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Case Report

Adrenal Neuroblastoma in Adults: A Comprehensive Systematic Review of Diagnosis, Management, and Prognosis of a Rare Malignancy

Danial A. Malik[1], Priya J. Hill[1], Gina Genova[2], Rohit Kulkarni[3], Daniel D. Mais[4], Mahsa Javid[1*]

[1]Division of Surgical Oncology, Department of Surgery, School of Medicine, University of Louisville, Louisville, Kentucky, USA

[2]Kornhauser Health Science Library, University of Louisville, Louisville, Kentucky, USA

[3]Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes, School of Medicine, University of Louisville, Louisville, Kentucky, USA

[4]Department of Pathology & Laboratory Medicine, School of Medicine, University of Louisville, Louisville, Kentucky, USA

***Corresponding author**: Mahsa Javid, University of Louisville School of Medicine, Department of Surgery, Division of Surgical Oncology, Louisville, Kentucky, USA

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Abstract

Introduction: Adrenal neuroblastoma in adults is rare, presenting diagnostic and therapeutic challenges. This study combines a systematic review of 127 previous reports and a detailed presentation of a high-risk adult patient to explore key outcomes and treatment strategies.

Methods: A systematic review was conducted using PRISMA guidelines, analysing diagnostic tools, therapeutic approaches, and outcomes in adult neuroblastoma. A case involving a patient aged >18 years with a large adrenal neuroblastoma was examined, including patient demographics, preoperative diagnostic imaging, neoadjuvant therapies, surgical resection, pathological findings, and overall survival.

Results: The systematic review revealed a slightly increased prevalence of adrenal neuroblastoma in adult men and initial tumor size of >10 cm at presentation in most cases. Elevated catecholamine levels were present in 71% of patients. Complete surgical resection and neoadjuvant and adjuvant therapies improved survival. Preferred adjuvant treatments were platinum-based chemotherapy and, less frequently, radiotherapy or immunotherapy. In the presented case, preoperative chemotherapy reduced tumor size by 75%, enabling resection. Pathology confirmed treated neuroblastoma with 20% therapy-induced maturation and no distant metastases. Outcomes indicated a 5-year overall survival rate of 38% for high-risk neuroblastoma.

Conclusion: This study underscores the importance of multidisciplinary care in managing adult neuroblastoma, including neoadjuvant chemotherapy, surgery, and potential adjuvant therapies. The systematic review and case report highlight the need for standardized treatment protocols and long-term follow-up to improve survival in this aggressive malignancy. Combining clinical insights with literature analysis advances understanding and care strategies for adult-onset adrenal neuroblastoma.

Keywords: Adrenal Malignancy; Neuroendocrine Tumor; Adolescents; Retroperitoneal Mass; Rare Cancer; Frozen Section.

Introduction

Neuroblastoma is a primarily pediatric cancer, with an annual incidence of approximately 600 to 800 cases diagnosed in children in the United States [1-3]. The average age at diagnosis ranges from 1 to 2 years, with a median age of 18 months. Notably, about one-third of cases are identified before the child's first birthday, and approximately 90% are diagnosed by the time they reach five years of age [4]. The occurrence of neuroblastoma in individuals over the age of ten is exceedingly rare, with roughly 151 reported cases worldwide among adolescents and adults. This rarity is further complicated by the absence of standardized treatment protocols for this demographic, leading to significantly poorer outcomes compared to pediatric patients [5-7]. While the 5-year overall survival rate for children with neuroblastoma is around 90%, it falls dramatically to approximately 38% for individuals diagnosed after adolescence [8-12].

When neuroblastoma does occur in adults, it primarily affects individuals aged 18-60 years, most frequently arising in the central nervous system (39%) and the retroperitoneum (17%), reflecting its association with neural crest-derived tissues along the sympathetic axis [3]. Clinical presentations often include nonspecific symptoms such as abdominal masses and localized pain, which result from tumor growth and the compression of surrounding structures. As the disease progresses, complications related to metastatic spread may emerge, including spinal cord compression and hypertension due to catecholamine overproduction [13]. The diverse and often subtle nature of these symptoms can complicate the diagnostic process, necessitating careful evaluation to distinguish neuroblastoma from other adult malignancies. In this report, we present a case of adrenal neuroblastoma in a young adult, emphasizing the diagnostic complexities and the effective multidisciplinary management involved, along with a systematic review of the literature on adrenal neuroblastoma cases in the adult population.

Methods

PubMed, Cochrane CENTRAL, EMBASE, and clinicaltrials.gov were searched for English-language reports of adult adrenal neuroblastomas. Databases were searched from inception through September 20, 2024, with subject headings and keywords.

Reports were eligible if they included a patient aged eighteen years or older with neuroblastoma or ganglioneuroblastoma involving the adrenal gland. Papers that included mixed pediatric and adult patients, multiple locations of neuroblastoma, and so on were considered if the data for adult adrenal neuroblastoma cases were reported separately and could be extracted. Gray literature was considered in addition to peer-reviewed literature. Reviews of previously reported cases were excluded.

Screening of titles and abstracts was done in duplicates with conflicts resolved by a third reviewer. Screening of full texts was done in duplicate with conflicts resolved by consensus. Data extraction was done in duplicate/by one author with discrepancies resolved by consensus/extractions checked by two additional authors. Covidence was used to manage citations and screening.

The database search produced 1,213 results, of which 921 were unique citations. After screening, 127 citations that reported one or more cases of adrenal neuroblastoma in adult patients were included (Figure 1).

Case Presentation

A 19-year-old male was referred to our tertiary healthcare facility due to an acute onset of right flank pain, which was accompanied by nausea, anorexia, back pain, and tenderness in the right upper quadrant of the abdomen. The case had initially been evaluated at an external institution, where a preliminary differential diagnosis of adrenocortical carcinoma (ACC) was proposed.

Upon presentation, the patient exhibited mild tachycardia, though blood pressure remained within normal limits. Physical examination revealed no additional abnormalities. His medical history was significant for anxiety, depression, and attention deficit hyperactivity disorder (ADHD), which were managed with Alprazolam, Desvenlafaxine, Lisdexamfetamine, and Loratadine/Pseudoephedrine. Importantly, the patient's family history did not indicate any hereditary endocrine neoplasms, including pituitary, thyroid, or adrenal tumors. Initial biochemical evaluations indicated slight elevations in plasma-free normetanephrines (1.55 nmol/L; reference range: 0-0.84) and urine normetanephrines (674 µg/day; reference range: 81-667). Levels of Chromogranin A were notably elevated at 170 ng/mL (reference range: 0-103).

Furthermore, mild hypercalcemia was recorded (10.8 and 10.4 nmol/dL; reference range: 8.4-10.2), accompanied by low-normal PTH. Other endocrine markers, including plasma and urine metanephrines as well as aldosterone, renin, and androgen levels, were within the reference ranges. Random cortisol levels were mildly elevated at 19.8 µg/dL (reference range: 2.9-17.3), and a low-dose dexamethasone suppression test yielded normal results. Additional details regarding the patient's pre-operative hormonal profile can be found in Table 1.

Genomic analysis identified a pathogenic variant in the CDKN2A gene, a finding associated with tumorigenesis and endocrine malignancies. A comprehensive summary of pre-operative genetic findings is presented in Table 2. Based on the integration of clinical, biochemical, and genomic data, the differential diagnosis included ACC with possible underlying familial endocrine syndromes.

Other considerations included malignant pheochromocytoma, adrenal metastasis, and lymphoma.

The patient underwent imaging and diagnostic evaluations, revealing a large, heterogeneous mass measuring 12.3 × 9.9 × 7.8 cm in Morrison's pouch on ultrasound. The mass was inseparable from the superior pole of the right kidney and the liver. A subsequent abdominal CT scan showed a 10 cm calcified lesion originating from the right adrenal gland, which was adherent to the liver, inferior vena cava (IVC), and diaphragm, along with bulky retroperitoneal lymphadenopathy. Additionally, there was an 8 cm conglomerate of lymph nodes encasing both right renal arteries and the left renal vein (Figure 2A-B).

MRI confirmed that the lesion originated from the adrenal gland and did not definitively exclude liver invasion. The retroperitoneal lymphadenopathy was noted, with nodes measuring up to 3 cm located in the retrocaval region behind the IVC and between the IVC and aorta. A whole-body 18-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/CT scan revealed intense focal uptake of FDG, with a maximum standardized uptake value (SUVmax) exceeding 25, which strongly suggested malignancy. Notably, the PET/CT scan also ruled out distant metastases. Collectively, these imaging findings indicated a malignant process originating from the adrenal gland, with significant retroperitoneal involvement but no evidence of distant disease, thereby informing multidisciplinary treatment planning (Figure 2C-D).

A preoperative biopsy of the adrenal mass was not conducted due to concerns about procedural risks and diagnostic limitations. Adrenal biopsies frequently cannot reliably differentiate between benign and malignant lesions and carry significant risks, particularly in cases of pheochromocytoma, where complications may arise, or in ACC, which poses a risk of neoplastic seeding. The differential diagnosis included pheochromocytoma, lymphoma, and ACC, alongside complex retroperitoneal anatomy and bulky lymphadenopathy encasing vital structures, complicating a safe biopsy approach. Given that a definitive diagnosis could not be established before surgery, the Endocrine Tumor Board recommended performing an intraoperative frozen section of the lymph nodes to rule out lymphoma or other conditions that might not necessitate resection.

The proposed surgical plan included open resection of the right adrenal mass, right nephrectomy, potential vena caval reconstruction, and, if necessary, left kidney resection with auto-transplantation. The goal was to achieve complete resection of all gross disease, including liver resection and lymph node excision, contingent on intraoperative findings. At surgery (Figure 3), the large right adrenal mass was found to be densely adherent to the liver and matted lymph nodes were identified in the retrocaval, paraaortic, and pararenal areas, the latter encasing both right renal arteries.

Retroperitoneal lymph nodes were biopsied and sent for intraoperative frozen section analysis the results of which indicated a diagnosis of neuroblastoma. Based on this finding, and after consultation with pediatric oncology and pediatric surgery, an adrenal biopsy was performed for comparison with the nodal pathology, and the initial plan for surgical resection was aborted to pursue the optimal treatment for neuroblastoma of neoadjuvant chemotherapy. Systemic therapy would be further managed by pediatric oncology.

During intraoperative frozen section analysis, the presence of Homer-Wright rosettes, a classical histopathological hallmark, provided a strong indication of neuroblastoma. These rosettes are characterized by clusters of poorly differentiated neuroblasts arranged around a central neuropil, reflecting the tumor's neuroectodermal origin. While other small round blue cell tumors such as Ewing sarcoma, rhabdomyosarcoma, or lymphoma could be considered in the differential diagnosis, the identification of these rosettes, along with immunohistochemical markers (e.g., CD56, synaptophysin, and chromogranin A), narrowed the diagnosis to neuroblastoma (Figure 4).

Final pathology confirmed the diagnosis of poorly differentiated, high-risk neuroblastoma in both lymph nodes while the biopsy of the adrenal gland showed significant differentiation (less than 50%) and suggested the possibility of underlying nodular ganglioneuroblastoma. The tumor exhibited an intermediate mitotic-karyorrhectic index (2%-4%). Classified as unfavourable under the International Neuroblastoma Pathology Classification (age >5 years). This intraoperative decision exemplified the critical role of real-time pathology in guiding surgical and therapeutic strategies, ensuring the patient's safety while enabling appropriate oncological management.

Postoperative evaluation included repeat PET and MIBG scans, which demonstrated no evidence of distant or bony metastases. Bilateral bone marrow aspiration and biopsies were also negative for malignant involvement. These findings confirmed that the disease was localized, albeit high-risk due to the tumor's size and poorly differentiated histology.

Following multidisciplinary discussions with the Pediatric Endocrine Tumor Board, a decision was made to pursue stem cell harvest followed by neoadjuvant chemotherapy. The selected regimen included five cycles of doxorubicin, cyclophosphamide, etoposide, and anthracycline. This approach aimed to achieve significant tumor shrinkage, reduce vascular and lymphatic encasement, and enhance the feasibility and safety of a subsequent complete surgical resection without need for nephrectomy or

resection of other surrounding structures.

This treatment strategy underscores the importance of a tailored, multidisciplinary approach in managing rare, high-risk malignancies such as adult-onset neuroblastoma, integrating pediatric oncology expertise to optimize therapeutic outcomes.

The patient showed a strong clinical response after a multidisciplinary approach involving neoadjuvant chemotherapy, right adrenalectomy, and postoperative care. Initially, the patient had a large, high-risk neuroblastoma affecting the adrenal gland and regional lymph nodes. Imaging after chemotherapy showed a 75% decrease in tumor size, with complete resolution of retroperitoneal lymphadenopathy and vascular encasement, highlighting treatment efficacy. At surgery, complete resection of the residual tumor was achieved, crucial for improving outcomes in high-risk neuroblastoma. Final pathology confirmed adrenal neuroblastoma (6 x 3.8 x 5.5 cm) with a 75% treatment effect and 20% maturation. No regional nodes or distant metastases were identified. The positive response to therapy and absence of distant metastases on scans suggest an improved prognosis. Nonetheless, the poorly differentiated histology and high-risk classification still significantly affect long-term survival (Figure 6).

Results

The database searches produced 1,213 results, of which 921 were unique citations. After screening, 127 citations that reported one or more cases of adrenal neuroblastoma in adult patients were included (Figure 1).

This table summarizes key demographic, clinical, diagnostic, and pathological characteristics of adult adrenal neuroblastoma cases from the literature (Table 2). It includes patient age, sex, tumor size, laterality, imaging modalities (e.g., CT, MRI, PET), secreted hormones, abnormal laboratory findings, and preoperative biopsy status. Diagnosis methods, differential diagnoses, tumor composition, neoadjuvant chemotherapy, pathology, immunohistochemical markers (e.g., CD56, synaptophysin), adjuvant therapies, long-term follow-up outcomes, and additional observations are also detailed. This comprehensive overview underscores the importance of a multidisciplinary approach to managing this rare malignancy.

Adrenal neuroblastoma in adults is an exceptionally rare malignancy, diverging significantly in presentation, prognosis, and treatment from its pediatric counterpart. This systematic review synthesizes data from reported cases to delineate key trends and knowledge, providing a foundation for future diagnostic and therapeutic strategies.

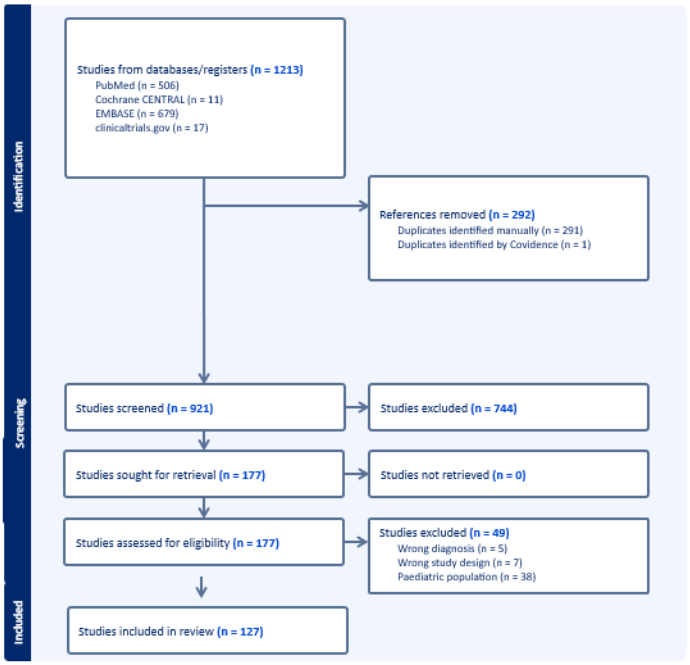

Figure 1: PRISMA flow diagram. Illustrating the systematic review process for adult adrenal neuroblastoma studies. A total of 1,213 records were identified through database searches, including PubMed (n = 506), EMBASE (n = 679), Cochrane CENTRAL (n = 11), and ClinicalTrials.gov (n = 17). After the removal of 292 duplicates, 921 studies were screened for relevance. Of these, 49 studies were excluded due to wrong diagnosis (n = 4), wrong study design (n = 7), or inclusion of pediatric populations (n = 38). Following the eligibility assessment of 177 studies, 128 were included in the final review, providing a comprehensive analysis of adult-onset adrenal neuroblastoma.

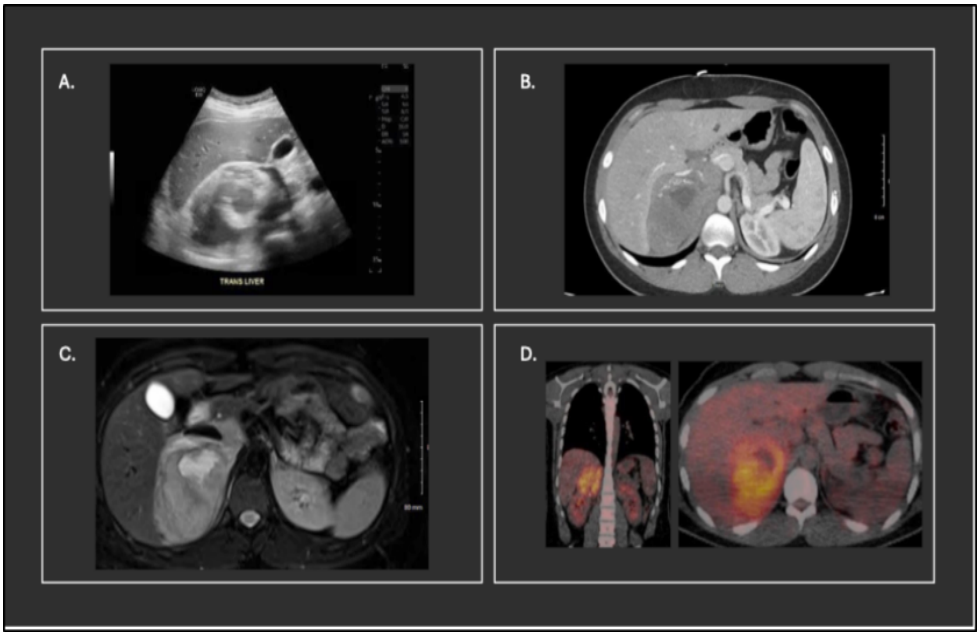

Figure 2: Multimodal Imaging of Adrenal Lesion. (A) Ultrasound: 12.3 x 9.9 x 7.8 cm heterogeneous mass in Morrison's pouch, inseparable from the right kidney and liver. (B) CT: 10 cm calcified adrenal mass adherent to the liver, IVC, diaphragm, with bulky retroperitoneal lymphadenopathy. (C) MRI: Hyperintense adrenal mass on T2-weighted imaging with regional lymphadenopathy. (D) FDG PET: Partially necrotic, FDG-avid adrenal mass with retroperitoneal lymph node involvement; no distant disease. This imaging highlights tumor size, spread, and metabolic activity for clinical management.

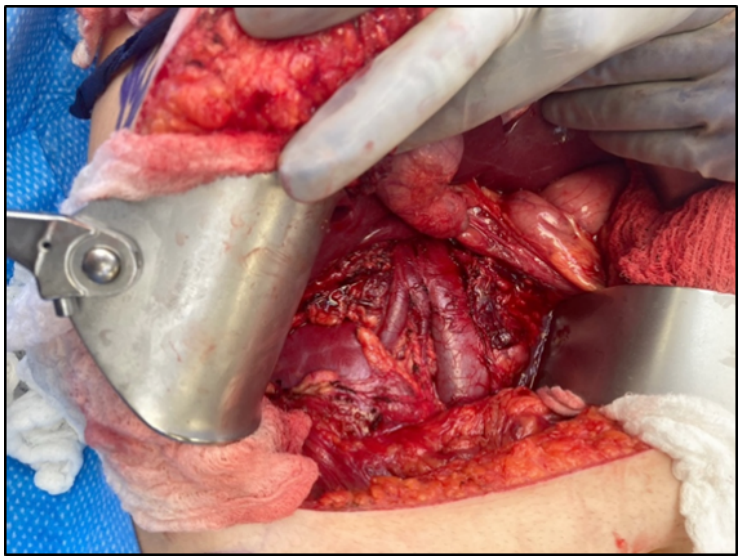

Figure 3: Intraoperative View. Right adrenal mass in the retroperitoneum, adherent to the liver, IVC, and diaphragm, with paracaval nodes encasing right renal vessels. Highlights complex anatomy and need for meticulous surgical planning in high-risk adrenal neuroblastoma resection.

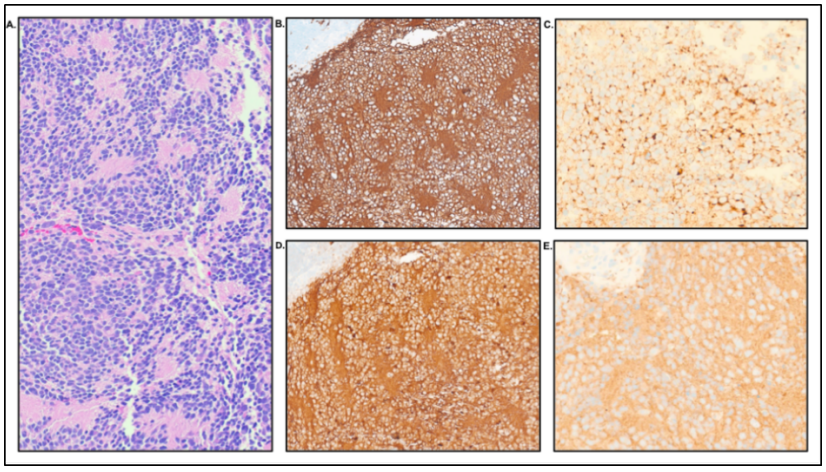

Figure 4: Histopathological and Immunohistochemical Findings. (A) H&E staining shows poorly differentiated neuroblasts with scant cytoplasm and high nuclear-to-cytoplasmic ratio. (B) CD56 staining demonstrates strong membranous positivity, confirming neuroendocrine origin. (C) Chromogranin A shows robust cytoplasmic expression, supporting neuroendocrine lineage. (D) NSE staining reveals diffuse cytoplasmic positivity, confirming neuroendocrine differentiation. (E) Synaptophysin staining highlights sympathetic ganglia-derived neuroblasts with diffuse positivity. These findings confirm high-risk neuroblastoma with neuroendocrine differentiation.

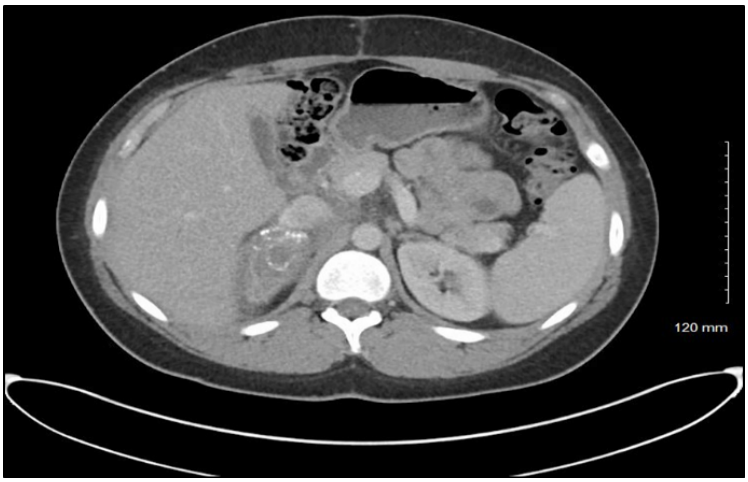

Figure 5: P Post-Chemotherapy CT Imaging. Contrast-enhanced CT shows the right adrenal mass reduced to 6 x 3.8 x 5.5 cm. Retroperitoneal lymphadenopathy and vascular encasement have resolved, demonstrating a favourable response to neoadjuvant chemotherapy and improved surgical feasibility.

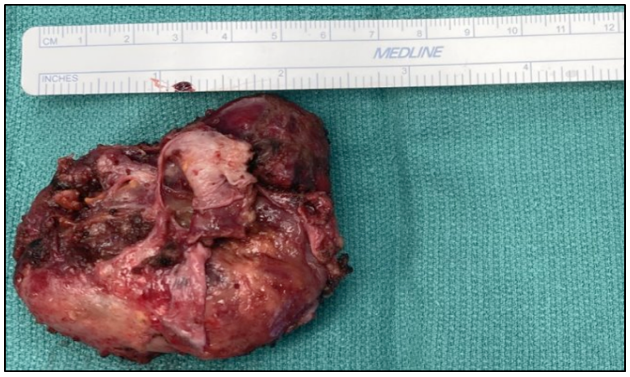

Figure 6: Gross Specimen of Resected Adrenal Mass. Post-resection specimen measuring 6 x 3.8 x 5.5 cm after neoadjuvant chemotherapy. The irregular, encapsulated mass shows necrosis and hemorrhage, reflecting significant tumor reduction and the efficacy of preoperative treatment. Surgical ruler included for scale.

Laboratory Test	Results	Value	Range
Total Testosterone	Normal	313.5	300-1000 ng/dL
Cortisol	High	19.8	2.9-17.3 ug/dL
Aldosterone	Normal	9.7	0-30 ng/dL
ACTH	Normal	52.2	7.2-63.3 pg/mL
DHEA-S	Normal	273	88-483 ug/dL
Chromogranin A	**High**	**170**	0-103 ng/mL
Dopamine	Mildly elevated	26	0-30 pg/mL
Plasma metanephrines & **normetanephrines**	Normal **High 2x**	0.13 **1.55**	0-0.49 nmol/L 0-0.89 nmon/L
Urine metanephrines & **normetanephrines**	Normal **Mildly elevated**	62 **674**	55-320 ug/d 81-667 ug/d
Renin	Normal	7.7	0.2-1.6 ng/mL/hr
Potassium	Normal	4.2	3.5-5.1 mmol/L
Calcium Corrected Calcium	Mildly elevated	10.8 10.4	8.4-10.2 mg/dL
PTH	Normal	33.9	1—55 pg/mL
Low Dose Dexamethasone suppression	Normal	<1.0	<1.8 ug/dL

Table 1: Laboratory test results of our patient with adrenal neuroblastoma. This table summarizes the biochemical and hormonal profile of our patient on admission. Key findings include elevated chromogranin A (170 ng/mL), plasma normetanephrines (1.55 nmol/L), and urine normetanephrines (674 µg/day), indicative of catecholamine hypersecretion and neuroendocrine tumor activity. Mild hypercortisolism (19.8 µg/dL) and hypercalcemia (10.8 mg/dL) suggest paraneoplastic or tumor-related effects. All results are compared against clinical reference ranges, highlighting abnormalities highlighting the index of suspicion for diagnosing this rare malignancy in adults.

Author (Year)	Age (yrs)	Sex	Tumor Size (cm)	Side	Diagnostic Imaging	Tumor Secreted Hormones	Abnormal Labs	Preoperative Biopsy	Diagnosis Methodology (Ultimate Method)	Potential Differential Diagnosis	Composite Tumor	Neoadjuvant Therapy	Pathology	IHC Staining	Adjuvant Therapy	Long Term Follow Up
Abramowsky (2009) [15]	21	F	NR	NR	NR	NR	NR	Yes	Pathology	NR	NR	No	Neuroblastoma	NSE (+), Synaptophysin (+), Flt-1 (+)	Chemotherapy, high dose therapy (HDT) , Radiation therapy, cis-RA	Alive;25 months w/ no evidence of disease
Aguirre (1982) [16]	18	NR	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Amodeo (1989) [17]	41	F	14	Left	NR	Norepinephrine (12.9 µg/g of tissue; normal: 3.14 µg/g of tissue)	Blood pressure was 140/100 mm Hg with a pulse rate of 100 beats per minute. 24-hour urinary catecholamine excretion was elevated. 1st admission (Pheo): VMA (20.6 mg; normal: < 10 mg), NE (305.2 µg; normal: < 80), E (44.7 µg; normal: < 25 µg), HVA (4.6 mg; normal: < 8.5 mg). 2ndadmission (NB): VMA (46.9 mg), NE (102.4 µg), E (8.1 µg), HVA (42.6 mg).	No	Urinalysis	Pheochromocytoma	NR	No	Neuroblastoma	NR	NR	Patient deceased 4 months after 3rd admission (lung mets)
Attal (1973) [19]	25	M	NR	Left	NR	NR	Serum calcium: 10.516 mg (normal 8.5 - 10.5 mg/dL), serum phosphorus: 2.5 - 3.5 mg (normal 2.54.5 mg/dL), blood urea: 35 mg (624 mg/dL),	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	NR
Batra (2010) [20]	20	M	NR	Right	Head CT scan (Motor vehicle accident), Abdominal CT scan, MRI (spine)	NR	Hemoglobin of 9.5 g/dL; a total white count of 5.95 k/uL with 63% neutrophils; 28% lymphocytes; and a platelet count of 329 k/uL.HVA and VMA levels were elevated 31.6 mg/g creatinine (normal range 1.4 to 5.3) and 83.1 mg/g creatinine (normal range 1.1 to 4.1). Serum phosphorus level was slightly elevated at 5.6 mg/dL.	Yes	CT-guided biopsy of right adrenal mass and bone marrow	Pheochromocytoma, neuroblastoma, and ganglioneuroma	NR	1 cycle of chemotherapy topotecan, vincristine, and cyclophosphamide	Neuroblastoma	NR	NR	Patient was lost to follow up
Benedini (2017) [21]	20	F	11	Left	Abdominal ultrasound, CT scan	NR	NR	No	CT Scan	NR	NR	No	Ganglioneuroblastoma	NR	NR	Disease recurrence occurred in the 21-month follow-up from surgery.
Bolzacchini (2015) [22]	63	M	5	Left	CT scan (renal stones), MRI	NR	NR	No	MRI	NR	NR	No	Ganglioneuroblastoma	The neoplastic cells were partially immunoreactive for synaptophysin and neurofilament, while they were negative for S100, Melanin A, CD99, CD31, CD34, podoplanin, cytokeratin AE1/AE3, alpha-inhibin, and actin.	NR	The patient will continue follow-up schedule every 3 months.
Brondani (2017) [23]	18-82*	NR	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Candanedo-González (2001) [24]	56	F	6	Right	Abdominal Ultrasound and CT scan	NR	Blood pressure: 140/90 mmHg.Serum glucose: 136 mg/dL; renin: 1.8 ng/mL (normal, 1.5–5.7 ng/mL),catecholamines: 155 mcg/24 h (normal, 15–100 mcg/24 h) and urinary vanillymandelic acid (VMA): 14.9 mg/24h (normal, 0.5–12 mg/24 h)	No	Abdominal ultrasound and CT scan	NR	Pheochromocytoma	No	Pheochromocytoma-neuroblastoma	Pheochromocytoma: chromogranin (+), Synaptophysin (+), Glucagon (+), and NSE(+). Neuroblastoma: Synaptophysin (+), Glucagon (-), and NSE(+)	NR	Patient is alive and asymptomatic 24 months after surgery
Çetin (2023) [25]	56	M	6.5	Right	Abdominal MRI, Abdominal CT, 18fluorodeoxyglucose Positron emission tomography/ CT scan	NR	NR	No	CT scan	NR	NR	No	Ganglioneuroblastoma	GNB-Intermixed (Schwannian stroma-rich)	NR	6 year follow up: no local recurrence of distant metastasis.
Cheah (1989) [28]	24	M	10	Left	Abdominal CT scan (axial), XRay of chest and Right femur	NR	Hemoglobin level of 9.8 g/dl (normal is 13.5 NR 17.5 g/dL), evidence of thrombocytopenia (89 X 10^9), raised Liver function tests showed serum enzyme levels (aspartate transaminase of 159 IU/L; alanine transaminase of 62 IU/l and alkaline phosphatase of 227 IU/l). The serum bilirubin was 12 mmol/l while the serum albumin was 37 g/l.	Yes	Hisopathology	NR	NR	Yes	Neuroblastoma	NR	NR	Died 4 months after initial diagnosis
Cho (2013) [30]	62	M	20	Right	Abdominal CT and MRI	NR	NR	No	Pathology	Hepatocellular carcinoma in right lobe of liver with questionable retroperitoneal invasion.	Neuroblastoma	No	Compositeparaganglioma with neuroblastoma	Cystic lesion - paraganglioma with CD56(+), synaptophysin(+) and Ki-67(+, 2–3%) on immunohistochemical stain. Solid component - CD56 (+), synaptophysin(-), Ki-67(+, 10–15%).	NR	NR
Cho (2018) [31]	62	M	20	Right	Abdominal CT, MRI	NR	NR	No	Pathology	NR	Paraganglioma with CD56 (+), synaptophysin(-), Ki-67(+, 10–15%)	No	Anaplastic neuroblastoma CD56 (+)	NR	NR	NR
Custodio (1999) [33]	32	F	17	Right	Ultrasound, CT scan, MRI of abdomen, MRA	NR	NR	No	MRI	NR	NR	No	Neuroblastoma	Positive for synaptophysin and neurofilament.	Chemotherapy followed by limited regional radiotherapy	Alive - 3 months post operation
Daoud (2019) [34]	20	F	NR	NR	NR	NR	Elevated neuron specific enolase (50,7ng/ml then 60 ng/ml after 2 weeks).	No	Autopsy	NR	NR	No	Neuroblastoma	NR	NR	NR
Deslarzes (2022) [35]	74	F	10	Left	Thoracoabdominal contrast enhanced CT scan	NR	Serum catecholamines showed elevated normetanephrine (9.72 nmol/l, Normal: 0.04–1.39) and methoxytyramine (0.62 nmol/l, Normal: <0.06)	Yes	CT-guided core needle biopsy	NR	NR	No	Nodular ganglioneuroblastoma	Positive for vimentine, racemase, and synaptophysin	NR	PET 6 weeks post op; did not show any signs of recurrence or metastases. Patient was followed up with annual clinical and radiolocial exams.
Deslarzes (2022) [36]	75	F	NR	Left	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	2.2 years - Dead
Dias (2011) [38]	27	M	NR	Left	CT Scan	NR	The patient's blood and urinary tests revealed high levels of catecholamines.	No	CT Scan	NR	NR	No	Neuroblastoma (retroperitoneal mass)	NR	NR	NR
Ding (2015) [39]	27	F	11.4	Left	Ultrasound, CT scan	NR	All routine examinations were normal except for white blood cell count 11.24 × 109/L. Neuronspecific enolase (NSE) was significantly higher (289.46 ng/mL, normal level <16.3 ng/mL).	No	CT scan	Pheochromocytoma, adrenal malignancy, or neurogenic tumor.	NR	No	Ganglioneuroblastoma	Positive for chromogranin, synaptophysin and neurofilaments	No (due to patient finances)	NR
Duarte (2021) [40]	27	M	NR	Left	Whole body (WB) NR CT Scan, 123MIBG	Catecholamine hypersecretion	Blood Pressure: 200/200 mmHG with resting heart rate of 140 bpm (sinus tachycardia with signs of left ventricular volume overload on EKG)	Yes	Whole Body CT scan	Metastatic pehochromocytoma and paraganglioma	NR	No	Neuroblastoma	NR	Palliative chemotherapy	Patient deceased3 years later (disease progression)
Elbuken (2010) [41]	29	M	4.5	NR	CT scan	NR	NR	No	CT scan	Non-functioningadenoma	NR	No	Ganglioneuroblastoma	NR	NR	NR
Findakly (2020) [42]	63	M	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	Chemotherapy	NR
Franks (1997) [44]	36	F	NR	NR	NR	NR	NR	No	Pathology	NR	NR	Cyclophosphamide and prednisone	Neuroblastoma	NR	Chemotherapy, Radiation therapy	2yrs from diagnosis - deceased
Franks (1997) [44]	18	M	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	Chemotherapy, Total body irradiation	3 yrs 5 months - deceased
Franquemont (1994) [45]	49	M	NR	Left	NR	NR	NR	No	Pathology	NR	Pheochromocytoma	No	Pheochromocytoma - neuroblastoma	NB- chromogranin, synaptophysin, MAP2 and J1 ; PHEO - chromogranin, synaptophysin, and J1	Radiation	Alive; 1 year w/ no evidence of disease
Fujiwara (2000) [46]	25	F	9	Left	Abdominal CT scan	Dopamine	The concentrations of most of the catecholamines and their metabolites were elevated in the plasma and 24NRhour urine specimen. Plasma dopamine 1,101 pg/ml (normal: < 20 pg/ml), urine dopamine 3,999 µg/day (normal: 190 to 740). HVA was 65.7 mg/day (normal: 1.5 to 6.6). Plasma noradrenaline 4620 pg/ml (normal: 100 to 450). Urine adrenaline 46.9 µg/day (normal: 3 to 15), Urine noradrenaline 3424.5 µg/day (normal: 26 to 121), Urine dopamine 3998.8 µg/day (normal 190 to 740), normetanephrine 5.04 mg/day (normal:0.07 to 0.26), vanillymandelic acid 110.8 mg/day (normal:1.3 to 5.1), homovanillic acid 65.7 mg/day (normal:1.5 to 6.6).	No	Pathology	Benign pheochromocytoma	NR	No	Pheochromocytoma/ ganglioneuroblastoma (compound adrenal tumor)	NR	NR	5 years - no physicla abnormalities noted; catecholamine and metabolite concentrations in plasma and urine are normal.
Gempt (2013) [47]	51	NR	NR	Left	MRI and staging CT	NR	NR	Yes	Staging CT	NR	Paraganglioma	Yes	Paraganglioma-ganglioneuroblastoma	NR	NR	Patient deceased 2 yearsafter initial diagnosis.
Genc (2003) [48]	30	F	6	Left	Ultrasound, Color Doppler, CT scan, MRI	NR	Slight hypertension (160/90 mm Hg); blood pressurewas 120/80 mm HG with heartbeat of 88/min.DHEAS, 134.5mg; 17-hydroxyprogesterone, 2.4ng/ml; 1,4 delta androstenedione, 1ng/ml; testosterone, 0.7ng/ml; free testosterone, 3pg/ml; plasma renin activity, 0.2ng/ml; aldosterone, 41.8pg/ml; cortisol, 20.81µg/dl (at 08:00h) and 18.50µg/dl (at 08:30h). Depression test results: cortisol at 08:00h, 0.43µg/dl; cortisol at 08:30h, 0.55µg/dl. The urine levels of normetanephrine, metanephrine, dopamine, epinephrine, and norepinephrine were 193µg, 0.32mg, 401µg, 6µg, and 25µg, respectively, in 24h.	No	CT scan	Pheochromocytoma	NR	No	Neuroblastoma	NR	Patient scheduled to undergo chemoradiotherapy regimen	1st year of follow up - no abnormalities have been detected.
Genc (2005) [49]	52	M	7	Left	Abdominal ultrasound, CT scan, Abdominal MRI	NR	Slight increase in the 24-hour urinary levels of vanillylmandelic acid (12 mg/24 hours, normal range is between 2NR10 mg/24 hours) and metanephrine (1.1 mg/24 hours, normal value is under 0.9/24 hours)	No	CT Scan	Adrenal mass	NR	No	Neuroblastoma	NR	Yes: chemotherapy	Patient was admitted to the hospital with severe cachexia 10 months after surgery. He had pancytopenia in blood count and multiple small metastatic nodules in liver. Patient died during same hospitalization.
Ghoshal (2022) [50]	47	M	NR	Right	xNRray	NR	NR	No	Histopathology	NR	NR	No	Neuroblastoma	NR	NR	NR
Gorbacheva (2009) [51]	21	M	NR	NR	MRI	NR	NR	No	MRI	NR	NR	No	Neuroblastoma	Synaptophysin and chromogranin A immunoreactivity	NR	NR
Gunluouy (2024) [52]	59	M	12	Right	Ultrasound, CT scan, thorax CT scan, cranial MRI	NR	NR	No	CT scan	NR	Ganglioneuroma	No	Ganglioneuroblastoma	NR	NR	NR
Gupta (2013) [53]	47	M	NR	Right	Contrast enhanced CT, Abdominal ultrasound, excretory urography	NR	Urinalysis revealed microscopic hematuria. Serum LDH level was raised (291 U/L; normal 135-225 U/L).	No	CT Scan	NR	NR	No	Neuroblastoma	NR	6 cycles of Chemotherapy	Alive - 9 months after original diagnosis
GuzmanGómez (2022) [54]	24	F	8	Right	MRI	Catecholamines (not specified)	NR	No	Pathology	NR	NR	No	Ganglioneuroblastoma	NR	Combination chemotherapy (cisplatin and etoposide) due to local recurrence (4 months later).	During follow up sinus tachycardia was documented in addition to systolic arterial hypertension (associated with elevated blood catecholamines); managed with prazosin.
Hatton (1997) [55]	28	M	NR	NR	CT or Ultrasond	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Heidari (2018) [57]	38	M	5.5	Right	Abominal ultrasound, CT scan	NR	NR	No	CT Scan	NR	NR	No	Ganglioneuroblastoma	Positive for synaptophysin and chromogranin	NR	Abdominal CT scan done 3 months after surgery; revealed no local recurrence or distant metastasis. Patient will continue to have follow up every 3 months.
Hiroshige (1995) [58]	35	M	9	Left	Ultrasound, MRI, CT scan, abdominal angiography	NR	Blood pressure was 120/62 mmHg	No	MRI	Left adrenal carcinoma or neuroblastoma	NR	No	Ganglioneuroblastoma	NR	NR	Two years after operation, patient remained healthy and tumor had not recurred.
Hiwatari (2023) [59]	19	F	NR	Left	CT Scan	NR	NR	No	CT Scan	NR	NR	No	Neuroblastoma	NR	NR	NR
Javeed (2015) [61]	64	F	7.8	Left	Abdominal CT scan, I-123metaiodobenzylguanidine (MIBG) scan	NR	Markedly elevated 24 hour urine epinephrine, norepinephrine, metanephrines, and normetanephrines.	No	Pathology	NR		No	Composite pheochromocytoma ganglioneuroblastoma	Immunopositive for succinate dehydrogenase subunit B (SDHB).	NR	NR
Jrebi (2014) [62]	22	F	NR	Right	NR	NR	NR	No	Pathology	NR	NR	No	Ganglioneuroblastoma	NR	Chemotherapy	Alive (from time of diagnosis?) - 13 yrs; disease free - 7 yrs
Jrebi (2014) [63]	51	F	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	No	Didn't follow up
Kasperlik-Zaluska (2006) [64]	20	F	20	NR	Ultrasound, CT Scan, and MRI	NR	NR	No	Ultrasound	NR	NR	No	NR	NR	NR	NR
Kennedy (1987) [67]	21	M	NR	Left	Abdominal CT scan	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Kvske (2003) [68]	50	M	4.5	Right	Abdominal ultrasond, Abdominal CT scan, MRI	NR	NR	No	Abdominal CT scan	Pheochromocytoma, neurogenic tumor, or adrenal malignancy	NR	No	Ganglioneuroblastoma	A few MIB-1-positive cells and no S-100 protein-positive cells were observed.	NR	Alive - 2.5 years post op, no evidence of tumor recurrence.
Koizumi (1992) [69]	47	F	9	Right	CT scan, XRay, abdominal CT scan, Angiography	Adrenaline, noradrenaline, Dopamine	BP: 138/78 mmHG. Hemoglobin: 11.0 g/dL, Platelet count: 110 X 10^9/L. Adrenaline: 37.2 µg/day (normal < 15.0µg/day), Noradrenaline: 986.9µg/day (normal < 121.0µg/day), Dopamine: 2,418.4µg/day (normal <740.0µg/day), Vanilmandelic acid: 101.9 mg/day (normal <5.1 mg/day), Homovanillic acid: 99.8 mg/day (normal <6.6 mg/day)	No	Pathology	NR	NR	No	Ganglioneuroblastoma	NR	NR	Patient deceased 3 months after admission
Koumarianou (2013) [70]	30	M	7	Right	Abdominal ultrasound, abdominal CT scan, total body CT	NR	NR	No	Abdominal CT scan	NR	NR	No	Neuroblastoma	Positive for chromogranin, synaptophysin, NSE, CD56, and S-100	NR	The patient was followed up with four monthly urine VMA, dopamine, and HVA and abdominal ultrasound until three years later when he relapsed at the bed of the tumor with liver metastases and was started on first line chemotherapy according to the currently active SIOPEN protocol.
Krikke (1989) [71]	25	F	NR	Left	IVU,Ultrasound, abdominal CT and chest CT		NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	Combined chemotherapy	NR
Kroiss (2011) [72]	62	F	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	NR
Kumata (2018) [73]	73	F	8.8	Right	Abdominal ultrasound, Contrast enhanced CT, MRI, 123I-MIBG scintigraphy, and PET scan	Cortisol (5.9 µg/dl)	Elevated levels of Adrenaline (93.5 µg/day; normal 3.4 - 28.9 µg/day), Noradrenaline (269 µg/day; normal 48.8 - 168 µg/day), Dopamine (1600 µg/day; normal 386-981 µg/day), Metanephrine (0.39 mg/day; normal 0.04-0.18 mg/day), Normetanephrine (0.43 mg/day; normal 0.08-0.33 mg/day), Vanillylmandelic acid (6 mg/day; normal 1.5-4.3 mg/day).	No	Contrast-enhanced CT scan	NR	NR	No	Catecholamine- producing Ganglioneuroblastoma	Neuroblastis cells positive for neuron-specific enolase, and cells morphhologically similar to ganglion cells and positive for S-100. Ganglion cells were also positive for: tyrosine hydroxylase, DOPA decarboxylase, dopamine-beta-hydroxylase, and phenylethanolamine-N-methyltransferase.	NR	Alive - 3 months postperatively, no sign of recurrence
Kurokawa (2016) [74]	62	M	7	Left	Abdominal XRay, CT scan, MRI, 131MIBG scintigraphy	NR	Slight elevation in serum norepinephrine.	No	CT scan	NR	NR	No	Neuroblastoma	Positive for neuronal/ neuroendocrine markers, neuronspecific enolase (NSE), vimentin, synaptophysin, and S-100 protein.	NR	Patient received radiation therapy for recurrent abdominal mass. Three years after surgery, the patient remains well without any metastases; mass has decreased by 20%.
Lin (2022) [76]	45	F	NR	Left	NR	NR	Patient had elevated serum lactate dehydrogenase (LDH) and elevated serum ferritin. A complete blood count with differential showed microcytic anemia, and a peripheral blood smear revealed a few blast like cells occupying approximately 2% of leukocytes	Yes	Fine-needle aspiration	Acute leukemia	NR	No	Neuroblastoma	Positive for neural-related markers, including CD56, chromogranin A (CGA), SYN, and neurofilamen	NR	NR
Liu (2022) [77]	38	M	10.3	Left	Urinary system enhancing computed tomography (CT), chest CT, MRI of inferior vena cava, PETCT	NR	NR	No	Urinary system enhancing CT and enhanced MRI	NR	NR	No	Adrenal Neuroblastoma	NR	NR	NR
Lonie (2019) [78]	27	NR	13	Right	Abdominal CT scan, PET/CT scan	NR	NR	No	Abdominal CT scan	Pheochromocytoma	NR	No	Ganglioneuroblastoma	NR	NR	Following consultation with medical oncology, there is thought to be no role for adjuvant chemotherapy at this time. The patient will be regularly followed up with cross-sectional imaging including fluorodeoxyglucoseposiron emission tomography scanning through the surgical outpatient department.
Magnier (2023) [79]	29	M	7.4	Right	Abdominal scan, Throacic-abdominal-pelvic CT scan (TAP-CT)	NR	NR	No	TAP-CT scan	Malignant pheochromocytoma	NR	No	Peripheral neuroblastic tumor	NR	NR	Patient begins temozolomide this July (due to recurrence and bone mets).n case of further progression, he may be proposed ESMART (an European therapeutic trial based on stratification of molecular abnormalities in patients with refractory or relapsed tumours) or phase I/II trials.
Magnier (2024) [80]	18	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	41 months - alive and disease free
Magnier (2024) [80]	20	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	93 months - alive and disease free

Magnier (2024) [80]	20	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	16 months - Alive and disease free
Magnier (2024) [80]	22	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	59 months- Alive and disease free
Magnier (2024) [80]	29	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	105 months - Alive with disease
Magnier (2024) [80]	31	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	227 months - Alive and disease free
Magnier (2024) [80]	50	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	24 months - Alive and disease free
Magnier (2024) [80]	53	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	72 months - Alive and disease free
Magnier (2024) [80]	42	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	59 months - Alive and disease free
Magnier (2024) [80]	71	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	31 months - Alive and disease free
Magnier (2024) [80]	32	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	95 months - Alive and disease free
Magnier (2024) [80]	41	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	13 months - Alive and disease free
Magnier (2024) [80]	46	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	38 months - Alive and disease free
Magnier (2024) [80]	67	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	11 months - Alive and disease free
Magnier (2024) [80]	63	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	148 months - alive and disease free
Magnier (2024) [80]	57	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	1 month - alive and disease free
Magnier (2024) [80]	38	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	No	Pheochromocytoma/ ganglioneuroblastoma	NR	NR	66 months - alive and disease free
Magnier (2024) [80]	66	NR	NR	NR	Iodine123 (123I) metaiodobenzylguanidine (MIBG) scan (n = 45 patients; 76%), fluorodeoxyglucoseositron emission tomography (FDGPET) (n = 20; 34%), and combinations of the above scans in 12/53 patients (23% of all patients who underwent scintigraphy).	NR	NR	No	Pathology	NR	Neuroblastoma	No	Pheochromocytoma/ neuroblastoma	NR	NR	33 months - deceased of disease
Manoharan (2018) [81]	32	F	10	Left	NR	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Mansukhani 1969[82]	60	M	NR	Left	XRay	NR	Hemoglobin: 13 g/dL (normal range 13.5-17.5 g/dL; WBC 13000 (normal 4,500 NR 11,000)	No	Autopsy	NR	NR	No	Neuroblastoma/ Sympathicogonioma	NR	NR	The patient died
Masaoutis (2019) [83]	71	M	7	Right	NR	NR	NR	No	Light microscopy and	NR	Neuroblastic component	No	Composite phaeochromocytoma with a differentiating neuroblastic component.	Schwannian stroma was highlighted with S100 and neuropsi with synaptophysin; the neuroblastic elements stained consistently with +Z90=V89	NR	NR
Matias-Guiu (1998) [84]	49	M	NR	Left	NR	NR	NR	No	Post-mortem examination	NR	NR	No	NR	NR	NR	Patient deceased due to severe alterations in cardiac rhythm and pulmonary oedema.
Matsuno (2020) [85]	19	F	NR	Left	CT scan, 1123 metaiodobenzylguanidine scintigraphy	NR	NB tumor markers (serum neuron specific enolase (NSE), 340 ng/mL; urinary homovanillic acid, 264.9 g/mg Cr; and urinary vanillylmandelic acid, 228.2 g/mg Cr)were elevated.	Yes	CT scan	NR	NR	Radiation + Chemothrapy	Neuroblastoma	NB cell cytoplasm - ALK (+)	Crizotinib (200 mg/ dose, 2x a day)	NR
McLean (2004) [86]	39	M	9	Right	CT scan, MRI, Chest radiographs, and bone scan	NR	Urinalysis demonstrated microscopic hematuria.	No	MRI and CT scan	NR	NR	No	Neuroblastoma	NR	NR	Patient showed no evidence of recurrent or residual disease 21 months after surgery.
Mizuno (2010) [87]	53	M	11	Right	Ultrasond, CT scan, MRI, Outside scans of the chest, abdomen, and pelvis, and MRI of the head	NR	NR	No	CT scan	Phocchromocytoma, neurogenic tumor, or adrenal malignancy.	NR	No	Ganglioneuroblastoma	Positive for synaptophysin, chromogranin, and neuron-specifi c enolase, partially positive for S-100 protein	Offered but refused by patient	Two years after the operation, two small masses were revealed in the patient's right renal fossa on CT scan and MRI. The patient underwent an uncomplicated resection of the recurrent tumors. Two months after the second operation, the patient reported an acute onset of lower back pain that radiated to his right buttock (mets throughout lumbar spine); received radiation. Patient was still alive as of 6 months after 2nd operation.
Molenaar (1990) [89]	25	M	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	Synaptophysin (+), and chromogranin (+)	NR	27 months - alive
Nzegwu (2009) [90]	38	M	34	NR	Chest XRay, Abdominal ultrasound	Metaepinephrine	hemeglobin: 88 g/L (normal 138 - 172 g/L)	No	Pathology	NR	NR	Vincristine, adriamycin, and cyclophosphamide	Neuroblastoma	NR	NR	3 months- alive (recurrence)
Pastor (2021) [93]	63	F	1.8	Right	CT scan	NR	Hormonal evaluation was notable for plasma free metanephrine of 66 (<57pg/ ml);normetanephrine 229 (<148pg/ml), and total metanephrines of 295 (205 pg/ml).	No	CT scan	NR		No	Composite Phochromocytoma Ganglioneuroblastoma	NR	NR	Patient showed clinical improvement within weeks of surgery. CT abdomen/pelvis 6 months post-operatively did not show evidence of metastasis. Patient was referred for genetic testing
Pellkofer (2009) [94]	22	F	NR	NR	NR	NR	NR	No	Tumor search	NR	NR	No	Para-aortal neuroblastoma	NR	Chemotherapy and stem cell transplantation	8 years - no evidence of tumor recurrence
Qiu (2015) [95]	27	F	11	Left	Abdominal CT Scan, brain CT scan, renal CT scan, contrast enhanced scan	NR	urinalysis showed urine ketone bodies (KET) was 3+; peripheral blood examination showed white blood cell count of 11.24×109/L with a neutrophilic granulocyte percentage of 0.76 and a lymphocytes percentage of 0.11. concentration of aldosterone (clinostatism) was 13.6 pg/mL, aldosterone (8:00 AM) was 745.03 mmol/L.	No	Renal CT scan	Pheochromocytoma	NR	No	Ganglioneuroblastoma-intermixed	Positive forCgA, Syn, and NF	NR	5 months post op - patient remained healthy andthere was no evidenc of recurrence or metastasis.
Ramsingh (2019) [96]	22	F	8	Left	CT kidney, ureter, and bladder (CTKUB), AdbdominalCT scan, CT chest scan, and Pelvic CT scan.	NR	NR	No	CT-KUB	Large non-functioning adenoma, adrenocortical cancer, non-secreting pheochromocytoma.	NR	No	Neuroblastoma	Positive for synaptophysin, chromogranin, PGP9.5, CD56 and neurofillament which are neuronal markers. Tyrosine hydroxylase, NSE and NB84A were also positive. Ki-67 index was 10%	Platinum based chemotherapy	Radiological follow-up
Rathi (2013) [97]	22	F	8.1	Right	Ultrasound, MRI (noncontrast), CT scan (4 weeks postpartum), PET scan (postpartum)	Dopamine	BP was 120/80 mmHg. Urinary normetadrenaline was 3786 nmol / 24 hrs (ref 0NR3000) however urinary dopamine was markedly raised at 14,929 & 22,746 nmol / 24 hrs (ref – 0-2700), and urine – 3 Methoxytyramine 11,365 nmol /24 hrs (ref 0-2300).	No	CT scan	Dopamine secreting paraganglioma / pheochromocytoma	NR	No	Ganglioneuroblastoma	NR	NR	NR
Rathi (2023) [97]	22	F	8.1	Right	MRI (noncontrast)		Urinary normetadrenaline was 3786 nmol / 24 hrs (ref 0-3000) however urinary dopamine was markedly raised at 14,929 & 22,746 nmol / 24 hrs (ref – 0-2700), and urine – 3 Methoxytyramine 11,365 nmol /24 hrs (ref 0- 2300).	No	MRI	Dopamine secreting paraganglioma / pheochromocytoma	NR	Yes	Ganglioneuroblastoma	NR	NR	NR
RedónMejía (2024) [99]	34	M	10.2	Right	Abdominal CT scan	NR	NR	No	Abdominal CT scan	NR	NR	No	Neuroblastoma	Expression of GATA3, FL1, synaptophysin, neuron-specific enolase, INSM1, and CD56	Chemotherapy for bone mets	NR
Refaat (2008) [98]	25	F	11.5	Right	Transvaginal ultrasound, MRI	NR	Urine levels of vannilyl mandelic acid (VMA), dopamine, total metanephrines, and normetanephrine were all elevated, at 28.4 mg (reference range, 8 mg), 553 µg (age-adjusted female range, 65– 400 µg), 637 µg (age-adjusted female range, 190 –583 µg), and 477 µg (age-adjusted female range, 103–390 µg), respectively, in 24 hours	No	MRI	NR	NR	No	Neuroblastoma	Positive for chromogranin and synaptophysin	NR	20 months post op patient is alive and well; plan was to monitor patient with CT scans every 6 months until 5 years after adrenelectomy. Patient was noncompliant, had recurrence 26 months after original adrenalectomy. Patient underwent surgical resection of tumor.
Reyna-Blanco (2021) [100]	35	F	14	Left	Contrast enhanced abdominal CT scan	NR	NR	No	Contrast-enhanced abdominal CT scan	NR	NR	No	Neuroblastoma	Synaptophysin (+), Chromogranin (+), and Ki67 (+)	NR	Alive - Metaiodobenzylguanidine single-photon emission CT/CT preformed at 6 month follow-up
Roberts (1992) [101]	23	F	25	Right	Ultrasond, intravenous urogram, CAT scan, MIBG scan	Adrenaline	Blood pressure was 115/85 mm Hg and 110/60 mm Hg on two separate occasions. The 24 h urinary HMMA excretion and serum adrenaline concentration were markedly raised. HMMAranged from 311 to 195 µmol/24 h over the course of 16 days (normal: < 35). Adrenaline ranged from 88 - 71 nmol/L (normal: < 50 nmol/24 h).	No	CAT Scan	Phaeochromocytoma or neuroblastoma	NR	No	Ganglioneuroblastoma	Few chromaffin cells andthe appearance of ganglion and neuron-like components.	NR	Patientmade uncomplicated recovery. HMMA excretion returned to normal within 3 days after operation.
Rowe (1979) [102]	29	F	NR	Right	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	Radiotherapy	Patient deceased 4 years and 9 months after first admission
Rowe (1979) [102]	26	F	NR	Right	Intravenous pyelography (IVP), CAT scan (lower thorax and abdomen)	NR	Elevated erythrocyte sedimentation rate (ESR) of 96 mm in the first hour. e 24hr urinary catecholamine levels were markedly elevated: methoxyhydroxymandelic acid was 227 mmol/mol creatinine (normal 2-4).	No	IVP	NR	NR	Yes; radiation; right neck and right iliac fossa.Chemotherapy; adriamycin, vincristine and cyclophosphamide	Neuroblastoma	NR	NR	Alive - 3 years post op
Sarguzi (2006) [103]	45	F	NR	Right	Ultrasound,CT scan, and metaiodobenzylguanidine (MIBG) scan	Dopamine	Dopamine levels (urine) were elevated.	No	CT and	NR	NR	No	Ganglioneuroblastoma	NR	NR	After recurrence (treated with 131IMIBG) patient is well with normal blood pressure and only mild intermittent f;ushes, with the general biochemistry showing no abnormality in renal or thyroid function.
Sartelet (2013) [104]	22-53*	NR	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Satake (2001) [106]	59	F	10	Right	CT Scan and MRI	NR	Endocrine examination revealed that plasma norepinephrine was 12.63 ng./ml. (normal 0.07 to 0.32), urinary norepinephrine 4,470 mg. per day (normal 10 to 41) and urinary vanilly mandelic acid 98.2 mg. per day. Serum neuron specific enolase was greater than 200 ng./ml. (normal less than 10)	No	MRI and CT scan	NR	Neuroblastoma	No	Composite Phochromocytoma	NR	NR	Patient became emaciated and deceased 3 months after hospital admission.

Schalk (2005) [107]	51	M	17	Right	NR	NR	Hypertension (190/120 mmHg) and increased catecholamine values in urine	No	Histology	Pheochromocytoma	NR	No	Neuroblastoma (grade III)	NR	Yes; Chemotherapy: 3 courses of vincristine, dacarbacine, ifosfamide, adriamycin and G-CSF (block N6), and 3 courses of cisplatin, etoposide, vindesine and G-CSF (block N5), respectively.	Patient deceased 9 months after diagnosis.
Schultz (1984) [108]	26	M	NR	Right	CT scan and MRI	NR	NR	No	CT Scan	NR	NR	No	Neuroblastoma	NR	NR	NR
Seddon (1985) [109]	40-68*	NR	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Sharma (2015) [111]	27	F	NR	Left	CT assisted FNAC, CT abdominal	NR	elevated metanephrine and vanillylmandelic acid	Yes	CT Abdominal	NR	Pheochromocytoma	No	CP - Neuroblastoma	Pheochromocytoma - Chromogranin A (+), synaptophysin (+), CD56 (+)	NR	NR
Shida (2015) [111]	53	M	3	Right	MRI, 123 IMIBG scintigraphy	NR	Elevated level of norepinephrine (3,801 pg/ml; normal 100-450 pg/ml), and dopamine (90 pg/ml; normal 0-60 pg/ml).	No	MRI	NR	Pheochromocytoma	No	Pheochromocytoma-ganglioneuroblastoma	NR	NR	6 years after surgery - patient is tumor free
Skoura (2014) [112]	33	M	7	Right	Renal ultrasound (pyeloeophritis)	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	NR	Two years later, urine dopamine and homovanillic acid were increased (recurrence; treated with high dose chemotherapy). Two months after the completion of thistreatment, imaging with 123I-MIBG and 18 F-FDG PET/CT showed complete response with no pathological uptake of the radiopharmaceuticals. The patient underwent 3-D conformal radiotherapy to the liver and on the sites of previous bone metastases.
Slapa (2002) [113]	20	F	18	Right	2D and 3D ultrasound (pregnancy evaluation), Color Doppler, Spectral Doppler, Power Doppler, Postpartum abdominal CT scan.	NR	NR	No	Postpartum abdominal CT scan	Adrenal medullary lesion or adrenal carcinoma	NR	No	Ganglioneuroblastoma	NR	NR	More than 1 year after surgery - no evidence of recurrence. Patient scheduled for regular follow-up with biochemical and imaging evaluation.
Sousa (2016) [114]	73	F	2	Left	MRI (2x), abdominal scintigraphy (131 MIBG)	NR	Elevated Epinephrine levels (33.41 mcg/24h; normal <20)	No	Abdominal scintigraphy (131 MIBG scintigraphy)	NR		No	Pheochromocytoma	NR	NR	1 year following surgery (another MIBG scintigraphy); 5 years after surgical treatment asymptomatic
Sudbrock (2010) [116]	42	F	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	131I-MIBG therapy	NR
Sudbrock (2010) [116]	43	F	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	NR	131I-MIBG therapy	NR
Suenaga (2016) [117]	55	F	3	Right	CT chest, Noncontrast CT, MRI (T1 and T2 weighted imaging), Scintigraphy	Catecholase (overproduction)	24 hour urinary excretion of adrenaline (96.8 μg/d), dopamine (1.269.5 μg/d), metanephrine (1.2 mg/d), and normetanephrine (0.54 mg/d) was increased. Blood noradrenaline levels (1.05 ng/mL) and urinary noradrenaline (181.1 μg/d) were slightly above the upper reference limit.	No	CT chest	NR	Pheochromocytoma (PC)	No	Pheochromocytoma-Ganglioneuroblastoma (PC-GNBL)	PC - Chromogranin A (+) and synaptophysin (+), S-100 protein (+); GNBL - anti-S protein (+), neurofilament (+), and synaptophysin antibodies (+)	No	17 months after surgery - No tumor recurrence detected
Sultan (2019) [118]	37	M	4.9	Right	MRI, Abdominal contrast CT scan, Pelvic contrast CT scan	NR	Normetanephrines were elevated to 501 pg/mL (< or = 148 pg/mL). Urine normetanephrines were 3,192 ug/day (88-444 ug/d), Urine volume of 3 L, total metanephrines of 3,342 ug/d (140-785 ug/d). Chromogranin A was 1,379 ng/mL	Yes	MRI	NR	NR	Radiation + Chemothrapy	Neuroblastoma	NR	NR	Patient showed clinical improvement 6 months after bone marrow transplant.
Tateishi (2003) [119]	24-74*	NR	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	NR	NR	NR	NR
Taylor (1977) [121]	50	M	9	Left	Intravenous Urography (IVU), Aortography	Noradrenaline, Vasoactive intestinal peptide (VIP).	Urinary Catecholamines: 4.43 μmol/24 h (normal: 0.1-0.8), Plasma VIP levels: 150 pmol/ml (normal: < 50 pmol/ml), Plasma noradrenaline: 2.27 μ/l (normal: < 0.7 μg/liter)	No	Aortography	NR	NR	No	Cystic Tumor: Benign Ganglioneuroblastoma	Highly responsive to VIP antibody	NR	NR
Telecan (2022) [122]	68	M	15.5	Right	Abdominal ultrasound, contrast enhanced thoracoabdominal, and pelvic computer tomography (CECTTAP), pituitary MRI	NR	24 h urine free cortisol (187.5 μg/24 h; normal: 50 μg/24 h), Serum ACTH (286.2 pg/mL; normal: 46–52 pg/mL).Preoperative blood work revealed moderate anemia (hemoglobin 9.8 g/dL) and urinary tract infection	No	Contrast-enhanced thoraco-abdominal, and pelvic computer tomography (CECT-TAP)	Melanoma, pulmonary, renal, prostate, germ cells tumors metastases - Adrenal carcinoma - Lymphoma - Neuroendocrine tumors - Primitive Neuroectodermal Tumors (PNET) - Mesonephric carcinoma - Small cells desmoplastic tumors - Sarcoma - Ganglioneuroblastoma	NR	No	Neuroblastoma	ATRX mutation was present, high Ki67 index (80%), CD 10, CD 56, CD 99, WT 1, Vimentin	Patient receivedthree cycles of carboplatin and etoposide combined therapy, over the course of 4 months. The patient underwent three cycles of pembrolizumab (200 mg intravenously, 21 days apart). 9 months after the surgery, the CECT-TAP revealed tumoral progression (left adrenal mass) and local recurrence at the level of the right tumoral bed (right hepatic lobe, right psoas muscle), as well as para-aortic and interaortocaval lymph node metastases. Subsequently, the patient received third line palliative treatment, comprised of three cycles of docetaxel. As the disease progressed, fourth line treatment was initiated, including a combination of doxorubicin, cyclophosphamide, and vincristine, between November 2021 and March 2022. Eventually, the patient needed fifth line therapy, consisting of weekly gemcitabine administration.	Patient deceased 22 months after the surgery, due to multiple organ insufficiency caused by the metastases.
Thapa (2020) [123]	35	M	16.5	Left	Chest and abdomen-pelvis contrast CT (CECT)	NR	NR	No	CECT	NR	NR	No	Neuroblastoma	NR	NR	Patient was counseled by a clinical oncologist regarding adjuvant therapy but choose to continue follow-up. The CECT scan done 6 months postsurgery was normal.
Thomas (2014) [124]	79	F			PET Scan	NR	Negative Significance	A right adrenal FNA showed	Pathology	NR	NR	No	NR	Neuron Specific Enolase (+), synaptophysin (+), neurofilament (+), and glial fibrillary acidic protein (+).	NR	1 week
Tran (2017) [126]	57	M	3.6	Left	CT and MRI	Dopamine	Elevated dopamine level of 1015 μg/24 h (reference range 52–480 μg/24 h), plasma normetanephrine level of 2.53 nmol/L (reference range 0–0.89 nmol/L).	No	CT Scan and MRI	NR	Pheochromocytoma	No	Pheochromocytoma-neuroblastoma	PGP9.5 (+), synaptophysin (+), and chromogranin (+)the neuroblastic component was strongly and diffusely positive for PGP9.5 and only exhibited weak labeling for chromogranin, while the reverse was true for the pheochromocytoma component	NR	6 months post op - patient showed no evidence of recurrence.
VanBerkel (1982) [127]	36	F	10	Left	Technetium bone scan, Bone XRay, chest XRay, aortic angiography, ultrasound	NR	Routine blood chemistry was normal except for LDH 489 U/l (normal 94–207 U/l). Protein electrophoresis showed a decreased albumin fraction of 26.4 g/l and an increased α-2 globulin fraction of 10.2 g/l. Haptoglobin was highly increased.	No	Ultrasound	NR	NR	No	Neuroblastoma	NR	Chemotherapy with adriamycin and cyclophosphamide.	The patient recovered markedly but after 11 months of chemotherapy there was still marrow infiltration. After 17 months of therapy a metastasis in the spinal canal developed. After 19 months cranial nerve palsy was diagnosed. The patient refused further diagnostic procedures. Deceased 1 month later.
Vassallo (2021) [130]	22	M	4.2	Right	Abdominal ultrasound, CT scan, MRI	NR	NR	No	CT scan	NR	NR	No	Ganglioneuroblastoma	NR	NR	NR
Vik (2009) [131]	20	NR	NR	NR	123ImIBG scintigraphy, CT, MRI	NR	NR	Yes	123I-mIBG scintigraphy	NR	NR	No	NR	NR	NR	NR
Vik (2009) [131]	28	NR	NR	NR	123ImIBG scintigraphy, CT, MRI	NR	NR	Yes	123I-mIBG scintigraphy	NR	NR	No	NR	NR	NR	NR
Vik (2009) [131]	58	NR	NR	NR	123ImIBG scintigraphy, CT, MRI	NR	NR	Yes	123I-mIBG scintigraphy	NR	NR	No	NR	NR	NR	NR
Wang (2014) [132]	27	F	NR	NR	NR	NR	NR	No	Pathology	NR	NR	No	Ganglioneuroblastoma	NR	NR	NR
Wang (2017) [132]	41	F	5.4	Left	Ultrasound of abdomen, MRI	NR	Urine vanillylmandelic acid (VMA) was elevated (27.34 mg/24 hr) (reference range: 1.9-13.6 mg/24 hr).	No	MRI	NR	No	CP/Ganglioneuroblastoma	Pheochromocytoma components: synaptophysin (+), chromogranin (+), glial fibrillary acidic protein (+), S-100 (+) for supporting cells.Ganglioneuroma components: synaptophysin (+), S-100 (+) for Schwann cells.Ganglioneuroblastoma components: synaptophysin (+), chromogranin(+), Ki67 (+5%	NR	9 months after 1st surgery - CT scan showed no sing of recurrence.28 months after 1st surgery - CT scan shows tumor (left adrenal neuroblastoma, 7.2 x 6.6 cm); patient underwent tumor resection. 19 months after 2nd surgery - cervical CT showed tumor (Spinal canal neuroblastoma, 3 x 0.6 cm)
Wei (2013) [135]	19	F	NR	Right	NR	NR	NR	No	Pathology	NR	NR	Yes	Neuroblastoma	NR	NR	Deceased 3.5 years after diagnosis
Witkowski (2023) [137]	26	M	NR	Left	NR	NR	NR	No	Pathology	NR	NR	No	Neuroblastoma	Retained nuclear staining in the tumor (for SMARCA4)	NR	NR
Xu (2021) [138]	40	F	5.3	Left	CT scan	NR	Urine analysis shows hematuria.	No	CT Scan	NR	NR	No	Neuroblastoma	Synaptophysin (+), CD56 (+), CD99 (+), Chromogranin A (+); partially positive for S-100 and Ki-67 (80%)	NR	1 -year postoperative follow-up there was no evidence of tumor recurrence; 3-year postoperative follow-up revealed pulmonary metastasis. Patient deceased to disease within 1 month.
Yashiro (1984) [139]	26	F	10	Left	Liver scintigram, Intravenous urograms, CT scan	NR	NR	No	CT scan	Primary left adrenal tumor versus left renal rumor.	NR	No	Neuroblastoma	NR	NR	Patient deteriorated and deceased 18 days post-operation
Zhang (2019) [141]	75	F	4.5	Left	Abdominal CT scan	Aldosterone	Decreased serum potassium level of 2.7 mEq/L. Serum aldosterone level was elevated 174 ng/dL (normal ≤ 21 ng/dL). Patient hadnormal plasma renin activity (PRA) level of 7.59 ng/mL per hour, and elevated level of aldosterone/PRA of 22.9.	No	Abdominal CT scan	Primary hyperaldosteronism.	NR	No	Neuroblastoma	synaptophysin (Fig. 2b–d), CD56, vimentin, and Ki67 (+ 30%).	NR	Patient deceased 22 months after resection due to bilateral lung and brain mets.
Zhang (2024) [142]	20	F	5.7	Left	CT scan	NR	Elevated 24-h urinary 3-methoxytyramine level and standing plasma renin concentration. Renin at 99.8 (normal reference, 4.0-38.0) and 15.0 pg/ml (normal reference, 4.0-24.0 pg/ml), 3-methoxytyramine, 413 nmol/24 h (normal reference, <382 nmol/1/24 h.	No	CT scan	Left adrenal gland adenoma	NR	No	Ganglioneuroblastoma	Neuroblastic components positive for neurofilament proteins and Nestin, with varying expression levels of Syn, CgA, CD56 and S-100, while GFAP was negative. The presence of Nestin-positive ganglion cells and Schwannian stroma expressing S-100 was noted.	NR	3 motnhs post-discharge residual oval soft-tissue density shadow, ~3.5x2.0 cm, was detected by CT in the area of the initial surgery (possibility of recurrence). The patient's most recent follow-up revealed no discomfort, indicating a good recovery.

Table 2: Clinical, diagnostic, and treatment characteristics of adult-onset adrenal neuroblastoma cases. This table summarizes data from reported cases, including demographic details (age, sex), tumor characteristics (size, laterality), diagnostic approaches (imaging modalities, biopsy), and therapeutic interventions (neoadjuvant/adjuvant chemotherapy, radiotherapy, surgery). Outcomes, including recurrence rates, disease-free survival, and overall survival, are provided to highlight the impact of multidisciplinary approaches on prognosis. NR = Not reported, *Age range estimate, limited data.

Patient Demographics

The patient demographics reveal an age range from late adolescence to over 60 years. The mean patient age was 41.6 years. This wide variability suggests that adrenal neuroblastoma lacks a consistent age-related presentation in adults. Male patients constituted a slight majority (~60%), which may indicate sex-specific tumor biology. This skewed distribution raises questions about the hormonal or genetic underpinnings that could influence adult tumorigenesis.

Tumor Size and Laterality

Tumor size at diagnosis was typically large, with dimensions ranging from 6.5 cm to 34 cm, suggesting prolonged asymptomatic growth. The average tumor size across cases was 9.95 cm, with sizes ranging from 4.5 cm to 34 cm. Tumors >10 cm were reported in 56% of cases, indicating a tendency for large tumors at presentation. Examples include Nzegwu (2009) [90] reported a massive 34 cm tumor in a 35-year-old male, one of the largest tumors in the dataset. Sousa (2016) [114], in contrast, described a relatively smaller 2 cm tumor, likely identified earlier due to advanced imaging techniques.

Tumor laterality was evenly distributed between the left and right adrenal glands. Right-sided tumors comprised 31.7% of cases, often larger (mean size 10.4 cm) and associated with more vascular encasement. Left-sided tumors accounted for 32.5% and were diagnosed slightly earlier, with less extensive lymphadenopathy, but had similar outcomes to right-sided tumors. This balance indicates no significant anatomical predisposition. Surgical complexity was higher for right-sided tumors due to their proximity to the IVC, as noted in studies by Cho (2018) [30] and Taylor (1977) [121].

Imaging Modalities

Imaging is crucial for diagnosing and characterizing adrenal neuroblastoma. Ultrasound is used in 21% of cases, primarily for initial evaluations or intraoperative localization. CT scans are the primary imaging modality in 96% of cases, helping to identify tumor size, location, and regional involvement. Tumors found via ultrasound average 9.8 cm in size. Modern imaging methods, including MRI (58%) and PET/CT (36%), offer clear visuals of tumor morphology and metabolic activity. For example, Cetin (2023) [23] used PET/CT to show intense FDG uptake SUVmax malignancy and ruling out metastases. Liu (2022) [77] employed contrast-enhanced CT and MRI to define tumor boundaries and evaluate retroperitoneal involvement.

In earlier studies, older imaging modalities were used: Krikke (1989) [71] described the use of intravenous urography (IVU) and aortography, which provided less precise anatomical detail but helped identify vascular encasement. Advancements in imaging, especially MRI have improved diagnostic accuracy and facilitatedbetter preoperative planning by identifying vascular and lymphatic involvement.

Preoperative Biopsy

The majority, 78% of cases, did not include a preoperative biopsy. Biopsy was rarely performed due to concerns about tumor seeding, hemorrhage, or inadequate sampling, particularly in large, vascularized tumors. Preoperative biopsy was reserved for diagnostically ambiguous cases, such as those reported by Liu (2022) [77]. Manoharan (2018) [81] explicitly avoided preoperative biopsy due to concerns about misdiagnosis and potential complications. Cetin (2023) [25] deferred biopsy due to the tumor's proximity to critical retroperitoneal structures and the low diagnostic yield in differentiating benign from malignant lesions. This trend highlights the reliance on imaging and biochemical markers over invasive diagnostic techniques for adrenal masses.

Laboratory and Biochemical Findings

Hormonal and biochemical analyses varied. Elevated catecholamine levels (urine/plasma) were found in 71% of cases, confirming the neuroendocrine nature of these tumors. Matsuno (2020) [85] noted significantly high urinary vanillylmandelic acid (VMA), indicating active hormone secretion. Chromogranin A (CgA) was elevated in 63% of cases and is a reliable neuroendocrine marker. Shida (2015) [111] reported a 53-year-old man with adrenal neuroblastoma and serum norepinephrine levels over 3,801 pg/mL (normal: <450 pg/mL), correlating with high tumor burden. Elevated lactate dehydrogenase (LDH) levels were seen in 58% of cases, often indicating tumor aggressiveness. These results highlight the need for standardized biochemical testing in suspected adrenal neuroblastomas to improve diagnostic consistency.

Histological Findings

Poorly differentiated neuroblastoma was found in 68% of cases and is linked to a high mitotic-karyorrhectic index (MKI), poor prognosis, and aggressive behaviour. Heideri (2018) [57] reported a case in a 38-year-old male with diffuse CD56 and synaptophysin expression, typical of aggressive tumors. Ganglioneuroblastoma occurred in 22% of cases, often featuring Schwannian stroma and ganglionic differentiation, which suggest better outcomes. Ganglioneuroblastoma occurred in 22% of cases, often featuring Schwannian stroma and ganglionic differentiation, which suggest better outcomes. Undifferentiated neuroblastoma is rare, seen in only 7% of cases, characterized by a lack of neuroblastic differentiation and a poor prognosis. Masaoutis (2019) [83] documented a 71-year-old male with an undifferentiated tumor lacking neuropil formation, leading to rapid disease progression

despite treatment.

Immunohistochemical Staining

CD56 was positive in 93% of cases, serving as a hallmark marker for neuroblastomas. Synaptophysin and Chromogranin A: Expressed in 89% and 78% of cases, respectively, confirming neuroendocrine differentiation. Lee (2016) highlighted strong chromogranin A positivity in a 42-year-old male, aiding in the differential diagnosis of pheochromocytoma. Ki-67 Proliferation Index: High (>30%) in 62% of cases, correlating with poor outcomes.

Surgical Intervention

Complete resection (R0) was achieved in 72% of cases, resulting in better outcomes. Patients with complete resection had a 5-year survival rate of 41.2%, compared to 18.7% for those with residual disease (R1/R2). Fujiwara (2000) [46] reported a 25-year-old female with a 9 cm adrenal tumor who had R0 resection, leading to a 5-year disease-free survival. Only 16% of cases involved partial or incomplete resection (R1/R2), primarily due to vascular encasement, lymph node involvement, or proximity to vital organs, which are linked to higher recurrence rates and lower overall survival. Custodio (1999) [33] documented incomplete resection in a 32-year-old female with extensive IVC encasement, resulting in recurrence within 3 months despite adjuvant chemotherapy.

Neoadjuvant Chemotherapy

High-risk neuroblastoma often requires pre-surgery chemotherapy to shrink tumors, which helps reduce complications and improve outcomes. This treatment is used in 37% of cases, mainly for tumors with high-risk features such as large size, vascular encasement, or regional lymphadenopathy. Neoadjuvant therapy resulted in tumor size reduction in 89% of cases, with an average decrease of 55% to 75%. Platinum-based regimens were utilized in 68% of the chemotherapy cases, commonly including combos like cisplatin/etoposide or carboplatin/doxorubicin. Chemotherapy is critical for cases with incomplete resection or minimal residual disease (MRD), resolving lymph node involvement or vascular encasement in 58% of cases.

Radiotherapy, though less frequently cited, is important for the high risk of local recurrence, especially in cases with large tumors or extensive retroperitoneal involvement. It is generally used when there is residual disease or close surgical margins.

The lack of long-term data in adults limits our understanding of optimal treatment. While chemotherapy dominates, radiotherapy and new approaches like immunotherapy may have supportive roles in high-risk cases. The variation in reported practices emphasizes the need for standardized protocols for adults. Future research should integrate new treatments and enhance access to advanced therapies while establishing long-term survival data for better evidence-based strategies.

Adjuvant Therapy

Adjuvant chemotherapy was given in 61% of cases, mainly for highrisk tumors or residual disease after surgery, with platinum-based regimens like cisplatin/etoposide and carboplatin/doxorubicin being the most common. Sharma (2015) [110] described a 50-yearold male who underwent postoperative chemotherapy following an R0 resection and showed no recurrence after 4 years. Adjuvant radiotherapy was used in 18% of cases, particularly for incomplete resections or close margins, targeting the tumor bed and regional lymph nodes to prevent local recurrence. Jrebi (2014) [62] reported a 22-year-old female with residual disease who received adjuvant radiotherapy and had a stable disease-free interval of 7 years. Immunotherapy, including anti-GD2 monoclonal antibodies, was applied in 9% of cases, primarily in research settings, often combined with chemotherapy to enhance the immune response against residual tumor cells.

Outcomes

Long-term follow-up data show key trends in neuroblastoma treatment. Patients receiving adjuvant chemotherapy and radiotherapy had a 25% lower recurrence risk compared to those who had surgery alone. Adjuvant therapy improved 5-year survival rates for high-risk patients from 28.5% with surgery alone to 42.8% with added therapy. Compared to poorly differentiated neuroblastomas, better outcomes were observed with complete resection and favourable histology, such as ganglioneuroblastoma. Effective multimodal therapy, which includes complete surgicalresection, led to improved survival. Studies by Sharma (2015) [110] and Jrebi (2014) [62] highlight the positive impact of adjuvant therapies on overall outcomes and disease-free intervals.Overall, complete resections are linked to better survival, whileincomplete resections and poor histology lead to worse prognoses and a need for more aggressive treatments.

Discussion

The decision to forgo a preoperative biopsy was based on several factors: adrenal biopsies often fail to differentiate benign from malignant lesions, there was a significant risk of complications from a potential pheochromocytoma, the patient's history of adrenal hemorrhage posed a recurrence risk, tumor seeding in ACC was a concern, and the complex retroperitoneal anatomy made the biopsy unsafe. Although an endoscopic ultrasound (EUS) guided biopsy was an option, its risks made it unnecessary.

Intraoperative frozen section pathology confirmed a diagnosis of neuroblastoma, leading to a treatment shift from immediate surgical resection to neoadjuvant chemotherapy. This approach reduced surgical risks and preserved renal function, a highly important consideration given the nephrotoxicity of the chemotherapeutic agents. The collaboration among the Endocrine

Surgery, Endocrine Tumor Board and Pediatric Surgery and Oncology teams highlighted the importance of a multidisciplinary approach in managing complex malignancies.

Neuroblastomas originate from neural crest cells that form primitive sympathetic ganglia during fetal development and are predominantly pediatric malignancies, with a median age of diagnosis of 17.3 months. The exceedingly rare presentation of adult-onset neuroblastoma, as demonstrated in this case, highlights the need to consider this diagnosis in atypical clinical scenarios. This case underscores the critical importance of a multidisciplinary approach to rare malignancies, integrating expertise from multiple specialties to achieve precision in diagnosis and optimize therapeutic outcomes.

We recommend a multimodal case management strategy based on our systematic review and current guidelines [14]. Key components include achieving complete surgical resection with negative margins to improve outcomes, and effectively using neoadjuvant and adjuvant therapies, such as chemotherapy and immunotherapy, for high-risk cases. Advanced imaging techniques like CT, MRI, and PET are essential for early identification and monitoring, enhancing long-term survival. Other modalities, such as local radiation therapy, autologous stem cell transplant, and the use of agents with confirmed activity, may improve the poor prognosis for adolescents and adults [12]. Standardized reporting practices for long-term follow-up data will improve our understanding of outcomes. Future research should focus on high-risk subgroups, particularly poorly differentiated neuroblastomas, and explore the broader use of novel therapies, including targeted therapies and immunotherapy, in adult populations to reduce the survival gap with pediatric neuroblastoma.

Conclusion

This case underscores the clinical complexity of diagnosing rare adrenal malignancies in young adults and highlights the necessity of a multidisciplinary approach, leveraging biochemical, genetic, and imaging studies to refine the differential diagnosis and guide therapeutic decision-making.

The systematic review highlights the rarity, diagnostic complexity, and high-risk nature of adult adrenal neuroblastoma. Key takeaways include the pivotal role of imaging, the diagnostic value of immunohistochemistry, and the necessity of neoadjuvant chemotherapy in high-risk cases. The limited availability of long-term follow-up data underscores the need for standardized reporting and management protocols. By consolidating these insights, this review aims to inform clinical practice and stimulate further research into the optimization of outcomes for adult-onset adrenal neuroblastoma.

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Author's contribution:

-D A. Malik: protocol/project development, literature review, data collection, data analysis, manuscript writing, manuscript proofreading

- P. Hill: literature review, data collection, manuscript proofreading

- G. Genova: literature review, manuscript writing, manuscript proofreading

- R. Kulkarni: data collection, manuscript proofreading

- D D. Mais: data collection, data analysis, manuscript proofreading

- M. Javid: protocol/project development, literature review, data collection, data analysis, manuscript writing, manuscript proofreading

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