

Variability in perioperative management of pheochromocytoma in CanadaLinda C. Qu¹, Alexandra C. Istl², Elaine Tang¹, Richard C. Chaulk¹, Daryl Gray¹¹Western University, London, ON, Canada; ²Medical College of Wisconsin, Milwaukee, WI, United States

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ABSTRACT

Introduction: Despite recent consensus guidelines, there is substantial variability in the management of pheochromocytomas. Our study aimed to characterize the current state of perioperative pheochromocytoma management by Canadian surgeons.

Methods: A 23-item online survey was sent to Canadian surgeons who perform adrenalectomies for pheochromocytoma. We assessed personal and institutional practices, including preoperative and postoperative management.

Results: National response rate was 51.8%.

Surgeons from nine provinces responded; the majority were general surgeons (70.4%). Reviewing pheochromocytoma patients at a multidisciplinary tumor board was not routine practice (12%) and only 42.3% consistently referred patients for genetic testing. Preoperative α - and β -blockade at half of the respondent institutions were performed by endocrinology alone (53.8%), with the other half employing a multidisciplinary approach. Half of respondents admitted their pheochromocytoma patients to hospital prior to the day of surgery. Postoperatively, 11.5% of respondents routinely admitted their patients to the ICU for

KEY MESSAGES

- There are new guidelines recommending standardized practice patterns in the perioperative management of pheochromocytoma.
- Despite this, there exists significant heterogeneity in practice patterns in Canada resulting in lack of important aspects of care and potential unnecessary use of expensive healthcare resources.
- Namely, this includes a non-routine referral of patients to genetics following surgical management of pheochromocytoma, unnecessary admission to intensive care and step-down setting resulting in increased healthcare costs, and lack of multidisciplinary review.

monitoring based on personal preference or institutional convention. Multivariate analyses found no significant relationships between demographics or preoperative factors and perioperative management.

Conclusions: Perioperative surgeon management of patients undergoing adrenalectomy for pheochromocytoma was highly variable across Canada. Less than half of respondents routinely refer patients for genetic testing, despite recent practice guidelines. Surgeon preference and institutional convention are the main drivers behind preoperative admission and routine postoperative ICU admission, despite a lack of evidence to support this practice.

INTRODUCTION

Adrenalectomy is the first-line treatment for pheochromocytoma. Diligent preoperative medical optimization is imperative as catecholamine overproduction presents unique challenges in blood pressure management in the perioperative setting. Today, the combination of pharmacologic pre-treatment, surgical expertise, and close access to an intensive care unit (ICU) has greatly reduced the perioperative mortality from 45% to 2%.¹⁻³

In 2014, the Endocrine Society, the American Association for Clinical Chemistry, and the European Society of Endocrinology released joint clinical practice guidelines for the management of pheochromocytoma and paraganglioma.⁴ The guidelines strongly recommend close monitoring of blood pressure, heart rate, and plasma glucose for 24-48 hours in the post-operative period, with contributing evidence consisting primarily of retrospective studies and institutional experience.^{5,6} These guidelines do not specify utilization of a step-down unit or intensive care unit (ICU) post-operatively, nor do they discuss hospital admission prior to surgery.⁴

Despite these guidelines, practice continues to be heterogeneous between surgeons and across institutions. With respect to surgical approach, open, laparoscopic, or robotic transabdominal and retroperitoneal approaches have all been used successfully. In fact, several large single-institution series show laparoscopic adrenalectomy to be associated with less surgical morbidity than open surgery, and this is now the established standard of care.^{7,8} However, there is some emerging evidence, largely from retrospective studies, suggesting that the retroperitoneal approach is falling into favour.^{9,12}

In this study, we surveyed Canadian urologists and general surgeons who treat pheochromocytoma. Our intent was to explore the potential variability in preoperative α - and β -adrenergic blockade, surgical approach, ICU utilization, and postoperative care. This study is the first to characterize national pheochromocytoma management and presents preliminary data on the potentially heterogeneous nature of practice following the release of the 2014 consensus guidelines on the perioperative management of pheochromocytoma and is designed to act as a catalyst for further research on this topic.

METHODS

To our knowledge, there is no centralized directory of surgeons performing adrenalectomies for pheochromocytoma. To address the challenge of identifying these surgeons nationwide and to secure a representative sample, we began by filtering the American Association of Endocrine Surgeons (AAES) website for "Canada" and "Adrenal". The resulting list of surgeons was then further refined by examining the faculty directories on websites of Canadian universities affiliated with hospitals, specifically within the Departments of General Surgery and Urology. We did not further narrow our search by sub-specialty interests (e.g., minimally invasive surgery, surgical oncology, etc.). Instead, any surgeon listed as having a clinical interest in adrenal disease was included. This screening process was carried out by two research team members independently, with their findings subsequently consolidated and reviewed collectively to ensure the list was as complete as possible.

A 23-item electronic survey was sent to 54 surgeons in Canada identified in this process. This was a novel study designed to explore respondents personal practice managing pheochromocytoma and thus a validated questionnaire was not available. Our survey was piloted with both urologists and general surgeons prior to administration, and feedback regarding content and structure was incorporated into the final survey for distribution. The survey consisted of multiple choice and free-text question formats. Survey items included personal and institutional characteristics, aspects of pre-operative multidisciplinary management, preferred preoperative α - and β -adrenergic blockade agents, perioperative ICU utilization, and postoperative care practices. The survey was developed using Qualtrics software and distributed via email.¹³ A reminder email was sent to non-responders every two weeks from the initial request. Results were anonymously collected between October and December 2020. A full explanation of the purpose and nature of all procedures was provided, and electronic written consent was obtained from each participant before they were able to proceed with the survey. The study was approved by the Health Sciences Research Ethics Board at Western University.

Respondent and institutional demographics including case volumes and training history were presented with descriptive statistics. Measures of central tendency with standard deviations, interquartile ranges (IQR), and ranges as appropriate were used to describe rates of ICU utilization, pre-operative α - and β -blockade agents, operative planning, and other factors related to perioperative management. Univariate and multivariate analyses were conducted to evaluate associations between demographic characteristics and perioperative care preferences. Statistical analysis was conducted using Stata 14 statistical software.

RESULTS

A total of 54 Canadian surgeons who perform adrenalectomies were identified, of whom 28 responded. The overall survey response rate was 51.8%. Surgeon and institutional demographics are presented in Table 1. Surgeons from nine out of ten provinces responded to the survey with Ontario surgeons comprising 48.1% of respondents. General surgeons represented a larger proportion of the respondents compared to urologists (70.4% vs. 29.0%, respectively). Experience varied widely, with a median of 15.5 years in practice (range 2 – 34 years). Surgeons

performed an annual median of 3 (IQR 2 – 6) adrenalectomies for pheochromocytoma, with a range of 1 to 12 adrenalectomies per year. Almost all respondents worked in a university-affiliated academic centre (92.9%) and had undergone fellowship training after residency (92.9%) (Figure 1).

Overall, 31.1% of surgeons had cancelled a planned adrenalectomy due to inadequate preoperative blockade in their career, but only two cancellations were reported across our entire population in the last study year.

100% (IQR 95-100%) of respondents planned for minimally invasive adrenalectomy, with 77% preferring a transabdominal approach (Table 2). With respect to preoperative management, 16% of respondents always reviewed pheochromocytoma cases at multidisciplinary meetings (MDMs) prior to surgery, while 44% never reviewed cases at MDMs. Less than half of respondents routinely referred patients for genetic testing (42.3%). Fifty percent of surgeons routinely admitted patients prior to the day of surgery, and, of those, most admitted their patients to ward beds (92.3%). One respondent routinely admitted patients to a stepdown unit prior to surgery, defined in our survey as a non-critical care unit with capacity for continuous hemodynamic monitoring. No respondents routinely admitted patients to the ICU on the day before surgery.

At 57.7% of respondent institutions, an endocrinologist was responsible for all preoperative α - and β -blockade. Other respondents reported a multidisciplinary approach with variable combinations of specialists involved in preoperative blockade (Figure 3). Preferred preoperative blockade agents are shown in Figure 4. The α -blockade agents most frequently used were doxazosin (35%) and prazosin (30%). With respect to β -blockade agents, 62.5% of surgeons preferred metoprolol, while 25.0% reported that β -blockade agents were not consistently employed (Figure 4). Of responding surgeons, 23.1% reported a standardized preoperative α - and β -blockade protocol at their institution and 46.1% had developed a blocking protocol for their personal practice.

Three surgeons routinely admitted patients postoperatively to the ICU (11.5%), citing their rationale as institutional convention or concern for possible hemodynamic lability where free-text explanation was provided.

Post-operative disposition of patients to a ward bed was estimated for a median of 78% (IQR 41 – 93.8), while a median of 50% (IQR 1 – 67.5) were estimated to be admitted to a step-down unit, and a median of 5% (IQR 2 – 10) were admitted to the ICU (Table 3).

On univariate and multivariate regression analysis, we found no significant relationships between preoperative factors and peri- or postoperative management. Specifically, surgeon years in practice, case volume, use of blocking protocols, and the specialist performing preoperative blocking were not significantly associated with rates of case cancellations, admission prior to the day of surgery, postoperative disposition, or ICU admission.

DISCUSSION

This survey of surgeons who perform adrenalectomies for pheochromocytoma is the first to characterize national pheochromocytoma management. We investigated personal and institutional experience with pheochromocytoma, multidisciplinary review and care, preferred preoperative α - and β -adrenergic blockade, and perioperative ICU utilization.

Several results were consistent with the current treatment guidelines for pheochromocytoma. Notably, 92.9% of respondents are fellowship-trained surgeons based in university-affiliated hospitals, which is congruent with clinical practice guidelines that urge treatment of pheochromocytoma to be carried out at centres with appropriate perioperative expertise.⁴ With respect to the preoperative medical optimization and treatment of pheochromocytoma patients, the most recent Endocrine Society consensus guidelines recommend oral phenoxybenzamine or other α -adrenergic antagonists as the first-line agent for perioperative blood pressure control.⁴

Current evidence, however, suggests there is no superior α -blocker for the pre-treatment of patients with pheochromocytoma and this is reflected in our findings, which demonstrate the use of a variety of agents (Figure 4).¹⁴ The PRESCRIPT trial – the first randomized control trial to directly compare two α -blockade agents for pheochromocytoma - concluded that phenoxybenzamine was more effective in preventing intraoperative hemodynamic instability compared to doxazosin.¹⁵ It could not, however, establish if this translated to any clinically significant outcome.¹⁵ In our survey, the lack of preference for phenoxybenzamine likely reflects disadvantages of the drug, which include a cost that is double that of doxazosin and associated with more undesirable side effects.¹⁴

Our survey results also indicate the desire for further standardization in medical pre-treatment, as 23.1% of participating hospitals had an institutional protocol for preoperative α - and β -blockade and 46.1% of participating surgeons had established a personal protocol in their practice. Given that over 80% of institutions in our survey involve an endocrinologist in blocking patients, with more than half of preoperative blockades implemented by an endocrinologist alone, standardization through a multidisciplinary protocol with endocrinology participation is a natural next step to ensure consistent medical optimization for these complex patients.

Our survey highlighted patterns of referral for genetic testing that should be considered in the context of best practice guidelines. Since germ-line mutations exist in at least one third of all patients with pheochromocytomas or paragangliomas, genetic testing can confer valuable information that may impact management and prognosis.¹⁶ For example, mutation of the SDHB gene – one of more than 14 susceptibility genes associated with pheochromocytoma development – will lead to metastatic disease in over 40% of affected patients.¹⁷ Identifying the offending mutations and establishing a hereditary syndrome may result in earlier diagnosis and treatment in relatives.^{18,19} In light of this evidence, the Endocrine Society consensus guidelines recommend that genetic testing should be offered to all patients with pheochromocytoma or paraganglioma, and a diagnostic algorithm with clinical features should be used to establish the

priorities for specific genetic testing.⁴ Despite these recommendations supported by moderate quality evidence, this standard of care is practiced by only 42.3% of surgeons who responded to our survey. Barriers to referral for genetic testing need to be further explored in surgeons and patients alike.

Multidisciplinary care is integral to safe management of pheochromocytoma. In exploring the use of formal MDMs, only 16% of surgeons routinely discuss their pheochromocytoma patients at MDMs and 44% do not discuss pheochromocytomas at an MDM at all, despite working at centres with access to subspecialty expertise. MDMs are widely established in the management of chronic and complex diseases, demonstrating benefits in diagnosis, treatment, survival, and quality of life for cancers and benign diseases alike.²⁰⁻²⁷ The principle of a multidisciplinary approach could likely be beneficially extended to pheochromocytomas, as the combination of surgical, endocrine, and genetic expertise in the context of this rare condition will offer valuable prognostic information for each individual patient.

An ongoing topic of debate regarding pheochromocytoma patients is perioperative ICU utilization. One of the most common complications that may require monitoring in the ICU is postoperative hypotension. There are currently no available or validated indices to predict which patients will encounter this complication. Although, some evidence exists suggesting a correlation between higher preoperative adrenergic activity and postoperative hypotension.^{28,29} In recent years, the incidence of postoperative complications has decreased with the widespread adoption of aggressive medical pre-treatment, improvements in anaesthetic technique, and the use of minimally invasive surgery.³⁰ As a result, adrenalectomy for pheochromocytoma may only require selective rather than routine use of ICU monitoring in the postoperative setting.³¹ Regardless of this, 11.5% of survey participants routinely admit their patients to the ICU after surgery and more than half of patients are admitted to either an ICU (5%) or a stepdown unit (50%) for monitoring, even in the absence of hemodynamic instability. According to the Canadian Institute for Health Information, the average daily cost for an ICU bed is three times that of a general ward bed (\$3,592 versus \$1,135), with costs varying widely from province to province.³² Although there is no reliable data demonstrating the actual percentage of patients who experience postoperative hemodynamic instability, the number of patients admitted to the ICU likely far exceeds the number who truly require monitoring or treatment in an ICU setting. A cost-analysis is a logical next step in this research to better characterize the resource utilization of ICU admission for routine postoperative pheochromocytoma care. Postoperative ICU usage may depend on whether there is a stepdown unit available; however, this more nuanced reasoning was not explored in our survey.

Limitations of our survey are that there is likely incomplete capture of surgeons who treat pheochromocytoma as we retrieved physician contact information through the AAES database and Canadian university-affiliated hospital website directories resulting in a non-representative sample. Additionally, through this identification method, there is an inherent paucity of surgeons

practicing outside of academic centres included in the study. Ultimately, this lack of representation contributes to difficulties surrounding generalizability of the results. There is also an uneven distribution in types of subspecialists between general surgeons and urologists. Further work can be completed to assess whether there is further heterogeneity to assess practice differences between the two specialities that treat the same disease.

CONCLUSIONS

This survey highlights the potentially significant heterogeneity in practice patterns for pheochromocytoma management across academic surgeons and institutions in Canada. Although we acknowledge the underpowered nature of our sample size and the absence of non-academic centres, even amongst this small group, there exists significant heterogeneity and non-adherence to recent guidelines in the perioperative management of this disease. Continuous efforts should be made to adhere to the genetic testing recommendations outlined in the 2014 Endocrine Society consensus guidelines. Further, the true utility of routine preoperative admission and postoperative monitoring in an ICU setting should be explored in future studies as it is likely overused at significant cost without evidence to support benefit. Standardized blockade protocols and more formal multidisciplinary review may reinforce evidence-based care for patients with pheochromocytoma. The results of this survey present preliminary data that point to heterogeneity of practice demonstrating the need for further work specifically designed to address these opportunities for improvement in resource management within our publicly funded healthcare system and, more importantly, to enhance patient care for this complex disease.

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FIGURES AND TABLES

Figure 1. Province of practice.

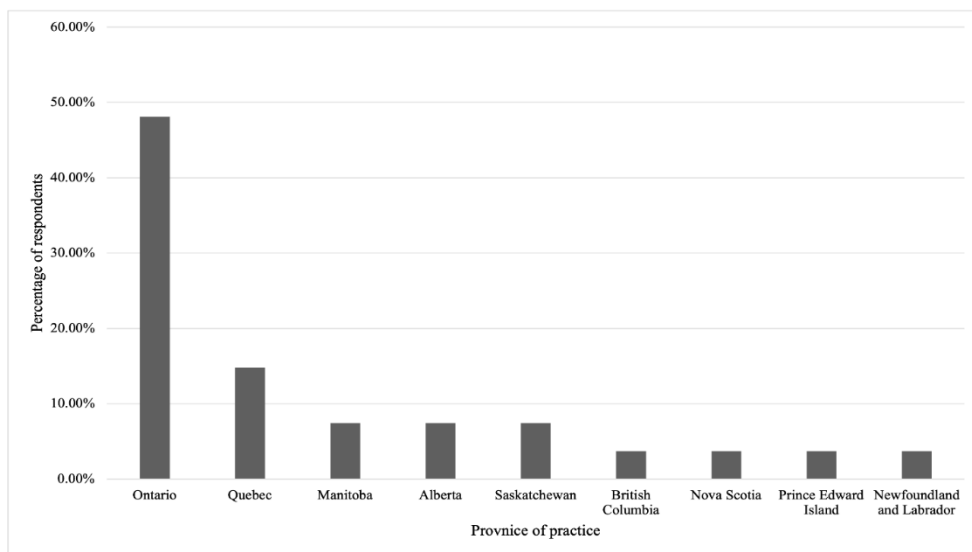


Figure 2. Subspecialty training amongst surgeons.

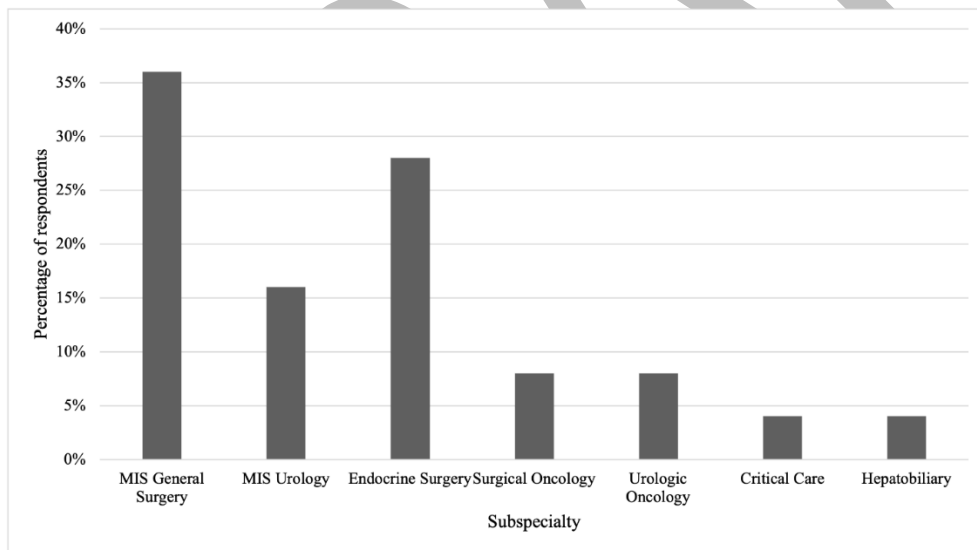


Figure 3. Make-up of multidisciplinary teams across Canada.

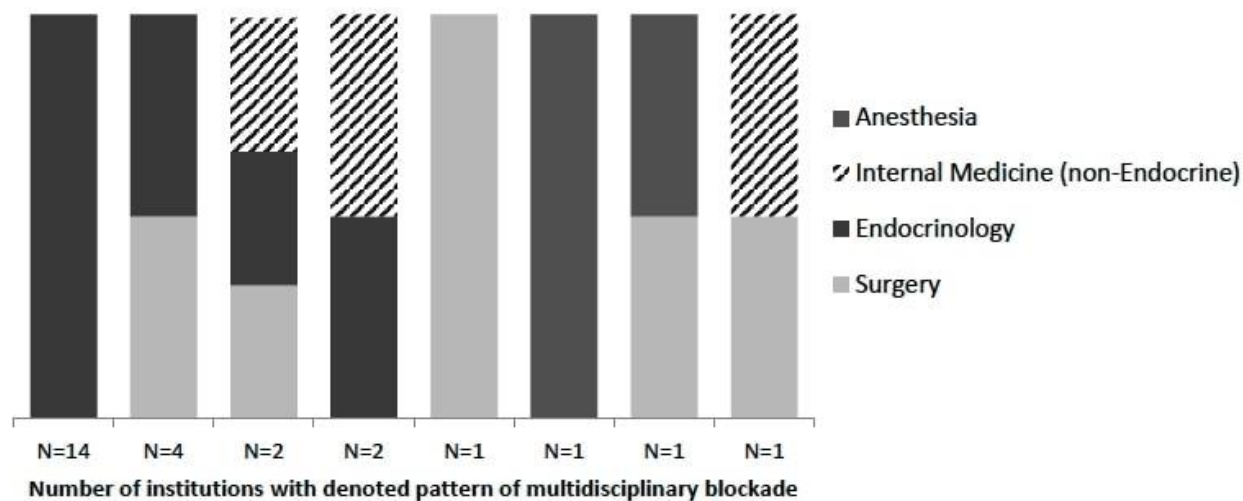


Figure 4. Preoperative alpha- and beta-blockade agents.

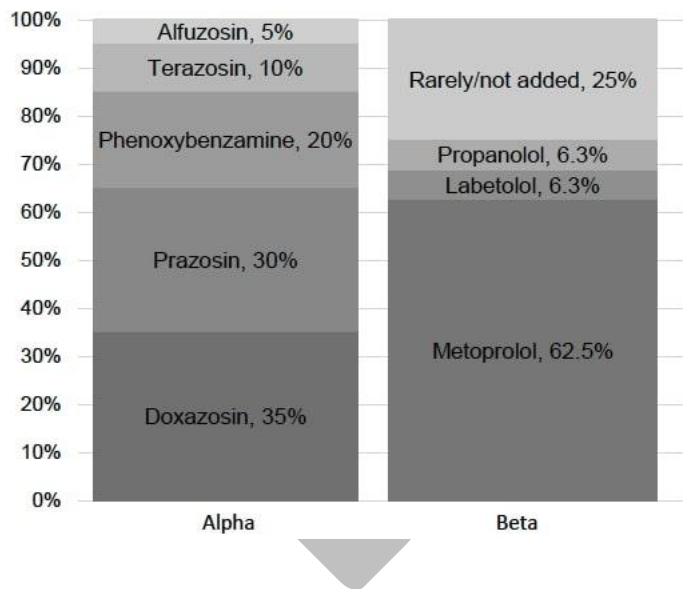


Table 1. Participant demographics	
Patient demographics	N=54
Surgical specialty	
General surgery	19 (70.4%)
Urology	8 (29.6%)
Practice setting	
Academic	26 (92.9%)
Community	2 (7.1%)
Fellowship training	26 (92.9%)
Years in practice (SD)	15.5 (7.6)
Median academic group size performing adrenalectomy (IQR)	3 (2–4)
Adrenalectomy per surgeon, per year (IQR)	3 (2–4)

Table 2. Perioperative and operative patterns	
Preoperative and operative statistics	
Adrenalectomy planned as minimally invasive surgery*, n (%)	54 (100%)
Preferred surgical approach, n (%)	
Anterior	20 (76.9%)
Retroperitoneal	5 (19.2)
Estimated percentage of patients reviewed at MDM preoperatively, n (%)	
100%	4 (16)
50%	3 (12)
25%	1 (4)
10%	6 (24)
0%	11 (44)
Routine referral for genetic testing, n (%)	11 (42.3)
Institutional protocol for preoperative α - and β -blockade, n (%)	6 (23.1)

Personal protocol for preoperative α - and β -blockade, n (%)	12 (46.1)
Routine admission prior to the day of surgery, n (%)	13 (50)

*Either laparoscopic or robotic.

Table 3. Postoperative practice patterns	
Estimated length of hospital stay after adrenalectomy in days, mean (SD)	
MIS*	2 (0.7)
Open	5 (0.9)
Routine postoperative admission to ICU, n (%)	3 (11.5)
Postoperative disposition, median % (IQR)	
ICU	5 (2-10)
Stepdown unit	50 (1-67.5)
Ward bed	78 (41-93.8)

*Either laparoscopic or robotic. IQR: interquartile range; MIS: minimally invasive surgery; SD: standard deviation.

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