RESEARCH PAPER

Urinary Bladder Paraganglioma: Diagnostic Challenges and Surgical Management of an Neuroendocrine Tumor in Uncommon Origin Case Study

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ABSTRACT

Paragangliomas of the urinary bladder are rare neuroendocrine tumors that frequently resemble high-grade urothelial carcinoma, especially in non-functional cases, which complicates diagnosis. This report describes a 49-year-old male who presented with painless hematuria and was initially diagnosed with high-grade urothelial carcinoma based on transurethral biopsy. Imaging identified a heterogeneously enhancing mass involving the anterior and posterior bladder walls and the right vesicoureteric junction, accompanied by ipsilateral hydroureteronephrosis. The patient underwent radical cystectomy with ileal conduit reconstruction. Histopathological analysis revealed nests of polygonal chief cells with eosinophilic cytoplasm and uniform nuclei arranged in a zellballen pattern. Immunohistochemical staining demonstrated strong chromogranin and synaptophysin positivity, CK-7 negativity, and focal S-100 expression in sustentacular cells. The tumor was moderately differentiated with a Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) score of 6 and no lymph node involvement. The case highlights the necessity of considering paraganglioma in the list of the mass types of the bladder and illustrates the significance of histopathology, immunohistochemistry, and imaging to reach the correct diagnosis and surgical treatment.

Keywords: Urinary bladder paraganglioma; Neuroendocrine tumor; Zellballen; Immunohistochemistry; Radical cystectomy

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INTRODUCTION

Paragangliomas are rare neuroendocrine tumors originating from extra-adrenal paraganglionic tissue of the autonomic nervous system 1. They account for about 10–20% of all pheochromocytomas and are most often found in the head, neck, and retroperitoneum 2. Although they share characteristics with adrenal pheochromocytomas, extra-adrenal paragangliomas exhibit greater anatomical diversity and clinical variability 3.

Urinary bladder paragangliomas are rare neoplasms, accounting for less than 0.06% of all bladder tumors and under 1% of all paragangliomas 4,5. Diagnosis most frequently occurs in young to middle-aged adults, with some studies reporting a higher incidence in females 6. These tumors can develop at any location within the bladder wall, but most often involve the trigone and dome. The functional status of the tumor determines the clinical presentation. Functional tumors secrete excess catecholamines, resulting in episodic hypertension, palpitations, diaphoresis, and headache, particularly during micturition. Non-functional tumors typically present with painless hematuria or nonspecific lower urinary tract symptoms 7,8.

Diagnostic challenges occur due to overlapping clinical and histological features between paragangliomas and other bladder neoplasms, especially high-grade urothelial carcinoma. Frequently, biopsy specimens that demonstrate muscle invasion resemble urothelial malignancy. This resemblance may result in misdiagnosis and inappropriate initial management9. Precise diagnosis is critical since the intraoperative manipulation of undiagnosed functional paragangliomas would result in the development of severe hypertensive crisis without preoperative alpha-adrenergic blockage and fluid optimisation10.

Immunohistochemistry that needs to be done histopathologically is a necessary step to definitive diagnosis. The typical microscopic appearances are the zellballen pattern in which polygonal chief cells are divided by fragile vascular stroma, and peripheral sustentorial cells. In immunohistochemistry, the neuroendocrine markers are chromogranin, synaptophysin and neuron-specific enolase, being positive with some cases having cytokeratin expression policy mostly negative, helping in eliminating the possibility of urothelial carcinoma1,11.

Aim

To present the report about the case of a rare urinary bladder paraganglioma, its clinical, radiological and histopathological picture, diagnostic issues and surgical treatment.

Objectives

1. To describe the clinical, radiological, and histopathological phenotypes of urinary bladder paraganglioma and identify the distinctions between the disease and urothelial carcinoma.
2. To determine management practices, perioperative factors, and short-term clinical outcome of urinary bladder paraganglioma.

METHODOLOGY

- This paper employed a single case report observational study design.
- The patient was a 49-year-old male who came to the clinic complaining of painless hematuria and a bladder mass, initially diagnosed with high-grade urothelial carcinoma.

- Imaging Studies:
  - CT KUB and CECT urogram were done to determine the location, size and involvement of the adjacent structures of the tumor.
  - Positron emission tomography-computed tomography (PET-CT) was done to assess the metabolic activity and to identify potential metastasis.
  - The surgical intervention performed on the patient was radical cystectomy and ileal conduit reconstruction.
  - The morphology of the tumor, muscle invasion, and margin status were examined with the help of the histopathological examination of the resected specimen.
  - Immunohistochemical staining for chromogranin, synaptophysin, cytokeratin 7 (CK-7), and S-100 was conducted to confirm neuroendocrine differentiation.
  - The Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) was applied to determine tumor differentiation and malignant potential.
  - Five lymph nodes received with the surgical specimen were examined for evidence of metastatic involvement.

Case Presentation

A 49-year-old male presented with painless gross hematuria persisting for two months. He had a 20-year history of chronic smoking and systemic hypertension, which was controlled with medication. No dysuria, flank pain, or constitutional symptoms were reported.

The patient had initially consulted an outside hospital, where a cystoscopic biopsy was reported as **high-grade urothelial carcinoma with invasion into the muscularis propria**. He was subsequently referred to our tertiary care center for further management, with a provisional plan for radical cystectomy and ileal conduit diversion.

Table 1. Patient Demographics and Clinical Presentation

Parameter	Details
Age / Sex	49 years / Male
Presenting Symptom	Painless gross hematuria (2 months)
Past Medical History	Hypertension (1 year, controlled)
Personal History	Chronic smoker (20 years)
Initial Diagnosis (Outside Hospital)	High-grade urothelial carcinoma with muscularis propria invasion
Referral Reason	Radical cystectomy with ileal conduit

Radiological Findings

A non-contrast computed tomography (CT) scan of the kidneys, ureters, and bladder (KUB) identified an infiltrative mass in the urinary bladder extending to the right vesico-ureteric junction (VUJ). Periserosal fat infiltration was observed, resulting in moderate right-sided obstructive uropathy. Cystoscopy with biopsy

confirmation and contrast-enhanced CT urography were recommended to exclude skip lesions.

A whole-body 18F-FDG PET-CT revealed a heterogeneously enhancing soft tissue growth at the base of the bladder, extending to the right anterior and posterior walls. The lesion measured **69.5 × 47.1 × 63.7 mm** (anteroposterior × transverse × craniocaudal dimensions) and showed increased metabolic activity. The tumour was noted to infiltrate perivesical fat and extend to the right vesico-ureteric junction, leading to ipsilateral moderate hydroureteronephrosis. No evidence of metabolically active disease was detected elsewhere in the body.

Table 2. Radiological Findings

Modality	Findings	Measurements / Notes
CT KUB (plain)	Infiltrative bladder mass involving right VUJ, periserosal fat infiltration	Moderate right-sided obstructive uropathy
CECT Urogram	Recommended for evaluation of skip lesions	–
PET-CT	Heterogeneously enhancing soft tissue mass at base, right anterior & posterior walls; perivascular extension infiltrating right VUJ	69.5 × 47.1 × 63.7 mm; increased metabolic activity; ipsilateral moderate hydroureteronephrosis; no other disease detected

Surgical Findings and Gross Pathology

Radical cystectomy with ileal conduit diversion was performed. The surgical specimen included the urinary bladder, bilateral ureters, urethra, and prostate. Gross examination revealed a brown, firm to hard tumor measuring **5 × 4.7 × 2.4 cm** originating from the anterior bladder wall and extending into the right lateral wall. The cut surface showed focal extension of the tumor to the inked resection margin.(Fig 1)

Fig 1. Cut Surface of the Tumor

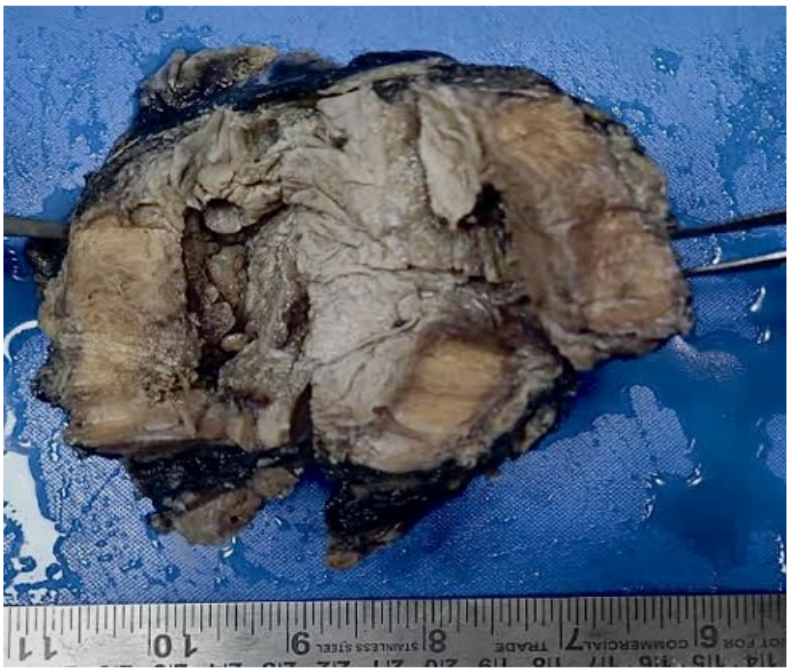


Table 3. Gross Pathology

Parameter	Findings

Specimen	Radical cystectomy including bladder, urethra, bilateral ureters, and prostate
Tumour Location	Anterior wall extending into right lateral wall
Tumour Size	5 × 4.7 × 2.4 cm
Consistency	Firm to hard
Margin Status	Focally extends up to inked anterior margin

Microscopic Findings

Histopathological examination revealed a tumour invading the muscularis propria, composed of nests of large polygonal cells with eosinophilic cytoplasm and uniform round nuclei. The nests were separated by delicate fibrovascular septa forming a **zellballen** pattern. Morphological features supported a provisional differential diagnosis of either the nested variant of urothelial carcinoma or paraganglioma.

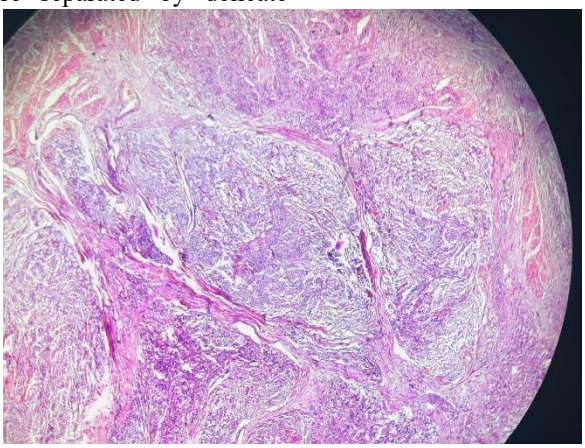


Figure 1 :Tumor cells arranged in zellballen pattern.

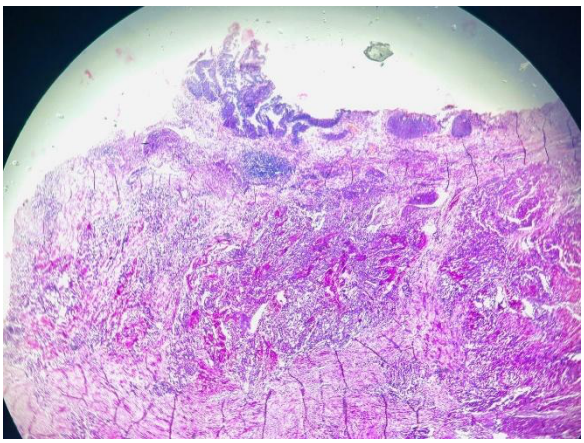


Figure 2:Low power view showing nests of tumor cells

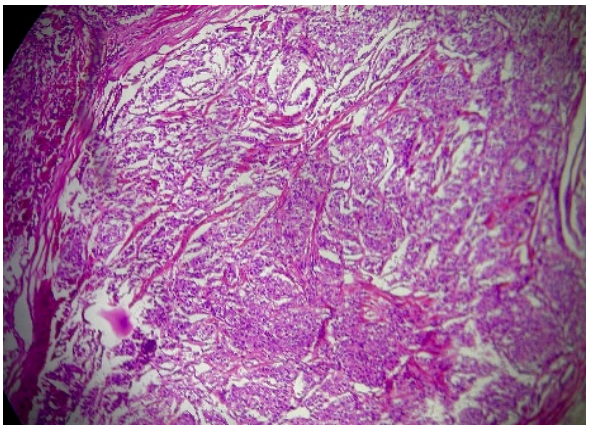


Figure 3:40x view showing tumor cells arranged in nests

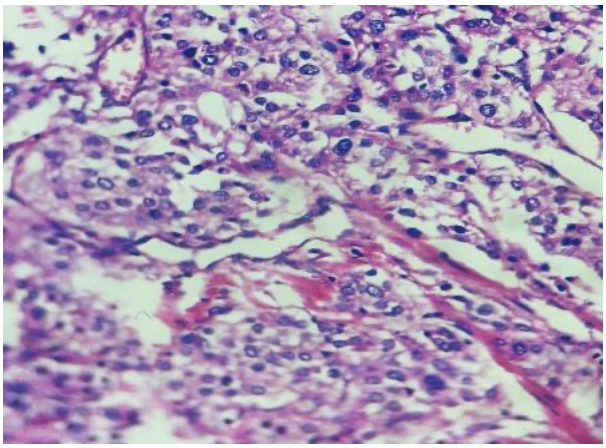
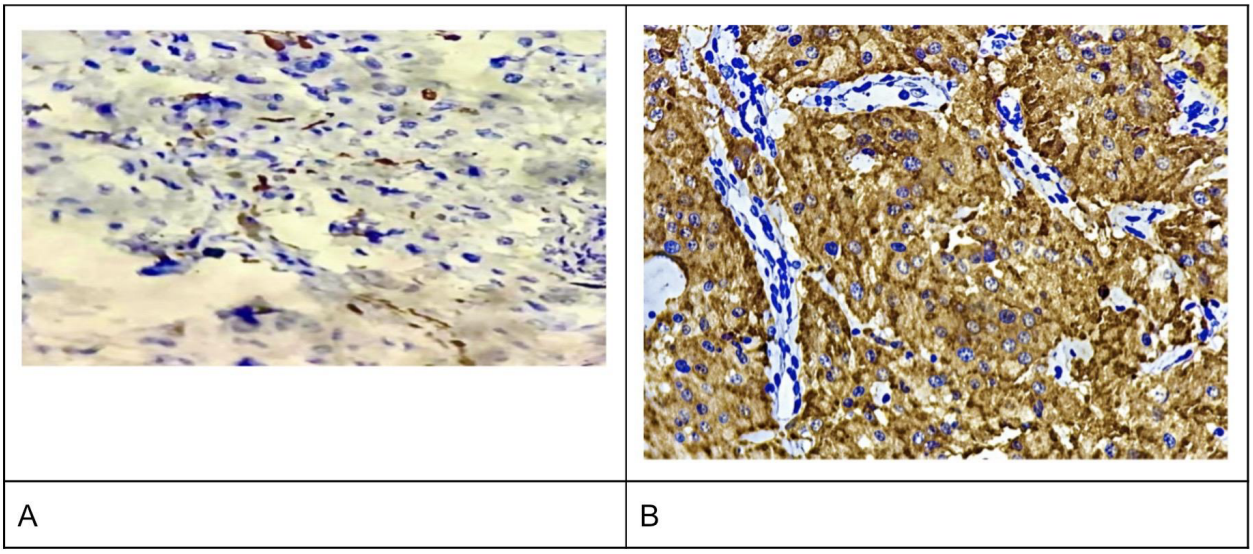


Figure 4: Tumor with pleomorphic chief cells.

Immunohistochemistry

Immunohistochemical analysis demonstrated strong positivity for **chromogranin** and **synaptophysin** in tumour cells, while cytokeratin 7 (CK-7) was negative. Sustentacular cells at the periphery exhibited focal **S-100** protein positivity. Collectively, these immunoprofiles support the diagnosis of **paraganglioma of the urinary bladder**.



A B

FIG 6 : A- IHC–Synaptophysin: Strongly cytoplasmic positivity is seen in 400.B- IHC – Chromagranin: Strongly cytoplasmic positivity is seen in 400.

Table 4. Microscopic and Immunohistochemistry Findings

Feature	Observation
Microscopy	Nests of large polygonal cells with eosinophilic cytoplasm and uniform nuclei; separated by delicate fibrovascular septa (zellballen pattern); muscularis propria invasion
Differential Diagnosis	Nested variant urothelial carcinoma vs paraganglioma
IHC: Chromogranin	Strongly positive
IHC: Synaptophysin	Strongly positive
IHC: CK-7	Negative
IHC: S-100	Sustentacular cells focally positive
GAPP Score	6 (moderately differentiated)
Tumour Extension	Perivascular soft tissue involvement; focal anterior margin; prostate involvement
Lymph Nodes	5 nodes received; negative

Histological Grading and Final Diagnosis

Grading was performed using the **GAPP (Grading System for Adrenal Pheochromocytoma and Paraganglioma)**, yielding a score of 6, corresponding to a moderately differentiated tumor. Microscopic examination revealed involvement of perivascular soft tissue and focal extension to the anterior margin. The prostate was involved, and the adjacent mucosa displayed reactive changes. Five regional lymph nodes were negative for tumour involvement. The final diagnosis was reported as **pT3a pN0 urinary bladder paraganglioma (neuroendocrine tumor) with a GAPP score of 6**.

Postoperative Course

The postoperative recovery proceeded without complications, and the patient was discharged in stable condition. At 12-month follow-up, clinical and radiological assessments demonstrated no evidence of recurrence.

Table 5. Final Diagnosis and Postoperative Outcome

Parameter	Details
Final Diagnosis	PT3a PN0 urinary bladder paraganglioma (neuroendocrine tumour)
Treatment	Radical cystectomy with ileal conduit
Postoperative Course	Uneventful; patient stable
Follow-up	12 months, no recurrence clinically or radiologically

DISCUSSION

Paragangliomas are rare neuroendocrine tumors that develop from extra-adrenal chromaffin cells linked to the sympathetic and parasympathetic nervous systems.1 Most extra-adrenal paragangliomas are found in the head, neck, or retroperitoneum. Involvement of the urinary bladder is very rare, making up less than 0.06% of all bladder tumors and under 1% of all paragangliomas.2–4 These tumors usually affect young adults between 20 and 40 years old and are more common in females, with a female-to-male ratio of about 3:1.7,8 Our patient, a 49-year-old male, shows that bladder paragangliomas can also appear in other demographic groups. Similar unusual cases have been described by Al-Zahrani2 and Pahwa et al.3

Bladder paragangliomas are classified as either functional or non-functional. Functional tumors secrete catecholamines and produce symptoms including post-micturition hypertension, palpitations, headache, and diaphoresis. In contrast, non-functional tumors typically present with painless hematuria, urinary frequency, or urgency 5,6 . In the present case, the patient exhibited only hematuria without adrenergic symptoms, a presentation consistent with non-functional tumors and like those described by Spessoto et al. 5 and Sherwani et al 6.

Preoperative diagnosis is often challenging. Small biopsy samples or deep muscular involvement can mimic high-grade urothelial carcinoma, particularly the nested variant.3,4 In this case, the initial transurethral biopsy performed at an outside hospital was misinterpreted as high-grade urothelial carcinoma with muscularis propria invasion, a scenario documented in prior case reports by Iwamoto et al.4 and Kappers et al.7.

Histologically, bladder paragangliomas exhibit **zellballen architecture**, consisting of nests of polygonal chief cells with eosinophilic or granular cytoplasm and uniform round-to-oval nuclei, separated by delicate fibrovascular septa.1,7 The examined tumor demonstrated classic zellballen patterns with invasion of the **muscularis propria** and focal involvement of the anterior margin, as well as secondary extension into the prostate and reactive changes in the adjacent mucosa.

Immunohistochemistry (IHC) is crucial for definitive diagnosis. Chief cells stain **strongly for chromogranin and synaptophysin**, are negative for CK-7, and surrounding sustentacular cells are **S-100 positive**, confirming neuroendocrine differentiation.9–11 Goldblum et al.14 and XiTu et al.15 reported similar IHC patterns, highlighting the importance of IHC in distinguishing paraganglioma from urothelial carcinoma variants.

The GAPP score of this tumor was 6, which means that it was a moderately differentiated tumor with intermediate malignant potential. Also, the negative lymph node involvement (pN0) is in line with published data, that correlates moderately differentiated, node-negative tumors with good prognoses.14,15.

Imaging is a significant process in preoperative planning and determining the extent of tumor. In this instance computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) showed a heterogeneously enhancing mass along the anterior and posterior bladder walls and the right vesicoureteric junction (VUJ) causing ipsilateral hydroureteronephrosis. It did not show any signs of distant metastasis. Likewise imaging features have been found Al-Zahrani2 and Iwamoto et al.4, emphasizing the importance of having cross-sectional imaging. Nonetheless, it requires histopathological diagnosis and immunohistochemistry to be firmly diagnosed (IHC).

Surgical excision is the first choice of treatment. Localized tumors are treated by partial cystectomy whereas large tumors that are infiltrative or multifocal lesions should be treated by radical cystectomy. In functional tumors, adrenergic blockade in preoperative period and close monitoring during the operation are important 12. In non-functional cases as it is in our case, antihypertensive coverage can be administered to minimize intraoperative

risk. When full excision is obtained, the postoperative outcomes are favourable, and few cases of recurrence are reported in the literature.8,13

Iodine-131 metaiodobenzylguanidine (131I-MIBG) therapy alone or in conjunction with external beam radiation has shown biochemical response in 67% and symptomatic response in up to 89% of patients with malignant or metastatic paragangliomas12,13 In severe cases of the disease, chemotherapy, like cyclophosphamide, vincristine, and dacarbazine (CVD) is usually used. Measurement of urinary catecholamine at 24 hours and a follow up at two weeks is a sure way of ensuring full removal of the tumor and normalcy of the biochemical markers.1

The case illustrates a few important points in respect to the diagnosis and treatment of bladder paraganglioma.

1. It is also worth mentioning the rarity and the unusual demographic since the patient is a middle-aged male with a diagnosis of non-functional bladder paraganglioma.

2. The chances of misdiagnosis are great as the first biopsy showed that it was high-grade urothelial carcinoma, which proves the difficulties of the diagnosis.

3. The use of immunohistochemistry (IHC) was vital, as chromogranin, synaptophysin, and S-100 staining proved that the cells were neuroendocrine differentiated.

4. Surgical treatment Surgical treatment radical cystectomy offered complete excision with a good prognosis.

5. Added to literature - contributes to the little that has been reported worldwide on bladder paragangliomas, with the necessity of urologists and pathologists being made aware of it.2–6,8–15

CONCLUSION

Urinary bladder paraganglioma is a very rare tumor that may resemble high-grade urothelial carcinoma, especially in non-functional cases manifesting itself in painless hematuria. Diagnosis is based on histopathology with immunohistochemistry, and chief cells have a positive result using neuroendocrine markers (chromogranin, synaptophysin) and other positive S-100 results of sustentacular cells. The identification of preoperative, attentive perioperative handling and proper excision of the tumor either partial or radical cystectomy, depending on the tumor size and invasion, is of paramount importance in maximizing patient outcomes and avoiding intraoperative complications.

The case discusses the significance of paraganglioma in the differential diagnosis of masses of the bladder irrespective of the demographics of the patient. To guide conclusive management, immunohistochemistry and radiological evaluation are necessary. Early diagnosis and total surgical excision are linked with a great prognosis. The reporting of rare cases like this will enhance clinical awareness and help in enhancing the diagnostic accuracy.

Limitations

This report has a single case study design, which limits the generalizability of the study. Some of the clinical history and preoperative investigations were acquired in other institutions and could have used non-standardized procedures. The briefness of the follow-up does not allow assessing the longitudinal outcomes, reoccurrence, and postoperative functional status. Another limitation is the lack of genetic or molecular studies including succinate dehydrogenase (SDH) mutation testing in evaluating hereditary biology and tumor biology.

Recommendations

1. Clinically observe paraganglioma in bladder masses, particularly, in cases of the initial biopsy of urothelial carcinoma with atypical histopathological characteristics.
2. Use extensive immunohistochemical profiling to make a correct diagnosis as opposed to urothelial carcinoma.
3. Use preoperative measures, such as the adrenergic blockade of patients with functional tumors, to reduce the morbidity associated with the perioperative period.
4. Recommend a long-term follow-up where imaging and urinary catecholamine testing are performed to enable an early detection of recurrence.
5. Take genetic testing into consideration of patients who have been selected to detect possible hereditary syndromes and inform family screening.

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