Perioperative Management of Pheochromocytomas and Sympathetic Paragangliomas

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Abstract
Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia, respectively. PPGLs have the highest degree of heritability among endocrine tumors. Currently, ~40% of individuals with PPGLs have a genetic germline and there are at least 12 different genetic syndromes related to these tumors. Metastatic PPGLs are defined by the presence of distant metastases at sites where chromaffin cells are physiologically absent. Approximately 10% of pheochromocytomas and ~40% of sympathetic paragangliomas are linked to metastases, explaining why complete surgical resection is the first-choice treatment for all PPGL patients. The surgical approach is a high-risk procedure requiring perioperative management by a specialized multidisciplinary team in centers with broad expertise. In this review, we summarize and discuss the most relevant aspects of perioperative management in patients with pheochromocytomas and sympathetic paragangliomas.

Key Words: pheochromocytomas, paragangliomas, perioperative, management

Abbreviations: CT, computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PPGL, pheochromocytoma/paraganglioma; SDHx, succinate dehydrogenase subunit x; VHL, von Hippel–Lindau.

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla (pheochromocytomas, 80%-85%) or extra-adrenal paraganglia (paragangliomas, 15%-20%), respectively [1]. PPGLs have the highest heritability among endocrine tumors [2]. Currently, about 40% of individuals with PPGLs have a genetic germline mutation and at least 12 different genetic syndromes are related to these tumors [3, 4]. This genetic diversity is more relevant in guiding a personalized approach in patients with PPGLs.

Metastatic PPGLs (mPPGLs) are defined by the presence of tumor in nonchromaffin tissues [5]. About 10% to 20% of the patients with PPGLs develop metastatic disease [6]. Due to its high malignant potential, curative surgical resection should be offered to all patients with localized disease. However, surgery is a high-risk procedure requiring perioperative management by a specialized multidisciplinary team in centers with broad expertise [7, 8]. Improving the clinical management, surgical techniques, and anesthetic support dropped the mortality rate of functioning PPGL surgery to around 0% to 2.9% [7, 9, 10]. In this review, we summarize and discuss the most relevant aspects of perioperative management in patients with pheochromocytomas and sympathetic paragangliomas.

Genetics and Pathogenesis
Approximately 40% of PPGL patients carry a germline mutation in one of about 20 related genes [11]. These driver genes are associated with 12 genetic syndromes. Paraganglioma, multifocal or metastatic disease, familial history, or age at diagnosis of younger than 45 years are associated with a higher risk of having germline mutation [8, 12].

Pheochromocytomas and paragangliomas can be classified by their pathogenesis into 3 main clusters (Table 1 and Fig. 1): (1) hypoxia/pseudohypoxia; (2) kinase signaling group; and (3) Wnt signaling pathway. Each subgroup has a distinct molecular-biochemical-imaging signature [3, 13]. Inactivating mutations in succinate dehydrogenase subunits (SDHx [SDHA, SDHB, SDHC, SDHD]), succinate dehydrogenase complex assembly factor 2 (SDHAF2), fumarase hydratase (FH), dihydrodipioamide S-succinyltransferase (DLS7), and malate dehydrogenase 2 (MDH2) result in the accumulation of Krebs cycle metabolites, such as succinate, fumarate, pyruvate, or glutamine, which is followed by activation of hypoxia-inducible factor alpha target genes (Cluster 1A). The von Hippel-Lindau tumor suppressor (VHL), endothelial PAS domain protein 2 (EPAS1), and egl-9 prolyl hydroxylase 1 and 2 (EGLN1/2) genes are directly involved in hypoxic signaling (Cluster 1B). Cluster 1A has a more aggressive phenotype with an increased risk of metastases, younger age presentation, and a higher frequency of paragangliomas when compared to other clusters [14, 15]. Nevertheless, Cluster 1B, mainly represented by VHL, has a low metastatic risk with more pheochromocytoma at presentation [3, 14].

Dysregulation of the PI3K/mTOR pathway/receptor kinase (Cluster 2) signaling results from mutations in the
### Table 1. Genetic, biochemical, and clinical characterization of the 3 main clusters of pheochromocytomas and paragangliomas

| Molecular pathway          | Genes | Mutation type | Metastatic risk | Tumor location | Biochemical | Other manifestations |
|---------------------------|-------|---------------|-----------------|----------------|-------------|----------------------|
| **Cluster pseudohypoxia** |       |               |                 |                |             |                      |
| **1A**                    |       |               |                 |                |             |                      |
| SDHA                      | G, S  | Moderate      | TA PGL          | N/D            | GIST        |                      |
| SDHB                      | G, S  | High          | TA PGL          | N/D            | GIST and RCC|                      |
| SDHC                      | G, M, S| Low           | HN PGL          | N/D            | GIST        |                      |
| SDHD                      | G, S  | Moderate      | HN PGL          | N/D            | GIST and pituitary adenomas | |
| SDHA2F                    | G     | ?             | HN PGL          | N              | NR          | Hemangioblastoma, RCC, pancreatic neuroendocrine tumors, retinal angiomas, testicular tumors |
| *FH*                      | G     | High          | PHEO/TAPGL      | N              | N/A         | Polycythemia, somatostatinomas, retinal abnormalities, organ cysts (Pacak-Zhuang syndrome) |
| **Cluster Pseudohypoxia** |       |               |                 |                |             |                      |
| **1B**                    |       |               |                 |                |             |                      |
| VHL                       | G, M, S| Low           | PHEO            | N              | Hemangioblastoma, RCC, pancreatic neuroendocrine tumors, retinal angiomas, testicular tumors |
| *EPAS1*                   | M, S  | High          | TA PGL          | N              | NR          | Congenital anomalies (Costello syndrome) |
| **Cluster 2 Receptor**    |       |               |                 |                |             |                      |
| **kinase signaling**      |       |               |                 |                |             |                      |
| *RET*                     | G, S  | Low           | PHEO            | A              | Medullary thyroid carcinoma, parathyroid adenoma |
| *NF1*                     | G, M, S| Moderate     | PHEO            | A              | Cafe-au-lait spots, Lisch nodules in the eye, neurofibromas |
| **Cluster 3 Wnt signaling** |     |               |                 |                |             |                      |
| **MAML3**                 | S     | High          | PHEO/TAPGL      | N/A            | NR          |                      |

Abbreviations: A, adrenergic; D, dopaminergic; G, germline; GIST, Gastrointestinal stromal tumor; HN, head and neck; M, mosaicism; N, noradrenergic; NR, not reported; PGL, paraganglioma; PHEO, pheochromocytoma; RCC, Renal cell carcinoma; S, somatic; TA, thoracic and abdominal.

RET proto-oncogene, neurofibrin 1 (NF1) tumor suppressor, H-RAS proto-oncogene, transmembrane protein 127 (TMEM127), Myc-associated factor X (MAX), B-Raf proto-oncogene (BRAF), or chromatin remodeler ATRX [16]. In this cluster, most PPGls have a low metastatic risk, except those with somatic ATRX mutations [13].

Recently, a third cluster was identified based on the presence of Cold shock domain-containing E1 gene (CSDE1) mutations and Mastermind-like family of transcriptional co-activators (MAML3) fusion genes, leading to Wnt signaling activation [17]. PPGls harboring somatic mutations in CSDE1 or MAML3 fusion genes are sporadic and associated with poor clinical outcome [17].

Around 70% of children with PPGls have germline mutations in PPGl susceptibility genes [18]. *SDHB* was the most frequent mutated gene in 39% of children with PPGls from Europe and the USA [19]. In contrast, children from South America with PPGls had a predominance of germline *VHL* mutations and a low rate of malignancy at 12% [18,20,21].

Genetic screening with a next-generation sequencing panel is recommended for all patients with PPGl, regardless of their age or familial history [14,22]. Lifetime penetrance of *SDHB* germline mutations varies from 15% to 22% by the age of 50 years but can be higher at older ages (40%-50%) [14,23,24]. The *SDHD* gene exhibits a higher penetrance (40%), but the maternal allele imprint limits the transmission of the disease [23]. Buffet et al demonstrated that an early and active surveillance of patients with germline *SDHx* or *VHL* mutations had a positive impact on their management and clinical outcome, including the diagnosis of metastatic lesions [25]. *SDHB* mutations are the most well-established risk factor to predict metastatic disease (40%-50% of cases) [13,26-28].

### Clinical Presentation and Diagnosis

The classical clinical presentation is paroxysmal episodes of hypertension associated with headache, sweating, and palpitation secondary to abrupt catecholamine release. The most frequent signs and symptoms are hypertension (81%), headache (60%), palpitation (60%) and diaphoresis (52%) [29]. Less common signs and symptoms are fatigue, nausea, weight loss, constipation, flushing, anxiety, pallor, tremulousness, chest or abdominal pain, and nausea [30]. Recently, a multicentric European study compared a cohort of 245 patients with PPGL with a cohort of 1820 patients in whom PPGL diagnosis was excluded [31]. Compared to patients without PPGL those with PPGL had significantly more diaphoresis, palpitations, pallor, tremor, and nausea whereas headache, flushing, and other symptoms did not differ.
Hypertension in PPGL patients has a higher blood pressure variability compared to essential hypertension [32]. Reverse or inverted dipping (the phenomenon characterized by higher nighttime compared with daytime blood pressure values) is present in 32% to 50% of patients with PPGLs [33, 34]. Nevertheless, some patients present only sustained hypertension without adrenergic crisis and can even be normotensive in 17% to 32% of cases [35]. Acute cardiovascular events are an important cause of mortality in PPGL patients [10]. Anesthesia, tumor manipulation, exercise, and many medications (opiates, metoclopramide, and glucagon) are common triggers for catecholaminergic crisis (Table 2) [29].

Biochemical diagnosis is the first step to investigate suspicious patients [8]. An increase (>2 times the upper limit of the normal range) in plasma or 24-hour urinary free normetanephrine and metanephrine are usually diagnostic [12]. Plasma free or 24-hour urinary 3-methoxytyramine is useful to detect dopamine-producing PPGLs [6]. It is known that plasma and urinary normetanephrines and metanephrines are more accurate than fractionated catecholamine (epinephrine, norepinephrine, and dopamine) and vanillylmandelic acid measurements [36]. These metabolites have a high diagnostic accuracy due to their continuous production from catecholamines leaking from storage vesicles within tumor cells [37]. Plasma or urinary free normetanephrines and metanephrines in the normal range reliably exclude PPGL in symptomatic patients. Measurements of plasma free normetanephrines and metanephrines have a higher diagnostic sensitivity (97.9%) than urinary free (93.4%) metabolites but similar specificities (94%) [38]. Plasma free normetanephrines and metanephrines are superior to urinary free metabolites in patients with highly suspected PPGL, such as individuals with a previous history of PPGL and/or hereditary risk for PPGL. Liquid chromatography with tandem mass spectrometry is the currently preferred method for biochemical measurement, with optimal accuracy and reduced analytical interference by drugs [6]. The supine position for at least 20 minutes before taking blood samples for plasma normetanephrine and metanephrine measurement is standard and reduces false-positive tests [39].

Any clinical condition causing chronically elevated sympathetic activity or medication use (antidepressants and antipsychotic agents) could cause mild elevations in endogenous catecholamines and lead to a false-positive test. Therefore, the medications might be discontinued (if possible) at least 2 weeks before hormonal reassessment [12]. If plasma free normetanephrines remain elevated (<2 times the upper limit of the normal range) after interfering removal, the clonidine suppression test can be helpful to exclude false-positive tests [40].

Computed tomography (CT) is the first-choice imaging modality to investigate tumors [36]. Magnetic resonance imaging (MRI) could be performed to detect head and neck paragangliomas, in patients with allergy to CT contrast, or in patients in whom radiation exposure is a concern [6]. Functional imaging modality like [123I]-metiodobenzylguanidine (123I-MIBG) scintigraphy, 68Ga-DOTA-somatostatin (68Ga-SSA), or 18F-fluorodihydroxyphenylalanine (FDOPA) positron emission tomography (PET)/CT analog is indicated for patients with an increased risk for metastatic or multifocal disease, large tumor (>5 cm) or paragangliomas of any size [6, 8, 12]. Recent findings showed that MIBG scintigraphy did not improve the diagnostic accuracy for initial localization of PPGLs [41]. Functional imaging preference should be modified according to the tumor location and genetic diagnosis. 68Ga-SSA is the most accurate functional imaging for paragangliomas and Cluster 1A (SDHx mutations) tumors,
whereas $^{18}$F-FDOPA and $^{123}$I-MIBG are the first-choice functional imaging in pheochromocytomas and Cluster 1B tumors [14, 42]

**Preoperative Care**

All patients with pheochromocytomas and sympathetic paragangliomas should benefit from adequate preoperative clinical care [43]. Nevertheless, this clinical management has a low quality of evidence with few prospective trials. The evidence is mainly based on observational studies and expert opinion [7]. The preoperative evaluation consists of cardiac risk assessment, blood pressure and heart rate control, and hypovolemia correction. This clinical preoperative care aims at avoiding paroxysmal PPGLs crisis before surgery and reduce intraoperative hemodynamic instability [44].

In order to estimate the perioperative risk, cardiac evaluation is necessary and should include an electrocardiogram and echocardiogram, besides a history and clinical examination [45]. The excessive catecholamine release and resultant hypertension can contribute to clinically significant changes in the cardiovascular system such as increased arterial stiffness, vasoconstriction of the coronary arteries, and tachyarrhythmias [9]. We recommend that normotensive patients should perform a 24-hour ambulatory blood pressure monitoring to exclude paroxysmal hypertension. The blood pressure monitoring could also provide better understanding for blood pressure adjustment, especially in outpatient care.

Blood pressure control is crucial before surgery [44]. A target blood pressure of less than 130/80 mmHg and an upright systolic blood pressure > 90 mmHg is recommended [8]. Antihypertensive medications should be initiated at least 14 days before surgery and the surgery should be postponed if blood pressure control was not complete achieved. The preoperative medication approach is illustrated in Fig. 2. According to the main consensus guidelines, the α-adrenergic receptor blockers (doxazosin or phenoxybenzamine) are the first-choice drug class to minimize perioperative complications (Table 3) [6, 8]. These drugs specifically block the overstimulation of α-adrenergic receptors by the high levels of circulating catecholamines [44]. Phenoxybenzamine, a nonselective and noncompetitive α, and α, adrenergic receptor blocker, has a longer duration of action and is more associated with orthostatic hypotension and reflex tachycardia [46]. Doxazosin, a selective α, adrenergic receptor blocker, has a shorter half-life and should be started at 1 mg twice per day and tittered to a median dose of 10 to 14 mg/day (up to 32 mg).

Whether selective (doxazosin) α-adrenergic receptor blockers are more preferred than nonselective (phenoxybenzamine) is not well known in the literature [6]. Either selective or nonselective may be given according to personal experience. Compared to phenoxybenzamine, doxazosin is most prescribed due to its lower cost and worldwide availability. Nonselective α-blocker are associated with less intraoperative hypertension rates than selective agents with similar hypotension and vasopressor needs [47]. Morbimortality is similar in these 2 types of α-blockers [10, 47]. The α-adrenergic blocker treatment is associated with orthostatic hypotension, reflex tachycardia, dizziness, and syncope particularly when using phenoxybenzamine [48, 49].

Doxazosin use should be discontinued around 12 hours before surgery to reduce hypotension after tumor removal. Because of its longer half-life, phenoxybenzamine should be stopped 24 hours before surgery.

Recently, the efficacy of phenoxybenzamine and doxazosin was evaluated in the PRESCRIPT trial [50]. The primary endpoint was the total duration of blood pressure during surgery outside a predefined target range and did not differ between phenoxybenzamine and doxazosin. Phenoxybenzamine was more effective in preventing intraoperative hemodynamic instability but its association with a better clinical outcome could not be established [50].

Calcium channel blockers are the most preferred add-on class of agent in PPGL patients with uncontrolled hypertension on α-blockers [51]. Calcium channel blockers therapy should be added in patients on α-blockers without blood pressure control or with side effects related to α-blockers, such as postural hypotension [6, 9]. Nicardipine, amlodipine, and nifedipine are the most frequently indicated. Calcium channel antagonists inhibit norepinephrine-mediated transmembrane calcium influx in vascular smooth muscles [9]. Few studies with small cohorts demonstrated similar intraoperative hemodynamic stability when comparing calcium channel blockers to α-blockers in monotherapy for perioperative PPGL management [51-53]. However, only small cohorts of PPGLs with less severe hypertension were studied. Therefore, the α-adrenergic blockers remain as the first treatment choice for blood pressure control in PPGL patients.

Metyrosine is a tyrosine hydroxylase inhibitor which acts by reducing circulating catecholamine levels by 50% to 80%. It should be considered before surgery in PPGL patients at high-risk for a large release of catecholamines and cardiovascular complications or when α-adrenergic blockers are not well tolerated or ineffective [54]. Their side effects are generally mild and self-limited, with sedation being very common. However, the metyrosine use is limited by its unavailability in several countries and high cost.

According to the main consensus, normotensive patients with pheochromocytoma and sympathetic paraganglioma require presurgical α-blockade; however, small studies did not show a benefit from α-blockade [6, 53, 56]. The rationale to support this recommendation is that these patients may also

![Figure 2. Clinical preoperative approach for patients with pheochromocytomas and paragangliomas. Abbreviations: BP, blood pressure; HR, heart rate.](https://academic.oup.com/jes/article/6/2/bvac004/6507789 by guest on 26 February 2022)
be at an increased risk of abrupt catecholamines release and intraoperative hemodynamic instability [6, 49]. In normotensive patients, α-blocker drugs should be gradually uptritrated to the highest tolerable dose.

Heart rate control is another important goal for perioperative management. The recommended target heart rate is 60-70 bpm seated and 70-80 bpm standing [6, 8]. Preoperative use of β-adrenergic receptor blockers is indicated to control reflex tachycardia only after administration of α-adrenergic receptor blocker use, because of the potential risk of hypertensive crisis due to an unopposed stimulation of α-adrenergic receptors [12, 35]. The lack of compensatory vasodilatation due to β-receptor inhibition is another reason to avoid β-blockers before α-blockade. Then, patients with the heart rate within the target range do not need to receive β-blockers, unless for another clinical indication. Both nonselective and β1-selective adrenergic receptor blockers can be used, as there is no evidence of clinical difference between both [35].

A high-sodium diet (3-5 g/d) is recommended during treatment with α-adrenergic receptor blockers, as well as an intravenous volume load with 1 to 2 liters of saline infusion in the last 24 hours prior to the surgery [8]. The rationale is to reduce the risk of preoperative orthostatic hypotension and postoperative hypotension. Nevertheless, the evidence to endorse this common practice is limited [8]. Caution is required in patients with fluid overload restrictions.

Drugs that stimulate α-adrenergic receptors, inhibit noradrenaline re-uptake, or interfere with catecholamine metabolism can precipitate a sympathomimetic crisis [6, 8, 44]. Unopposed β-blockers (before α-adrenergic blockade) should also be avoided in patients with PPGL (Table 2).

Pre-anesthetic hydrocortisone infusion is recommended for bilateral adrenalectomies even in patients undergoing cortical-sparing surgery. Stress doses of hydrocortisone might be reported to surgeons and anesthetist team before the procedure. These patients should receive hydrocortisone (50 mg intravenously every 8 hours) during the immediate postoperative period until the transition to oral hormone replacement with hydrocortisone (20-30 mg/d) and fludrocortisone (0.1 mg/d). Patients who undergo cortical-sparing surgery should be reevaluated for the dose and maintenance of hormone therapy.

### Hemodynamic Instability Treatment

#### Hypertensive Crisis

Severe hypertension frequently occurs abruptly during PPGL resection surgery [57]. This may be accompanied by tachycardia, particularly in patients using β-blockers preoperatively. Cardiovascular events are potential complications during this period. Treatment with parental vasodilators drugs is recommended:

1. Sodium nitroprusside: a potent (short-acting) vasodilator that produces nitric oxide release. Its main advantage is the rapid onset and short duration [9, 58, 59]. However, it can cause severe hypotension with consequent tachycardia and should be used with caution. It can be used in continuous infusion when needed.

2. Phentolamine: antagonist to α1 and α2 receptors, being used intraoperatively for the control of hypertensive crises [58]. It has an effect of approximately 1 hour and should be used with caution as it may lead to severe hypotension. The high cost and low availability of the medication are limits for its large-scale use.

3. Magnesium sulfate: It has recently gained prominence in the intraoperative management of PPGL patients. Since extracellular calcium entry is required for calcium exocytosis by neuronal endings in the adrenal medulla, magnesium sulfate potentially blocks calcium entry and catecholamine release [57]. In addition, the vasodilatory and antiarrhythmic effect of magnesium is also beneficial [60, 61]. Intraoperative use of magnesium sulfate is performed in a 40 to 60 mg bolus/kg before tracheal intubation, followed by continuous infusion of 2 g/h [62].

#### Hypotension

After renal vein ligation, there is an abrupt fall in sympathetic activity, which could cause severe hypotension. The use of α-blockers reverses the downregulation of the α-adrenergic receptors caused by the prolonged elevation in circulating catecholamines and prevents postoperative hypotension or unresponsiveness to vasopressor treatment after surgical removal [9]. However, preoperative use of α-blockers does not guarantee the absence of hypotension after tumor removal and the use of vasoconstrictor drugs may be necessary very shortly after tumor withdrawal. Intraoperative volume infusion also helps to reverse this situation, especially if bleeding complications are present.

#### Postoperative Care

Hemodynamic instability and hypoglycemia are the 2 specific complications in postsurgical PPGL. Postoperative hypotension is attributed to abrupt fall in circulating catecholamines after tumor removal, residual effects of long-acting antihypertensive medications, hypovolemia associated with PPGL and surgery blood loss [63]. According to a retrospective Chinese study, 29% of the PPGL patients presented severe complications mostly due to cardiovascular morbidity [64]. A low body mass index, large tumor size, coronary heart disease, no preoperative crystal/colloid administration, and intraoperative hemodynamic instability were independent risk factors for cardiovascular morbidity in this cohort [64]. Another observational study found that the size of the adrenal
tumor and diabetes were significant factors for hemodynamic instability [65]. A very close cardiovascular vigilance in the intensive care unit is encouraged in all postsurgical patients during the immediate postoperative period. Furthermore, hypotension should be precociously treated with volume load and vasopressor regimens if necessary.

Severe hypoglycemia can occur in 13% of the cases, usually 2 to 4.5 hours after tumor resection [66]. The mechanism is supposedly related to enhanced insulin release due to the sudden withdrawal of catecholamines [67]. Epinephrine-predominant tumors are more associated with hypoglycemia [68]. Capillary or blood glucose monitoring is recommended during the first 48 hours of the postoperative period.

**Postsurgical Follow-Up**

Due to the risk of locally recurrent, multifocal, or metastatic disease, postsurgical surveillance is mandatory for all PPGLs [5]. To confirm complete biochemical remission, plasma or urinary free normetanephrines and metanephrines for all functioning PPGLs and 3-methoxytyramine (for paragangliomas with elevated preoperative levels) should be measured 2 to 6 weeks after surgery [6]. In high-risk patients, imaging screening, preferentially with MRI to reduce radiation exposure, should be performed annually during the first 5 years and then every 1 to 2 years. Patients with low-risk disease, pheochromocytoma with adrenergic phenotype and < 5 cm can be followed by annual metanephrine measurement. In this situation, imaging can be optional if annual biochemical investigation is negative.

There is no consensus about how long low-risk patients should be followed with biochemical and imaging screening. The risk of metastases is present even after a 5-year disease-free survival period [69]. High-risk patients (young patients and those with a genetic disease [mainly those with SDHB mutations], > 5 cm pheochromocytoma, and/or a paranglioma of any size) should have lifelong annual follow-up [6]. Patients with syndromic disease require a personalized approach according to specific affected genes based on the association with other tumors and the risk of multifocal or metastatic lesions (Table 4) [8, 70, 71]. The screening recommendations for asymptomatic mutation carriers are beyond the scope of this article.

**Conclusions**

Surgery is the therapy of choice for all PPGL patients. Before surgery, all patients with pheochromocytoma or sympathetic paraganglioma should undergo a perioperative treatment with α-receptor blockers to control symptoms of catecholamine excess and blood pressure. In addition, all PPGL patients should be evaluated by a multidisciplinary team with expertise in the perioperative management. Patients should be closely monitored during follow-up (mostly the higher risk group) because PPGL tumors have a potential risk of recurrence due to hereditary/multifocal disease or metastasis development.

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**Disclosures**

The authors have nothing to disclose.

**Data Availability**

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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