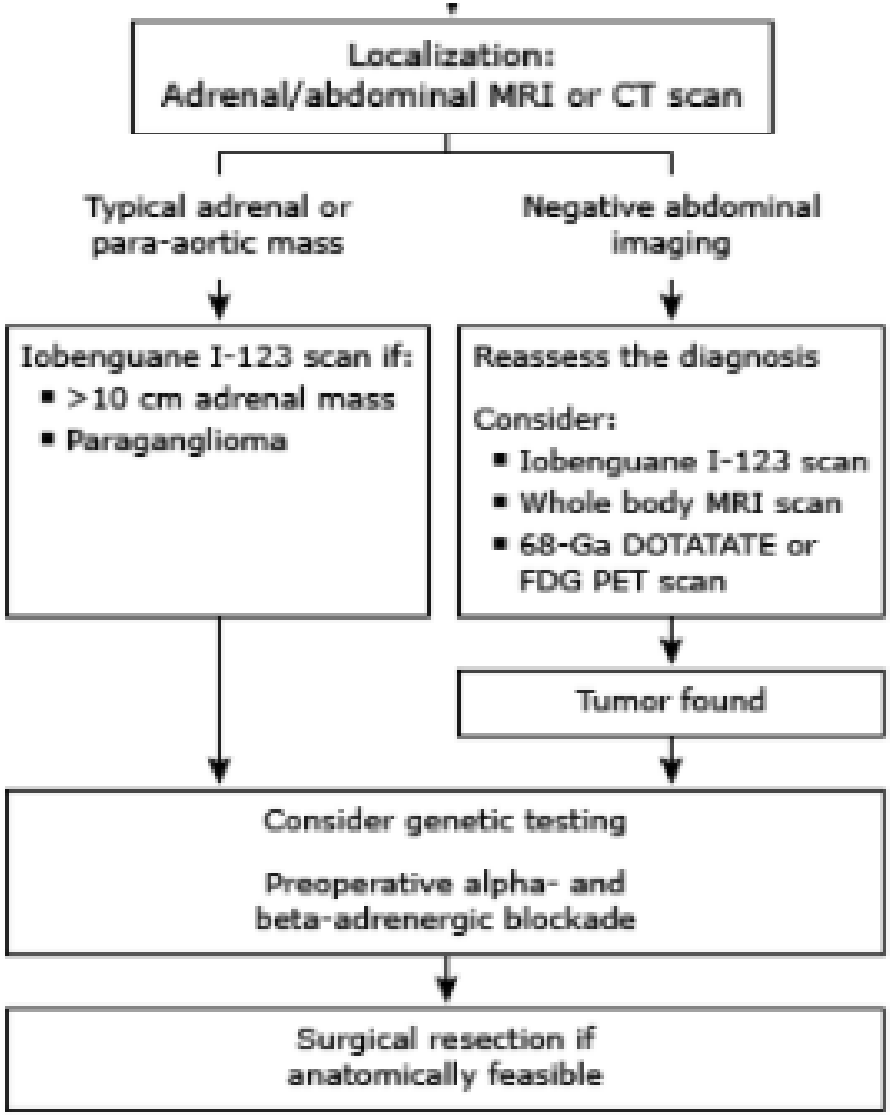
Work-up



- History & Physical exam
- Family history!!!
- Biochemical testing
  - Plasma free metanephrines
  - 24-hour urinary fractionated metanephrines and catecholamines

- Imaging
  - CT
  - MRI
  - Iobenguane I-123
  - FDG PET
  - 68-Ga DOTATATE PET

- Genetic testing



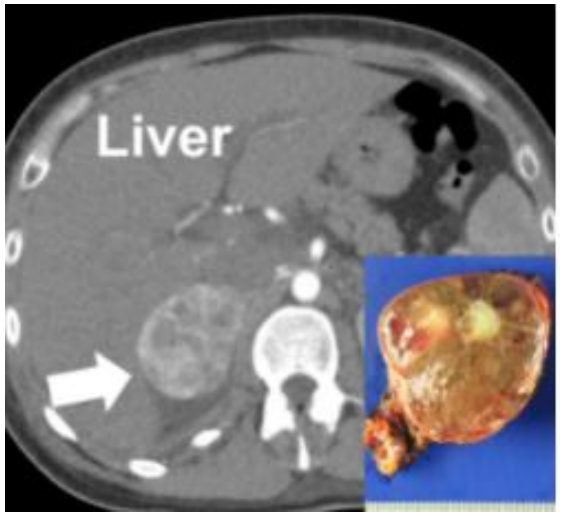
Biochemical testing

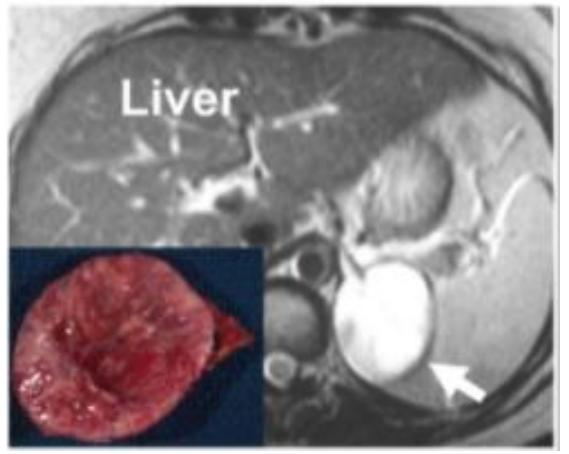
	24-hour urine fractionated metanephrines and catecholamines	Plasma fractionated metanephrines
Sensitivity	98%	98%
Specificity	96-100%	85-89%
Pitfalls	Difficult in children	Positional
Indication	Patients with low risk for PPGL	Patients with high risk for PPGL

*For individuals with familial PPGL syndrome, plasma fractionated metenephrines are recommended

Imaging

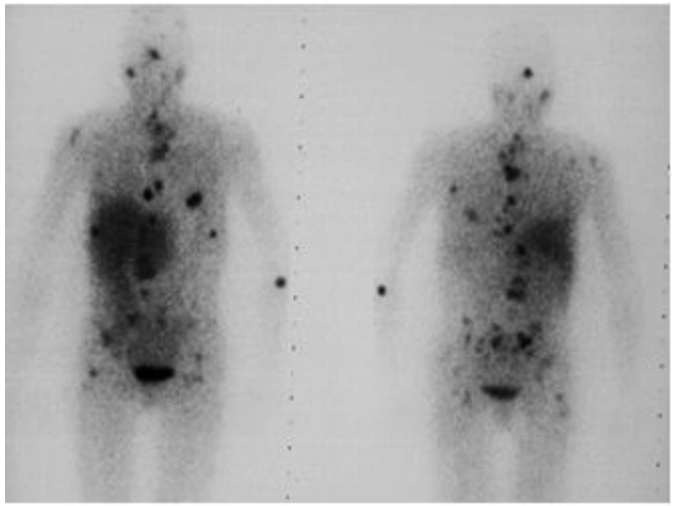
- CT and MRI
  - They are both highly sensitive and specific
  - Increased attenuation on non-enhanced CT
  - Increased vascularity
  - Delay in contrast washout
  - High signal intensity on T2-weighted MRI
  - Cystic and hemorrhagic changes

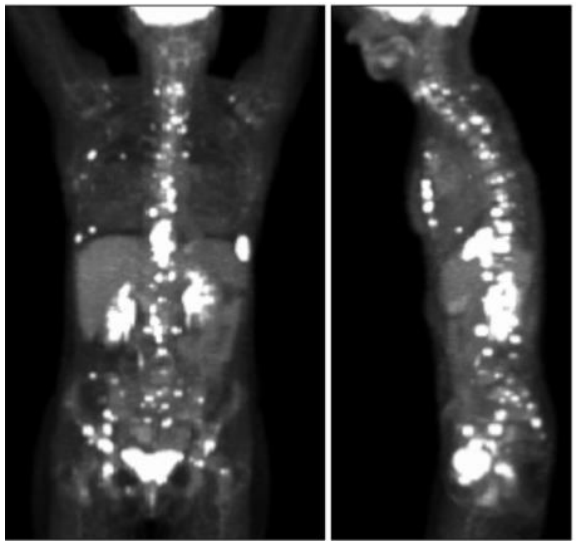




Imaging

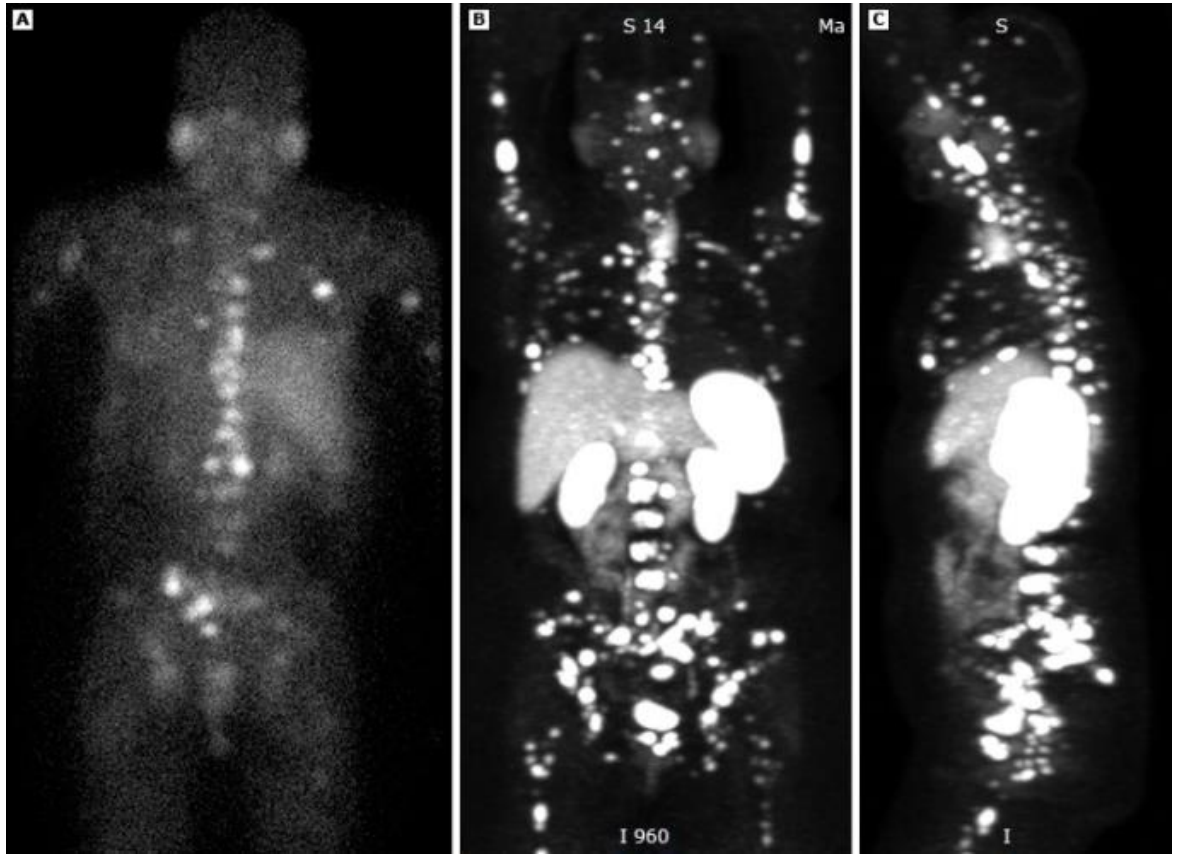
- Iobenguane I-123 (aka MIBG scan)
  - Negative CT/MRI
  - Metastatic work-up
- FDG PET
  - Metastatic work-up
  - More sensitive than MIBG





Imaging

- 68-Ga DOTATATE PET
  - More sensitive than CT/MRI, MIBG, or FDG PET



Eur J Nucl Med Mol Imaging (2016) 43:1784–1791
DOI 10.1007/s00259-016-3357-x

ORIGINAL ARTICLE

PET/CT comparing ^{68}Ga-DOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma

Ingo Janssen[1,2] · Clara C. Chen[3] · Corina M. Millo[4] · Alexander Ling[5] · David Taieb[6] · Frank I. Lin[7] · Karen T. Adams[1] · Katherine I. Wolf[1] · Peter Herscovitch[4] · Antonio T. Fojo[8] · Inga Buchmann[2] · Electron Kebebew[9] · Karel Pacak[1]

- 22 consecutive patients with sporadic metastatic PPGL

Table 3 Lesion detection rates for ^{68}Ga-DOTATATE, ^{18}F-FDG, ^{18}F-FDOPA and ^{18}F-FDA PET/CT, and CT/MRI

Lesion location	^{68}Ga-DOTATATE PET/CT		^{18}F-FDG PET/CT		^{18}F-FDOPA PET/CT		^{18}F-FDA PET/CT		CT/MRI	
	Detection rate (%)	95 % CI (%)	Detection rate (%)	95 % CI (%)	Detection rate (%)	95 % CI (%)	Detection rate (%)	95 % CI (%)	Detection rate (%)	95 % CI (%)
All compartments	97.6	95.8 – 98.7	49.2	44.5 – 53.6	74.8	69.0 – 79.9	77.7	71.5 – 82.8	81.6	77.8 – 84.8
Mediastinum	100	92.3 – 100	56.5	42.3 – 69.8	70.8	50.8 – 85.1	100	84.5 – 100	58.7	44.3 – 71.7
Lungs	94.7	95.1 – 97.1	55.3	45.3 – 65.0	98.1	90.1 – 99.7	68.4	52.5 – 80.9	94.7	88.2 – 97.7
Abdomen	100	95.1 – 100	56.8	45.3.4 – 67.4	73.2	58.1 – 84.3	92.1	79.2 – 97.3	77.0	66.3 – 85.1
Liver	87.5	75.3 – 94.1	12.5	5.9 – 24.7	84.5	57.8 – 95.7	69.2	42.4 – 87.3	93.8	83.2 – 97.8
Bone	100	98.1 – 100	50.3	43.4 – 57.1	64.0	54.7 – 72.3	71.2	62.2 – 79.9	79.4	73.3 – 84.4

Conclusion

- Gallium 68 DOTATATE scan is superior in detecting sporadic metastatic PPGLs compared to other functional and anatomical imaging modalities

Endocrine-Related Cancer (2012) **19** 83–93

False-negative ^{123}I-MIBG SPECT is most commonly found in *SDHB*-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease

Jay S Fonte[1,4], Jeremyjones F Robles[1,4], Clara C Chen[2], James Reynolds[2], Millie Whatley[2], Alexander Ling[3], Leilani B Mercado-Asis[4], Karen T Adams[1], Victoria Martucci[1], Tito Fojo[5] and Karel Pacak[1]

- 21 patients with false negative MIBG SPECT

Table 1 Characteristics of patients at the time of false-negative ^{123}I-MIBG SPECT

Patient	Age (years)/sex	Reason for consult at NIH	Hypersecretion in plasma		Hypersecretion in urine		Gene mutation
			Meta-nephrines	Cate-cholamines	Meta-nephrines	Cate-cholamines	
1	13/F	P	NMN, MN	NE, E, DA	–	–	Apparently sporadic
2	47/F	P	NMN, MN	E	NMN, MN, T	None	*RET*
3	51/F	P	NMN, MN	NE, E	NMN, MN, T	NE, E	Apparently sporadic
4	61/M	P	None	DA	–	–	*SDHB*
5	49/F	P	NMN	NE	NMN, T	NE	Apparently sporadic
6	46/F	P	NMN, MN	None	–	–	Apparently sporadic
7	36/F	New P	NMN	NE	NMN, T	NE	*SDHB*
8	40/F	R	NMN	NE	NMN, T	NE, DA	Apparently sporadic
9	55/M	Met + New P	NMN	NE, DA	NMN, T	NE	Neg for *SDHx*
10	54/M	Met + New P	NMN	NE, DA	NMN, T	NE, DA	*SDHB*
11	42/F	Met + New P	NMN	NE, DA	NMN, T	NE	*SDHB*
12	36/F	Met	NMN	NE	NMN, T	NE	*SDHB*
13	32/M	Met	NMN, MN	None	None	None	Apparently sporadic
14	47/F	Met	None	None	–	–	*SDHB*
15	43/F	Met	NMN	NMN	NMN, T	None	*SDHB*
16	34/M	Met	NMN	NE, DA	–	–	*SDHB*
17	37/M	Met	NMN	NE, DA	–	–	*SDHB*
18	43/F	Met	None	None	–	–	*SDHB*
19	45/F	Met	NMN	NE	None	NE	Apparently sporadic
20	33/M	Met	None	None	–	–	*SDHB*
21	22/F	Met	NMN	NE	NMN, T	NE	Apparently sporadic

Conclusion

- Patient characteristic
  - Noradrenergic biochemical phenotype
  - Metastasis
  - 52% had SDHB mutation
- Patients with false negative MIBG to be tested for SDHB mutation and undergo closer follow-up

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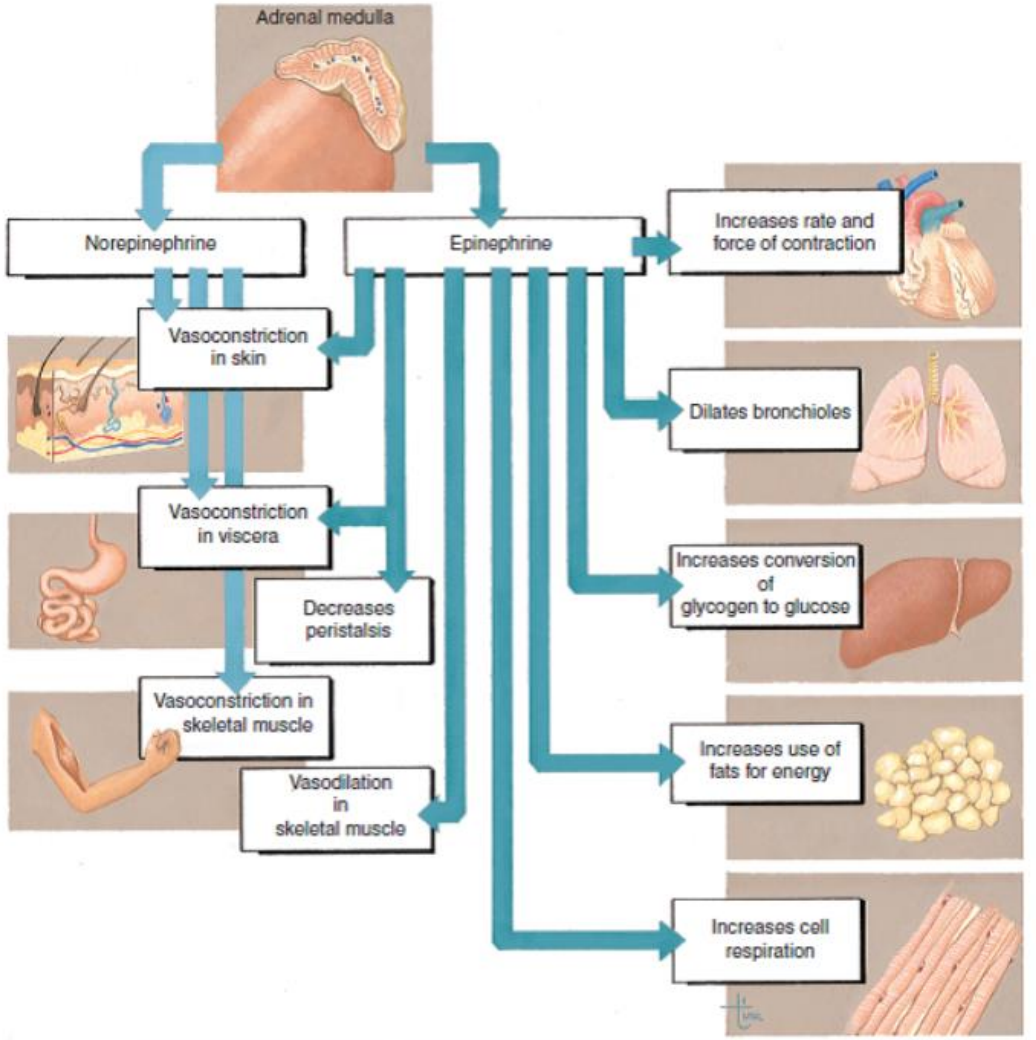
Pathophysiology

- Epinephrine and norepinephrine over-production
- Reactive hypovolemia



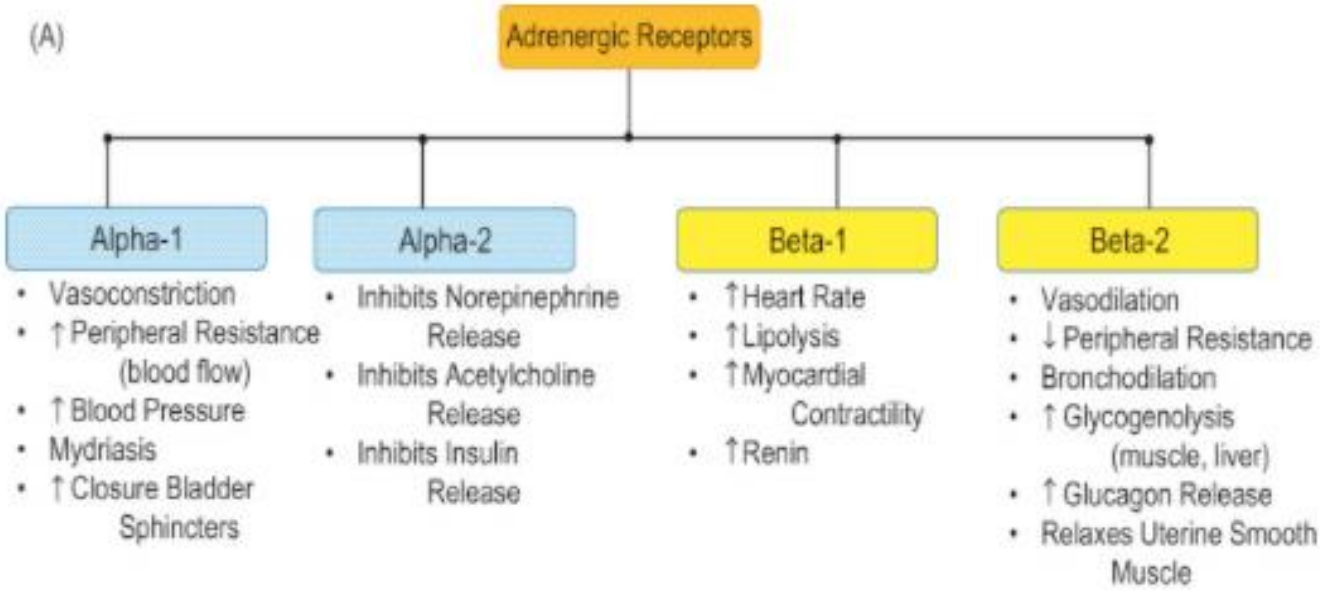
Chegg, Essentials of Anatomy and Physiology

Figure 10-9 Functions of epinephrine and norepinephrine.

Perioperative Management

- Alpha blocker
- Beta blocker
- Volume resuscitation

(A)



(B)

Alpha-1	Alpha-2	Beta-1	Beta-2
NE > E	E > NE	E = NE	E >> NE
NE = Norepinephrine; E = Epinephrine			

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Figure 6.1. Adrenergic receptor subtypes. (A) Physiological effects of catecholamine binding to the specific receptor. (B) Affinity of the receptor subtypes for each catecholamine. ↑=increase, ↓=decrease.

Efficacy of α-Blockers on Hemodynamic Control during Pheochromocytoma Resection: A Randomized Controlled Trial

Edward Buitenwerf,[1] Thamara E. Osinga,[1] Henri J. L. M. Timmers,[2] Jacques W. M. Lenders,[3,4] Richard A. Feelders,[5] Elisabeth M. W. Eekhoff,[6] Harm R. Haak,[7–9] Eleonora P. M. Corssmit,[10] Peter H. L. T. Bisschop,[11] Gerlof D. Valk,[12] Ronald Groote Veldman,[13] Robin P. F. Dullaart,[1] Thera P. Links,[1] Magiel F. Voogd,[14] Götz J. K. G. Wietasch,[14] and Michiel N. Kerstens,[1] for the PRESCRIPT Investigators

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J Clin Endocrinol Metab, July 2020, 105(7):2381–2391

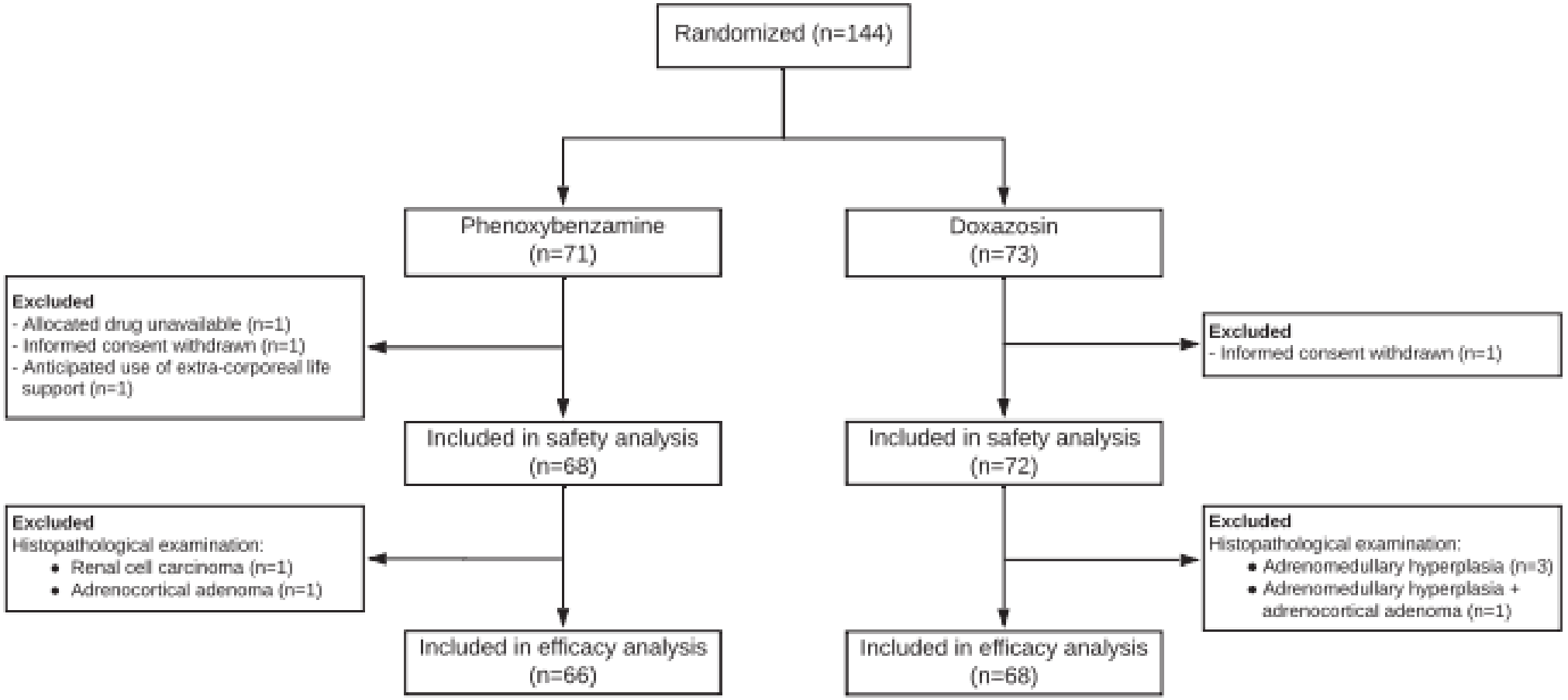

Figure 1. Flow-chart of the trial procedure.
Abbreviations: BP, blood pressure; HR, heart rate; ER, extended-release; i.v., intravenous.

J Clin Endocrinol Metab, July 2020, 105(7):2381–2391

Conclusion

- 134 patients with non-metastatic PPGL
- There was no difference in the duration of blood pressure outside the target range during surgery
- Phenoxybenzamine was more effective in preventing intraoperative hemodynamic instability, but could not be established whether this was associated with a better clinical outcome

Overview

- Work-up
- Perioperative management
- Surgical interventions

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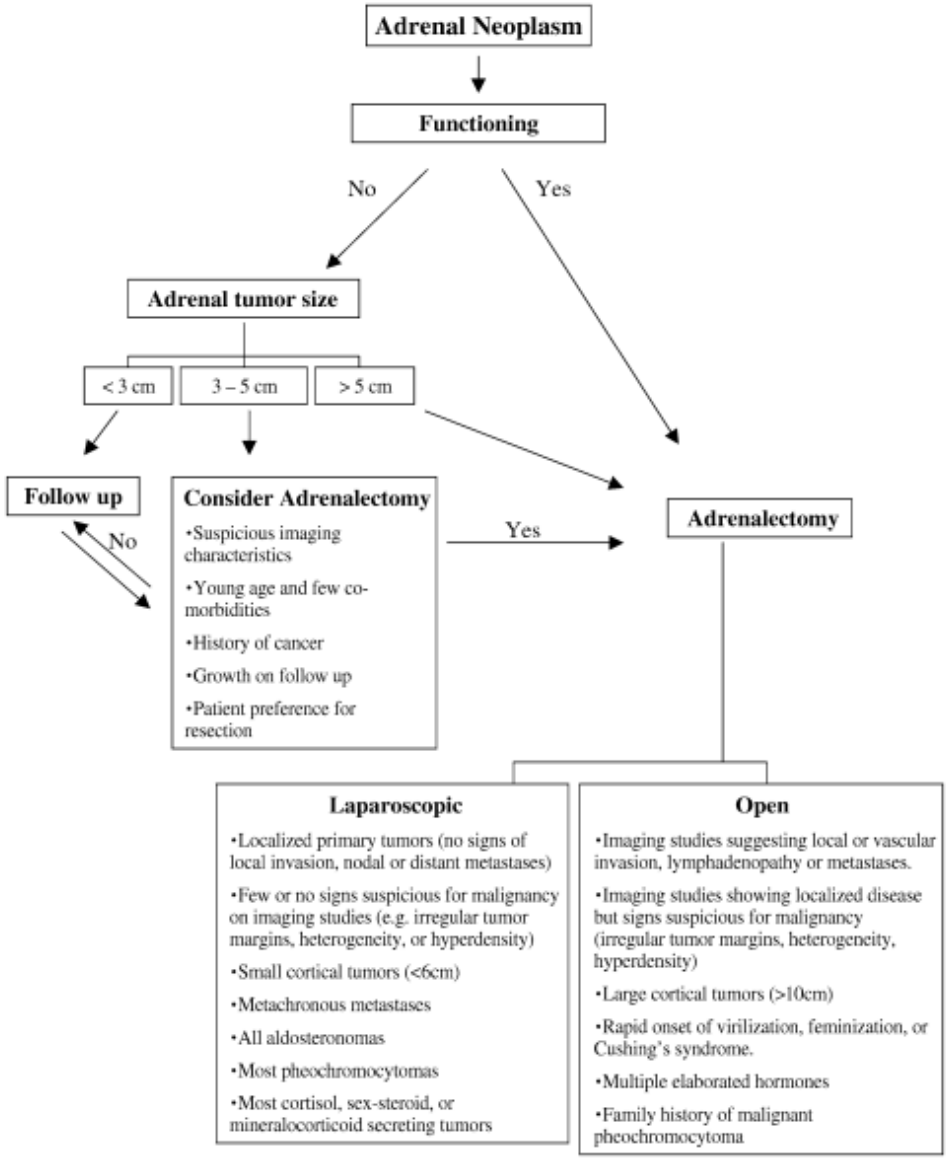
Surgical Intervention

- Open
- Minimally invasive

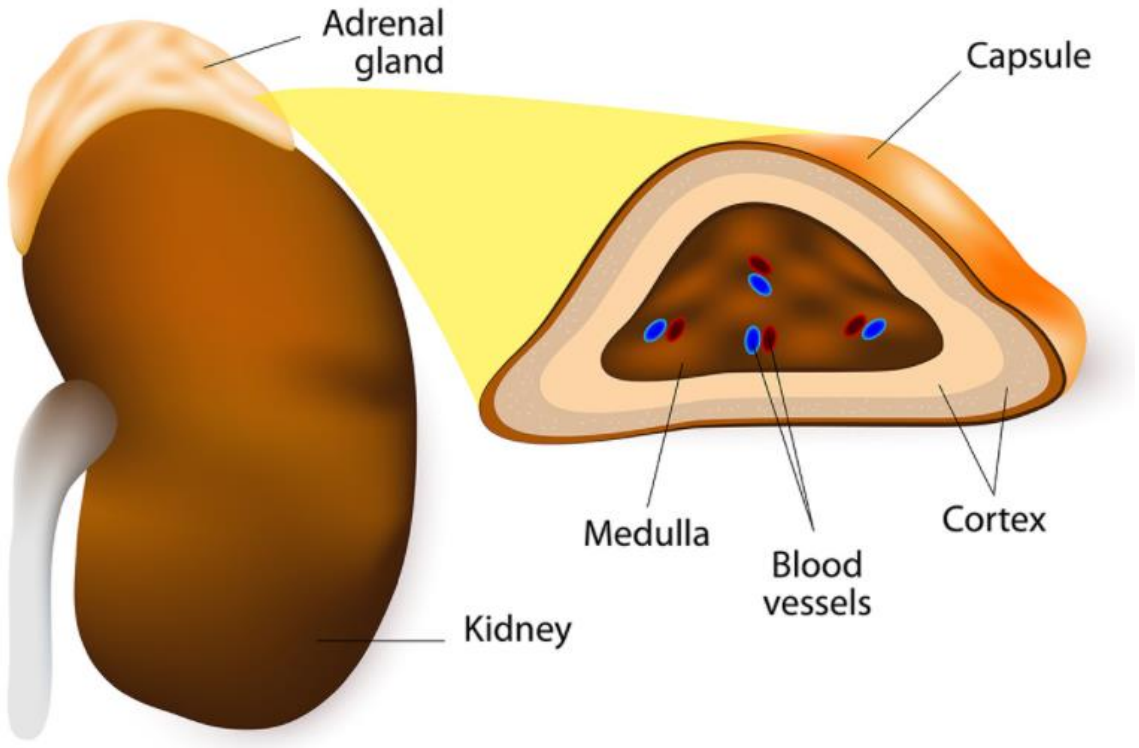


C. Sturgeon, E. Kebebew / Surg Clin N Am 84 (2004) 755–774

Fig. 1. Algorithm for the surgical management of adrenal neoplasms.

Surgical Intervention in Patients with Hereditary PPGL

- Higher incidence of bilateral disease in hereditary PPGL
- Consider partial (cortical-sparing) adrenalectomy



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Surgical Intervention in Patients with Hereditary PPGL

Original Investigation | Diabetes and Endocrinology

Comparison of Pheochromocytoma-Specific Morbidity and Mortality Among Adults With Bilateral Pheochromocytomas Undergoing Total Adrenalectomy vs Cortical-Sparing Adrenalectomy

Hartmut P. H. Neumann, MD; Uliana Tsoy, PhD; Irina Bancos, MD; Vincent Amodru, MD; Martin K. Walz, MD; Amit Tirosh, MD; Ravinder Jeet Kaur, MBBS; Travis McKenzie, MD; Xiaoping Qi, MD; Tushar Bandgar, MD; Roman Petrov, MD; Marina Y. Yukina, PhD; Anna Roslyakova, MD; Anouk N. A. van der Horst-Schrivers, MD, PhD; Annika M. A. Berends, MD; Ana O. Hoff, MD; Luciana Audi Castroneves, MD; Alfonso Massimiliano Ferrara, MD, PhD; Silvia Rizzati, MD; Caterina Mian, MD; Sarka Dvorakova, MD, PhD; Kornelia Hasse-Lazar, MD; Andrey Kvachenyuk, MD; Mariola Peczkowska, MD; Paola Loli, MD; Feyza Erenler, MD; Tobias Krauss, MD; Madson Q. Almeida, MD, PhD; Longfei Liu, MD; Feizhou Zhu, PhD; Mònica Recasens, MD; Nelson Wohllk, MD; Eleonora P. M. Corssmit, MD; Zulfiya Shafigullina, MD; Jan Calissendorff, MD, PhD; Simona Grozinsky-Glasberg, MD; Tada Kunavisarut, MD; Camilla Schalin-Jäntti, MD; Frederic Castinetti, MD, PhD; Petr Vlček, MD, PhD; Dmitry Beltsevich, MD, PhD; Viacheslav I. Egorov, MD, PhD; Francesca Schiavi, PhD; Thera P. Links, MD, PhD; Ronald M. Lechan, MD, PhD; Birke Bausch, MD; William F. Young Jr, MD, MSc; Charis Eng, MD, PhD; for the International Bilateral-Pheochromocytoma-Registry Group

JAMA Network Open. 2019;2(8):e198898. doi:10.1001/jamanetworkopen.2019.8898

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Surgical Intervention in Patients with Hereditary PPGL

- Multi-center cohort study to assess long-term outcomes of patients with bilateral pheochromocytomas treated with either total vs partial adrenalectomy (1950-2018)
- In 505 of 526 tested patients, 282 (54%) had RET, 184 (35%) had VHL, and 39 (7%) had mutation in other genes
- Of 849 adrenalectomies performed in 625 patients, 324 (52%) were planned as partial adrenalectomy, and successful in 248 of 324 patients (76.5%)
- Primary adrenal insufficiency developed in 23.5% of patients who underwent partial adrenalectomy
- 33 patients (13%) treated with partial adrenalectomy developed another pheochromocytoma after a median of 8 (4-13) years

Surgical Intervention in Patients with Hereditary PPGL

- MEN2
  - Concomitant bilateral disease in 30% of cases
  - 50% develop disease in contralateral adrenal gland within 10 years
  - Higher incidence of paroxysmal attacks, HTN, and cardiovascular problems
  - If bilateral pheo >2 cm, consider bilateral complete total adrenalectomy

Surgical Intervention in Patients with Hereditary PPGL

- VHL
  - Less diffuse medullary involvement
  - Consider partial adrenalectomy when feasible
  - VHL type 2A has a higher chance of malignant pheo, therefore, partial adrenalectomy should be avoided

Open Surgery

- Major abdominal surgery
  - Trans-abdominal approach
  - Extra-peritoneal approach

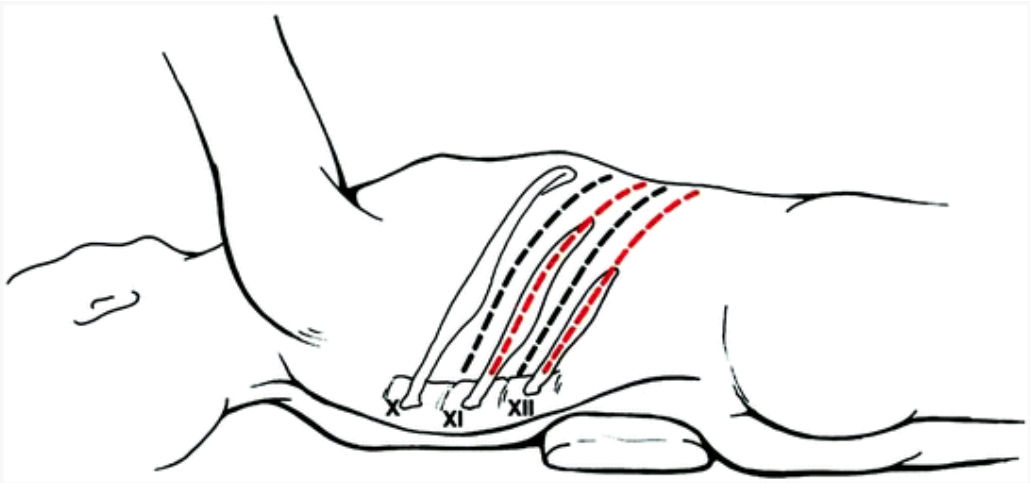


Fig. 12.13
Lateral extraperitoneal adrenalectomy with incision performed in the tenth or 11th intercostal space or on the body of the 11th or 12th rib, with or without costal resection

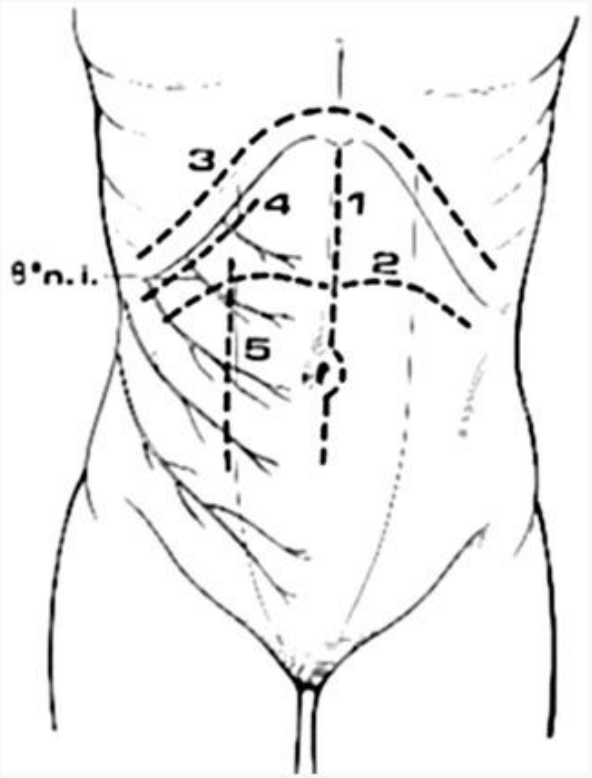


Fig. 12.2
Transabdominal open adrenalectomy: options for skin incision

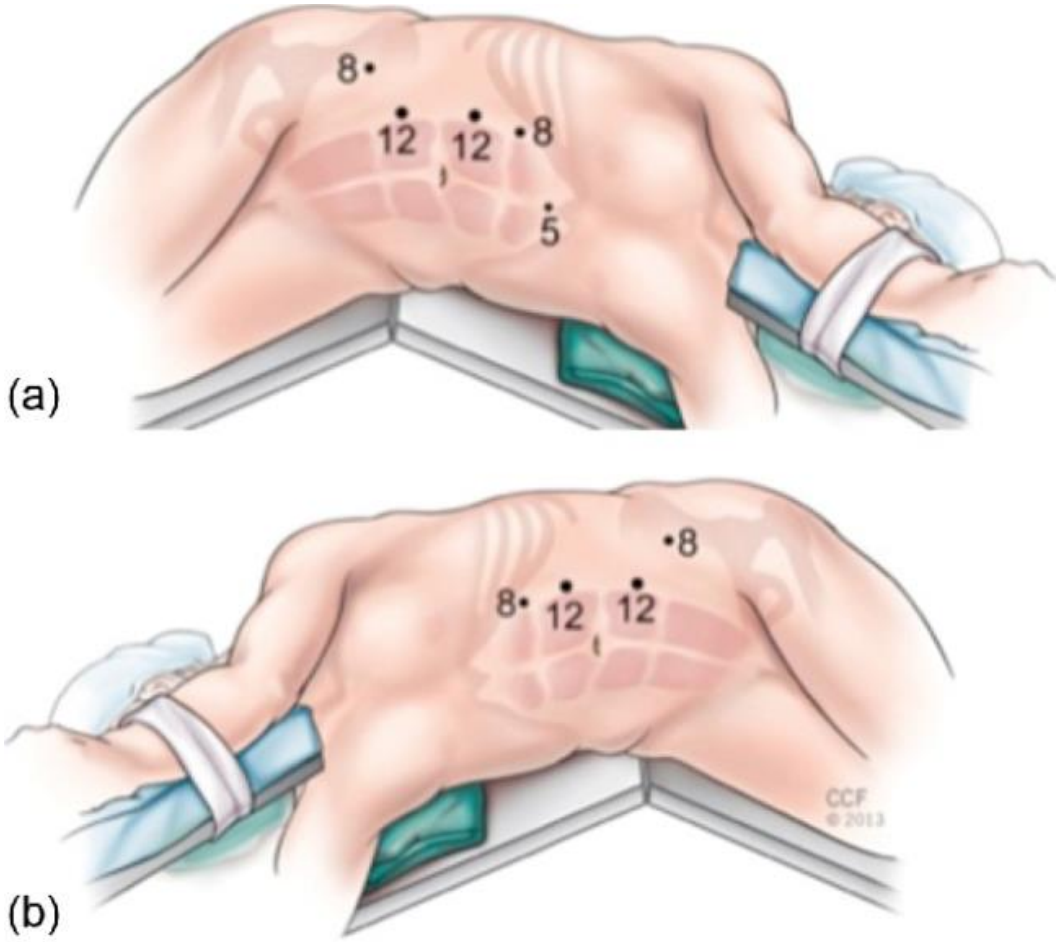
De Toma G., Polistena A., Cavallaro G. (2013) Open Adrenalectomy. In: Valeri A., Bergamini C., Bellantone R., Lombardi C. (eds) Surgery of the Adrenal Gland. Springer, Milano. https://doi.org/10.1007/978-88-470-2586-8_12

Minimally Invasive Surgery

- Trans-abdominal adrenalectomy
  - Laparoscopic
  - Robotic
- Posterior retroperitoneoscopic adrenalectomy (PRA)

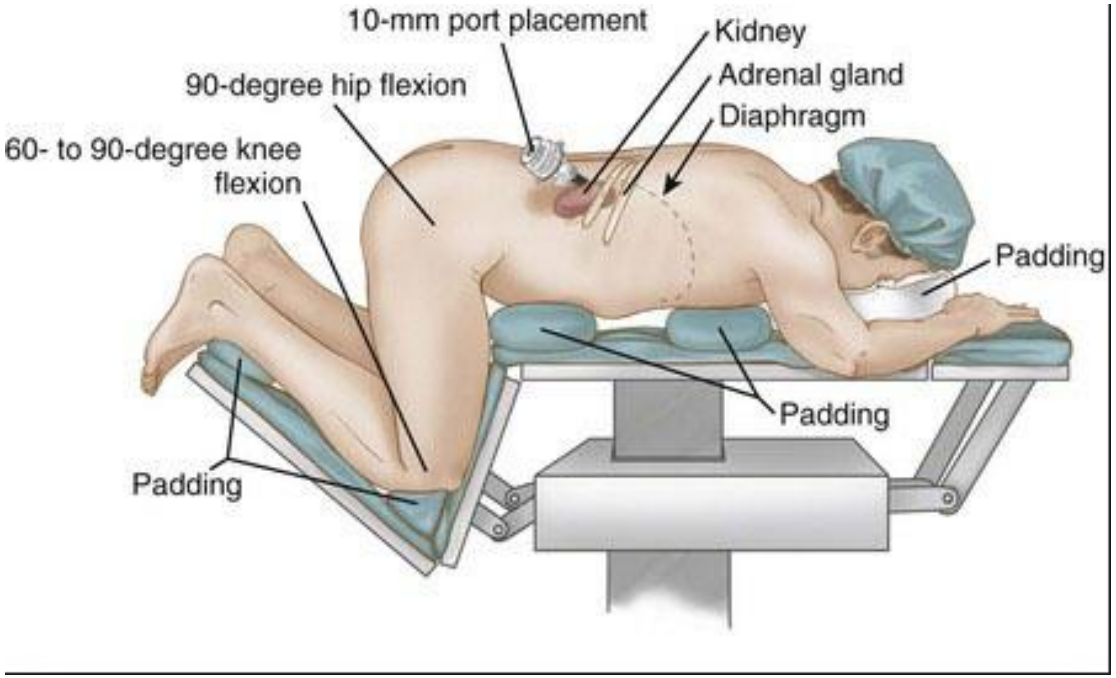
Trans-abdominal

- Less blood loss
- Faster recovery



PRA

- Less surgery time
- Less blood loss
- Less scarring
- Faster recovery
- Good for someone who had multiple previous abdominal surgeries



Open vs Minimally Invasive Surgery

- Minimally invasive adrenalectomy is recommended for most pheochromocytomas
- Open resection is recommended for a large (>6 cm) or invasive pheochromocytoma
- Open resection is recommended for paragangliomas, but minimally invasive surgery can be considered for small, non-invasive paraganglioma in surgically favorable locations

Summary

- Biochemical testing
- Genetic testing
- Multi-disciplinary evaluation and care
- Surveillance

Thank you!!

CEU code 6441

- Questions?

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