

**Canadian Urological Association Best Practice Report on the long-term followup for patients with pheochromocytomas**

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**Introduction****Background**

Pheochromocytoma is a tumor of the catecholamine-producing cells of the adrenal medulla. The incidence is estimated to be 1 to 2 cases per 100,000 individuals and they make up approximately 5% of incidental adrenal masses<sup>1</sup>.

Classical symptoms of pheochromocytomas include headache, episodic perspiration, tachycardia, flushing, nausea, and hypertension, although many can be asymptomatic<sup>1</sup>. These tumors can be sporadic or hereditary<sup>2</sup>. Familial cases account for up to 30% of tumors<sup>3</sup>. Pheochromocytomas can also occur outside the adrenal gland, known as paragangliomas, in up to 25% of cases<sup>4</sup>.

About 10% of pheochromocytomas are malignant<sup>5</sup>. Although there are several clinical and genetic factors that are associated with an increased risk of malignancy, at this time, there are no molecular, cellular, or histologic criteria that can reliably differentiate benign from malignant disease<sup>5</sup>. Therefore, malignancy is defined by the presence of clinical metastases. The most common sites for metastases are lymph nodes, bones, liver and lungs<sup>6</sup>.

Evaluation of suspected pheochromocytoma begins with confirming a biochemical disturbance by measuring plasma free metanephrines or urinary fractionated metanephrines, followed by computed-tomography (CT) imaging. Once a pheochromocytoma is confirmed, complete surgical resection of the tumor is advised, preferably via laparoscopic or robot assisted

adrenalectomy. The full details regarding work-up and treatment of pheochromocytomas is beyond the scope of this review, but there are recent published guidelines on this topic<sup>7</sup>.

Following surgery, patients are at risk for tumor persistence and recurrence. Despite an overall good prognosis, the disease can recur in up to 16% of patients within 10 years following surgery<sup>8,9</sup>. Recurrences may be local or metastatic and have been reported up to 53 years post initial resection, making long-term followup essential.<sup>10</sup> Extra-adrenal disease, hereditary pheochromocytomas, right sided tumors, bilateral tumors, and larger tumors are thought to be risk factors for recurrence. Currently, there is no consensus on the proper methodology for followup. There have been no randomized studies addressing optimal followup nor prospective registries to provide higher quality evidence for this issue. Important clinical questions remain regarding duration of followup and which tests should be used to detect and monitor recurrences.

### **Objective**

This *Best Practice Report* (BPR) aims to standardize clinical care regarding the long-term followup of patients operated on for pheochromocytomas, specifically with respect to the duration of follow up and the monitoring methods.

### **Methodology**

This best practice statement was developed using methodology consistent with GRADE. We limited our evidence synthesis to previously published studies examining the long-term followup of surgical patients with pheochromocytoma using PubMed, Medline, and the Cochrane Library database. The bibliographies of relevant articles were searched to avoid exclusion of meaningful articles. In this narrative review, focus was given to systematic reviews, related guidelines and comparative studies. In particular, a freely accessible clinical practice guideline on this topic was published in 2016 by the European Society of Endocrinology. This guideline addressed similar subject matter and scope that is of interest to the Canadian urology community. Therefore, recommendations from this guideline were endorsed or adapted to a Canadian urology context. Of the 11 recommendations from the European Society of Endocrinology, 2 were excluded as they were deemed not applicable and beyond the scope of our review, 4 were adopted with modifications to better suit a Canadian urologist's context and 5 were adopted without modification. Other statements were based on a systematic review of the literature and one clinical principle was added.

### **Genetic testing**

Pheochromocytomas and paragangliomas (PPGLs) carry a higher degree of heritability than most solid tumours. In the past 15 years, germline mutations in a dozen genes have been identified and it is estimated that ~40% of patients carry a causal germline mutation. Hereditary disease linked with pheochromocytomas include neurofibromatosis type 1 (caused by mutations in *NF1*), multiple endocrine neoplasia type 2 (MEN2; linked with mutations in *RET*), von Hippel–Lindau disease (associated with mutations in *VHL*), hereditary paraganglioma (caused by

mutations in the SDHx group of genes [*SDHA*, *SDHB*, *SDHC*, *SDHD* and *SDHAF2*]), familial pheochromocytoma (caused by mutations in *TMEM127* or *MAX*), polycythemia paraganglioma syndrome (associated with mutations in *EPAS1* [also known as *HIF2A*]) or hereditary leiomyomatosis and renal cell cancer syndrome (linked with mutations in *FH*)<sup>12</sup>.

Identification of an underlying mutation is critical in guiding patient management and genetic counseling. For example, patients with mutations in *SDHB* can develop particularly aggressive and rapidly progressing pheochromocytomas/paragangliomas as well as other renal cancers and gastrointestinal stromal tumours<sup>12</sup>. Furthermore, identification of a hereditary syndrome allows for earlier diagnosis and treatment of pheochromocytomas and other syndromic manifestations in relatives.

**Recommendation #1: We recommend all patients with PPGLs be considered for referral for genetic testing.** (*Strong recommendation, moderate quality evidence*)

### *Perioperative workup*

Traditionally, biochemical testing for pheochromocytomas was done by measurements of urine catecholamines, often in conjunction with catecholamine metabolites such as vanillylmandelic acid and metanephrines. Advances in assay technology and our understanding of catecholamine metabolism have led to a newer emphasis on measurements of urine and plasma metanephrines, including normetanephrine and metanephrine, as well as methoxytyramine, a dopamine metabolite. Compared to catecholamines, measurement of metanephrines is advantageous in detecting tumors that release catecholamines episodically or in low amounts and they are a more specific marker for catecholamine produced in chromaffin cells and associated tumors<sup>13</sup>.

Lenders et al. provided early evidence that plasma free metanephrines had a superior diagnostic sensitivity and equivalent specificity compared to the other tests<sup>14</sup>. This was supported by a larger National Institutes of Health multicenter cohort study published in 2002 involving over 800 patients which compared plasma metanephrines versus plasma catecholamines, urinary catecholamines, urinary total and fractionated metanephrines and urinary vanillylmandelic acid<sup>15</sup>. They reported a sensitivity of 99% for plasma free metanephrines versus a sensitivity of 64 to 97% for the other biochemical tests. The specificity of plasma free metanephrines was 89%. Given these findings they concluded that plasma free metanephrines provided the best test for excluding or confirming pheochromocytoma. There have been multiple subsequent studies confirming the high diagnostic accuracy for plasma free metanephrines.

In 2007, Perry et al. showed that urine fractionated metanephrines measured by mass spectrometry provided a sensitivity of 97% and specificity of 91% for the diagnosis of pheochromocytomas and paragangliomas, results comparable to those reported of plasma metanephrines in other studies<sup>16</sup>. There has not been a direct comparison of plasma metanephrines versus urinary fractionated metanephrines measured by mass spectrometry, and thus it remains unclear if one test is superior to the other. It is important to highlight that these

studies have been done in the diagnostic phase (i.e. pre-resection) and have been extrapolated to be accurate in the setting of monitoring for disease recurrence.

In patients with elevated metanephrines preoperatively, metanephrine determinations should be repeated post-operatively to document complete resection of the tumor. When the postoperative metanephrines fail to normalize, persistent disease should be strongly suspected. Further imaging testing to confirm and locate residual catecholamine-secreting tissue should be undertaken.

**Recommendation #2: We suggest repeating plasma and/or 24-hour urinary metanephrines at first postoperative followup to ensure complete resection.** (*Strong recommendation, low quality evidence*)

**Recommendation #3: We suggest monitoring for PPGL recurrence by annually measuring plasma free metanephrines and/or 24-hour urinary fractionated metanephrines.** (*Strong recommendation, low quality evidence*)

### ***Duration of followup***

In a recent systematic review, Amar et al. studied the incidence and factors associated with recurrence or new tumors after complete resection of pheochromocytomas<sup>17</sup>. They included 38 studies from 1980 to 2012 on patients with pheochromocytomas who had complete resection and at least 1 month follow up. The incidence rates from individual studies were pooled in a meta-analysis.

Of the 38 studies included, there was one randomized control trial and one prospective cohort study, with the rest being retrospective cohorts. There was a total of 2509 patients. The median age of patients was 42 years and median tumor size was 48mm. The duration of followup ranged from 14 to 180 months, with a median of 84 months<sup>17</sup>.

The overall rate of recurrent disease was calculated as 0.95 events/100 person-years (95% confidence interval (CI) 0.68, 1.21), which equates to a 5-year cumulative incidence of 4.7%. Of these new events, 22% were new tumors, 23% were local recurrences, and 55% were metastases. The median time from surgery to recurrent disease was 60 months, and ranged from 3 to 204 months<sup>17</sup>.

Factors associated with recurrence were also studied. Familial disease was identified as a main independent risk factors of recurrent disease. The presence of extra-adrenal disease (paraganglioma) was a strong predictor and younger age and large tumor size were weak predictors of recurrence<sup>17</sup>.

The European Society of Endocrinology guideline reported results from the European Network for the Study of Adrenal Tumours (ENS@T) database comprised of 1153 patients from six centers<sup>11</sup>. 701 patients had complete resection of the primary tumor and documented follow

up of at least 6 months. In this database 34% had a genetic or syndromic disease, median age was 46 years and median tumour size was 44mm. Median follow up was 54 months.

The risk of recurrence was 10 % over the first 5 years of follow up (new tumors 42%, local recurrences 13% and metastatic recurrences 45%). The incidence of new events did not decline after 5 years of followup, but estimates after 10 years of followup were imprecise due to the small numbers of patients for whom data were available. Again, extra-adrenal disease, age < 20 years, familial pheochromocytoma, and tumor size >150 mm appeared to correlate with an increased risk of recurrence<sup>11</sup>.

In both these studies, the incidence of new events is lower than previous estimates. Even after long and uneventful follow up there can be recurrent disease. This appears more common in cases of familial and extra-adrenal disease. There is no tumor size below which there is no risk of a new event nor is there any subgroup in which follow up may be safely abandoned.

**Recommendation #4: We suggest annual followup for at least 10 years following complete resection to monitor for local or metastatic recurrences or new tumors.** (Weak recommendation, very low quality evidence).

**Recommendation #5: We suggest high-risk patients (young, genetic disease, larger tumor and/or a paraganglioma) be offered life-long annual followup.** (Weak recommendation, very low quality evidence).

### *Specific conditions*

#### *Mild or borderline elevations in metanephrines*

Some patients only have a mild or moderate elevation in free plasma metanephrines levels (less than fourfold increase) preoperatively. In this subset, secondary confirmatory testing can be pursued, often facilitated by an endocrinology referral. These include clonidine suppression testing and chromogranin A testing.

Clonidine suppresses norepinephrine production by the sympathetic nervous system but not by pheochromocytomas. Determining normetanephrine levels before and after clonidine administration can help confirm the diagnosis in equivocal cases<sup>18</sup>.

Chromogranin A determination exists in secretory vesicles of the neuroendocrine and nervous systems and has been shown to be elevated in patients with pheochromocytoma. Determining pre-operative chromogranin A levels can help confirm the diagnosis, and in such cases can also be used for annual post-operative surveillance<sup>19</sup>.

**Recommendation #6: We suggest using annual clonidine suppression or chromogranin A testing for follow up of patients with positive pre-operative results** (Weak recommendation, very low quality evidence).

***Biochemically negative disease***

Pheochromocytomas can rarely be biochemically negative. This appears to occur most frequently in cases of extra-adrenal disease located in the skull base/neck and secondary to mutations in *SDHx*<sup>20</sup>. Evidence suggests these tumors lack the biosynthetic machinery necessary for catecholamine production. In such cases, imaging studies are the principal means of detecting tumors. Such patients remain at risk for the development of biochemically active tumours after initial tumor resection<sup>21</sup>.

**Recommendation #7: We suggest imaging tests be obtained every 1-2 years, in addition to yearly metanephrines for patients with biochemically negative disease. (Weak recommendation, very low quality evidence).**

***Imaging***

Computed tomography and magnetic resonance imaging are excellent imaging modalities for characterizing adrenal lesions. Imaging should be sought in patients with elevated metanephrines post-operatively, as well as patient whose metanephrines were normal or not measured preoperatively. A subset of patients with elevated post-operative metanephrines, will have no detectable disease on CT or MRI. Historically, metaiodobenzylguanidine (MIBG) scintigraphy has been the preferred test in this setting to localize disease. MIBG is a small-molecule analog of norepinephrine, and when tagged with iodine is a highly sensitive and specific test for pheochromocytoma<sup>4</sup>. More recently, Fluorine-18 fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET) has emerged for definitive staging in patients with pheochromocytoma. In a study of over 200 patients with adrenal and extra-adrenal pheochromocytoma, <sup>18</sup>F-FDG PET had superior test characteristics compared to CT, MRI, and MIBG scintigraphy for almost all patients<sup>22</sup>. <sup>18</sup>F-FDG PET, however, is not widely available and is limited due to cost. The specific indications for each imaging test are beyond the scope of this review but can be found in the 2014 Endocrine Society Clinical Practice Guideline on pheochromocytomas and paragangliomas<sup>7</sup>.

**Recommendation 8: For biochemical recurrence, we suggest CT/MRI as first line imaging modalities, and <sup>123</sup>I-metaiodobenzylguanidine (MIBG) scintigraphy as second line. (Weak recommendation, very low quality evidence)**

***Malignant pheochromocytoma***

Malignant pheochromocytomas are rare. They are associated with significant morbidity due their ability to invade organs and dysregulate the autonomic nervous system<sup>23</sup>. Given its rarity, there are few prospective studies investigating potential therapies for the disease, and their impact on survival and quality of life is difficult to ascertain. Management is largely guided by retrospective studies' findings, expert consensus and clinical experience. Therapies that have

been pursued include surgery, therapeutic  $^{131}\text{I}$ -labeled metaiodobenzylguanidine (MIBG) internal radiotherapy, chemotherapy, targeted therapies, and watchful waiting<sup>23</sup>.

***Clinical principle: Malignant pheochromocytoma treatment should be discussed in a multidisciplinary setting including surgeons, interventional radiologists, endocrinologists, oncologists, and nuclear medicine physicians.***

### Conclusions

The risk of recurrence following complete resection of pheochromocytoma is low but significant. Recurrences can occur many years after surgery and are seen more frequently in patients with a genetic disease, young age, large tumor, and extra-adrenal disease. All patients should be considered for genetic testing. Patients should be screened with plasma and urinary metanephrines post-operatively, and yearly thereafter for at least ten years, and potentially indefinitely for higher-risk patients.

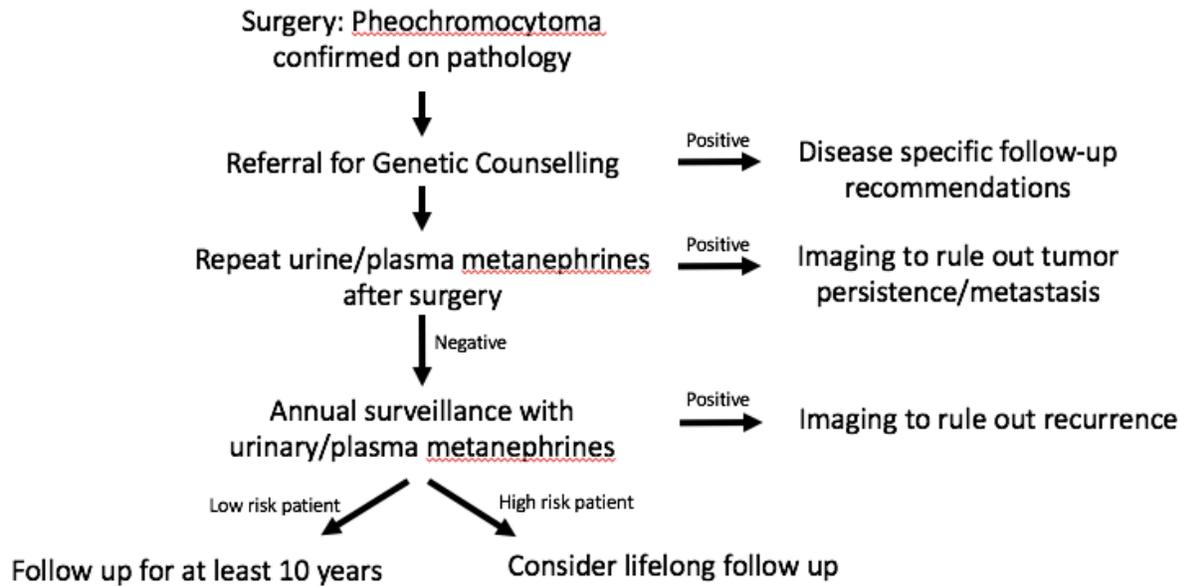
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Figures and Tables

Fig. 1. Algorithm for followup of pheochromocytoma.



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<b>Table 1. Summary of recommendations</b>	
<b>Recommendation</b>	
#1	<b>We recommend all patients with PPGLs be considered for referral for genetic testing.</b> ( <i>Strong recommendation, moderate quality evidence</i> ).
#2	<b>We suggest repeating plasma and/or 24-hour urinary metanephrines at first postoperative followup to ensure complete resection.</b> ( <i>Strong recommendation, low quality evidence</i> ).
#3	<b>We suggest monitoring for PPGL recurrence by annually measuring plasma free metanephrines and/or 24-hour urinary fractionated metanephrines.</b> ( <i>Strong recommendation, low quality evidence</i> ).
#4	<b>We suggest annual followup for at least 10 years following complete resection to monitor for local or metastatic recurrences or new tumors.</b> ( <i>Weak recommendation, very low quality evidence</i> ).
#5	<b>We suggest high-risk patients (young, genetic disease, larger tumor and/or a paraganglioma) be offered life-long annual followup.</b> ( <i>Weak recommendation, very low quality evidence</i> ).
#6	<b>We suggest using annual clonidine suppression or chromogranin A testing for follow up of patients with positive pre-operative results</b> ( <i>Weak recommendation, very low quality evidence</i> ).
#7	<b>We suggest imaging tests be obtained every 1-2 years, in addition to yearly metanephrines for patients with biochemically negative disease.</b> ( <i>Weak recommendation, very low quality evidence</i> ).
#8	<b>For biochemical recurrence, we suggest CT/MRI as first line imaging modalities, and <sup>123</sup>I-metaiodobenzylguanidine (MIBG) scintigraphy as second line.</b> ( <i>Weak recommendation, very low quality evidence</i> ).
#9	<b>Malignant pheochromocytoma treatment should be discussed in a multidisciplinary setting including surgeons, interventional radiologists, endocrinologists, oncologists, and nuclear medicine physicians.</b> ( <i>Clinical principle</i> )