Differences in Perioperative Hemodynamic Management for Pheochromocytoma and Paraganglioma

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ABSTRACT

Background

Pheochromocytomas (PCC) and paragangliomas (PG) are catecholamine-secreting tumors that can cause hemodynamic instability (HDI) in the perioperative period. Due to their similar pathology and clinical presentation, these tumors are often treated as a single disease. The hypothesis of this study is that patients with pheochromocytoma or paraganglioma will exhibit differing levels of perioperative HDI that may warrant disease-specific monitoring and/or treatment.

Methods

A retrospective analysis was performed on patients with pheochromocytoma or paraganglioma undergoing surgery at

our institution from 2006–2015. Demographics, tumor characteristics, and perioperative variables were compared among the two tumor groups using Fisher's Exact and Mann-Whitney-U tests with P values $\leq .05$ considered significant. Simple linear regression was performed to identify predictors of intraoperative HDI in the pheochromocytoma group.

Results

There were no differences in patient demographics, tumor characteristics, or medication type/dosage required to achieve adequate α -blockade prior to surgery for the pheochromocytoma ($n = 62$) and paraganglioma ($n = 15$) groups. Paragangliomas were resected more frequently

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with an open approach ($P = .001$) and had greater estimated blood loss ($P = .001$). Paraganglioma patients experienced significantly greater episodes of postoperative HDI ($P = .003$) on overall comparison and on subgroup analysis of the two tumor types after controlling for operative approach ($P = .05$). Significant predictors of intraoperative HDI in the pheochromocytoma group on simple regression included tumor size,

plasma normetanephrine/metanephrine levels, and operative approach.

Conclusions

Preoperative hemodynamic variables and blockade requirements were similar between pheochromocytoma and paraganglioma patients. However, patients with paraganglioma were prone to more complicated resections and HDI in the postoperative period.

Introduction

Pheochromocytomas (PCC) and paragangliomas (PG) are catecholamine-secreting tumors of neuroendocrine chromaffin cells with an estimated incidence of two-to-eight per million.¹ By convention, pheochromocytomas are neoplasms of the adrenal medulla, whereas paragangliomas arise from extra-adrenal ganglia of the autonomic nervous system.²⁻⁴ While infrequently malignant, these tumors can cause significant morbidity due to secretion of norepinephrine and epinephrine. Patients often present with symptoms of hypertension, palpitations, headache, diaphoresis, and/or anxiety, and are subject to complications such as stroke, arrhythmias, and myocardial infarction.^{5,6} Surgical resection is generally curative for these tumors and is widely considered the gold standard of treatment.⁷

The surgeon physically touching these tumors during surgery can cause them to secrete catecholamines that subsequently result in hemodynamic instability (HDI) hypertension (SBP > 140 mm Hg) or hypotension (SBP < 100 mm Hg), requiring an intervention.⁸ Patients undergoing surgical resection are also prone to labile blood pressures in the postoperative setting.⁹ Careful preoperative medical management is essential in order to control hypertension and minimize HDI in the perioperative period. Studies have shown that pharmacologic agents such as the nonselective α -adrenergic blocker phenoxybenzamine,

selective α_1 -adrenergic blockers (eg prazosin, doxazosin), β -adrenergic blockers, and calcium-channel blockers can be titrated to achieve preoperative blood pressure control while minimizing side effects.^{6,10-12}

Due to their similar pathology and clinical presentation, pheochromocytomas and paragangliomas are often treated similarly; however, recent studies have described significant differences between these tumors. Malignant paragangliomas behave more aggressively than their malignant pheochromocytoma counterparts, exhibiting more local and vascular invasion.² Additionally, patients with pheochromocytomas may exhibit lower survival rates than those with paragangliomas, possibly due to a more bioreactive hormone profile.⁸ Pheochromocytomas tend to produce significant amounts of both norepinephrine and epinephrine, while paragangliomas only produce clinically significant levels of norepinephrine and normetanephrine due to the lack of phenylethanolamine N-methyltransferase, which converts norepinephrine to epinephrine.¹³ Previous studies have shown that increased levels of catecholamines, alpha-blockade type, hydration, tumor size, and procedure type may be associated with perioperative HDI when resecting pheochromocytomas.⁶ While the differences in tumor features and clinical behavior between pheochromocytomas and paragangliomas have become more apparent in recent years, no study has examined differences in perioperative HDI

between these tumors that may warrant disease-specific treatment or monitoring. Our hypothesis was that pheochromocytomas would have more instances of intraoperative HDI (given their ability to release both epinephrine and norepinephrine) compared to PGs that only release epinephrine despite similar preoperative pharmacologic blockade. Additionally, we hypothesize that larger tumor size and using an open procedure will result in greater blood loss, which will increase instances of intraoperative HDI. Given the ability of pheochromocytomas to secrete both epinephrine and norepinephrine, we hypothesize that these patients would require a longer duration of preoperative pharmacologic blockade, as well as higher doses of phenoxybenzamine to achieve the blockade.

Methods

Study Population

Following approval from the University of Michigan Institutional Review Board (IRB), a retrospective analysis of medical records was performed for patients undergoing resection of pheochromocytoma or paraganglioma at the University of Michigan between 2006 and 2015. All patients included in the study had a biochemically active (abnormal preoperative metanephrine and normetanephrine) paraganglioma or pheochromocytoma and underwent pharmacologic blockade prior to surgery under the direction of our institution's surgeons. Patients with extra-abdominal paragangliomas (eg, carotid body) and biochemically inactive tumors (normal preoperative metanephrine and normetanephrine levels) were excluded from the analysis. The patient populations were not purposely matched for comparison between pheochromocytoma and paraganglioma groups. Five endocrine surgeons at our institution performed the majority of the pheochromocytoma and/or paraganglioma excisions in our study, and preference was given to the laparoscopic approach unless certain conditions (eg tumor location, invasion of adjacent abdominal

structures) necessitated an open approach. The choice of medication employed for preoperative blockade depended on surgeon preference and patient factors. Phenoxybenzamine is generally preferred as the first-line blockade agent.⁶ When its use was limited by inadequate health insurance coverage or patient side effects (eg orthostatic hypotension, nasal congestion), calcium channel blockers were used instead.

Comparison Variables

Patients with pheochromocytoma and paraganglioma were compared on the basis of demographics (age and sex), tumor characteristics, and perioperative variables. Tumor characteristics compared among the pheochromocytoma and paraganglioma groups included tumor size, tumor location, presence of genetic mutations (such as succinate-dehydrogenase, Von Hippel-Lindau syndrome, etc), and baseline plasma normetanephrine levels and metanephrine levels at the time of initial presentation. Preoperative comparison variables included percentage of patients on α -blocking agents including phenoxybenzamine, duration of α -blockade, and percentage of patients on β -blockers and calcium-channel blockers. Intraoperative comparison variables included operative approach, operative time, estimated blood loss, fluid input, episodes of HDI, and vasoactive medications administered. Intraoperative HDI in our study was defined as the number of hypertensive (SBP > 140 mm Hg) or hypotensive (SBP < 100 mm Hg) episodes in which the anesthesiologist had to respond with a vasoactive substance. Postoperative HDI and duration of stay were compared among the two tumor groups. Postoperative HDI included episodes of hypertension (SBP > 140 mm Hg) or hypotension (SBP < 100 mm Hg) in which antihypertensive medications or fluid boluses were administered, respectively, in the first 48 hours after surgery.

A subgroup analysis was then performed in which the perioperative variables listed previously were compared between patients with

pheochromocytoma and paraganglioma. In this subgroup analysis, comparison groups were stratified on the basis of operative approach (open vs laparoscopic) to elucidate differences in perioperative parameters independent of the influence of operative approach.

Statistical Analysis

Statistical analysis was performed with SPSS and GraphPad Prism. In the comparison of perioperative variables among the two tumor groups, Fisher's Exact Test was used for categorical variables, while the Mann-Whitney-U Test was used for continuous variables due to a nonparametric dataset. P values $\leq .05$ were considered significant. Simple linear regression was used for analyzing significant predictors of intraoperative HDI within the pheochromocytoma group, with $P \leq .05$ considered significant.

Results

Patient demographics, tumor characteristics, and preoperative management of patients are shown in Table 1. Sixty-two patients had a pheochromocytoma and 15 had a paraganglioma resection from 2006 to 2015. There were no significant differences in patient age or gender between the PCC and PG groups. Patients in the PG group demonstrated a higher rate of confirmed mutations (ie, succinate-dehydrogenase mutations) compared to patients in the PCC group (ie, Von Hippel-Lindau, Neurofibromatosis I, Multiple Endocrine Neoplasia Type II) by genetic testing ($p = .003$). Tumor sizes between the groups were similar, and all patients demonstrated elevated normetanephrine levels representing active hormone secretion from the tumor. As expected, PCC patients had higher plasma metanephrine levels compared to their PG

counterparts (0.99 nM/L vs 0.20 nM/L, $P = .002$). Normal plasma metanephrine levels for our laboratory: ≤ 0.20 nM/L. Location of tumors in the PG group included para-aortic (8), paracaval (1), periadrenal (2), renal vein (2), head of pancreas (1), and urinary bladder (1).

For control of preoperative blood pressures, α -blocking agents (phenoxybenzamine, doxazosin) were used in 63 patients (81.9%). A calcium-channel blocker (ie, Nicardipine) was used as the sole preoperative blood pressure control agent in 14 patients (18.1%). Both groups followed a similar preoperative course, with no significant differences in the number of patients on α -blockade, duration of blockade, final cumulative dose of phenoxybenzamine (mg/24 hr), or the number of patients on Ca^{2+} channel blockers or β -blockers (Table 1).

Operative parameters, intraoperative patient hemodynamics, and medications administered during surgical resection of PCC or PG are depicted in Table 2. An open approach to resection was performed more frequently in the PG group (80% vs 25.8% for PCC, $P = .001$). Similarly, the median operative time for PG resection was significantly longer than for PCC resection (238 minutes vs 153 minutes, $P = .003$). Patients in the PG group had greater blood loss (900 mL for PG vs 75 mL for PCC, $P = .001$) and required greater fluid resuscitation than their PCC counterparts (5.74 L for PG vs 4.21 L for PCC, $P = .02$). Patients in both groups experienced a similar number of episodes of HDI.

Postoperative outcomes are also depicted in Table 2. Patients in the PG group more frequently experienced HDI within the first 48 hours after surgery (53.3% PG patients vs 14.5% PCC patients, $P = .003$) and had longer median hospital stays (6 days for PG vs 3 days for PCC, $P < .001$) than patients with PCC.

TABLE 1. Patient Demographics, Tumor Characteristics, and Preoperative Management of Pheochromocytoma vs. Paraganglioma Groups

	<i>Pheochromocytoma</i> (<i>n</i> = 62)	<i>Paraganglioma</i> (<i>n</i> = 15)	<i>P Value</i>
Demographics			
Age (Age Range)	47 (13–87)	57 (20–72)	.66
Gender			
Male	27 (43.5%)	6 (40.0%)	> .99
Female	35 (56.5%)	9 (60.0%)	> .99
Genetic Mutation Identified	12 (19.4%)	9 (60.0%)	.003
Tumor Characteristics			
Tumor Size (cm)	4.10 (0.6–18.7)	5.30 (1.8–9.5)	.44
Plasma Normetanephrine levels (nM/L) ^{a,b}	4.90 (1.1–111.0)	2.40 (1.4–36.6)	.46
Plasma Metanephrine levels (nM/L) ^{a,b}	0.99 (0.20–25.0)	0.20 (0.20–0.23)	.002
PreOperative Management			
Patients on α -Blockade ^c	50 (80.7%)	13 (86.7%)	.73
Duration of α -Blockade (days)	36 (3–154)	29 (1–109)	.26
Cumulative Dose of Phenoxybenzamine (mg/24 hr)	60 (12–240)	85 (0–120)	.20
Patients on Ca ²⁺ -Channel Blockers	22 (35.5 %)	3 (20.0 %)	0.36
Patients on β -Blockers	41 (66.1 %)	9 (60.0 %)	0.77

Data are presented as median (range) or N (%)

SBP Systolic Blood Pressure, *DBP* Diastolic Blood Pressure

^a Baseline plasma normetanephrine and metanephrine levels were not known for 6 PCC patients and 1 PG patient

^b Reference range: normetanephrine levels $\leq$ 0.90 nM/L, metanephrine levels $\leq$ 0.20 nM/L

^c Doxazosin was used in place of phenoxybenzamine in 3 PCC patients and 1 PG patient

TABLE 2. Operative Parameters, Hemodynamic Instability, Medications Administered, and Postoperative Outcomes for Pheochromocytoma vs. Paraganglioma Groups

	<i>Pheochromocytoma</i> (<i>n</i> = 62)	<i>Paraganglioma</i> (<i>n</i> = 15)	<i>P</i> Value
Operative Parameters			
Open Procedures	16 (25.8%)	12 (80%)	.001
Operative Time (min)	153 (68–425)	238 (114–419)	.003
Intraoperative Hemodynamics			
Estimated Blood Loss (mL)	75.0 (2–6075)	900.0 (25–1300)	.001
IV Fluids Administered (L)	4.21 (1.30–13.4)	5.74 (0.72–8.06)	.02
Episodes of HDI	3 (0–13)	2 (0–7)	.99
Medications Administered			
Magnesium Sulfate	30 (48.4%)	7 (46.7%)	> .99
β-Blockers	37 (59.7%)	6 (40%)	.25
Other Vasoactive Medications ^a	47 (75.8%)	12 (80%)	> .99
Postoperative Outcomes	9 (14.5%)	8 (53.3%)	.003
Patients with HDI ^b			
Patients with Hypertension	5 (8.1%)	6 (40%)	.005
Patients with Hypotension	5 (8.1%)	4 (26.7%)	.07
Hospital Stay (days)	3 (2–42)	6 (1–21)	< .001

Data are presented as median (range) or N (%)

SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure

^a Including Epinephrine, Norepinephrine, Vasopressin, Ephedrine, Phenylephrine

^b Hypertension (SBP > 140 mm Hg) or Hypotension (SBP < 100 mm Hg requiring administration of anti-hypertensive meds or fluid boluses, respectively)

Given the higher rates of an open approach to resection for patients with paraganglioma, a subgroup analysis was performed, comparing perioperative hemodynamics among the two tumor groups controlled for operative approach (Table 3). Among patients undergoing an open approach to resection, those with pheochromocytoma experienced greater episodes of intraoperative HDI (4.5 episodes in PCC patients

vs 2.0 episodes in PG patients, $P = .04$). Conversely, patients with PG undergoing a laparoscopic resection were statistically more prone to greater intraoperative blood loss ($P = .03$) and longer postoperative hospital stays ($P = .006$) and were more likely to have postoperative HDI ($P = .05$) in the first 48 hours after surgery, compared to patients with PCC having a laparoscopic resection.

TABLE 3. Significant Differences in PeriOperative Hemodynamics Among Pheochromocytoma and Paraganglioma Groups Stratified by Operative Approach

	Open Approach (n = 28) ^a			Laparoscopic Approach (n = 49) ^b		
	Pheochromocytoma n = 16	Paraganglioma n = 12	P Value	Pheochromocytoma n = 46	Paraganglioma n = 3	P Value
<i>Episodes of Intraoperative HDI</i>	4.5 (0–13)	2.0 (0–7)	.04	2.0 (0–9)	4.0 (2–6)	> .99
<i>Estimated Blood Loss (mL)</i>	725 (30–6075)	763 (25–1300)	.34	50 (0–800)	1150 (75–1250)	.03
<i>Postoperative Hospital Stay (days)</i>	6.5 (4–10)	6.5 (2–42)	.83	2 (1–21)	5 (5–7)	.006
<i>Patients w/ Postoperative HDI^c</i>	4 (25.0%)	6 (50.0%)	.24	5 (10.9%)	2 (66.7%)	.05
<i>Patients w/ Postoperative Hypotension</i>	3 (18.8%)	2 (16.7%)	> .99	2 (4.3%)	2 (66.7%)	.02

Data are presented as median (range) or N (%)

^a 16 patients w/ pheochromocytoma and 12 patients w/ paraganglioma underwent open operations

^b 46 patients w/ pheochromocytoma and 3 patients w/ paraganglioma underwent laparoscopic operations

^c Hypertension (SBP > 140 mm Hg) or Hypotension (SBP < 100 mm Hg requiring administration of antihypertensive meds or fluid boluses, respectively)

Finally, to identify potential predictors of intraoperative HDI within the PCC group, simple linear regression was performed controlling for age, gender, tumor size, normetanephrine and metanephrine levels, pre-blockade SBP, duration of α -blockade, cumulative

phenoxybenzamine dose, surgical approach, operative time, pre-induction SBP, and estimated blood loss. Due to the small sample size, simple regression models were not appropriately powered for the PG group and therefore were not performed.

FIGURE 1. Operative Approach and Tumor Size Predict HDI in Pheochromocytoma Resection

There were 62 total patients with pheochromocytoma. N for the tumor size < median and tumor size > median is thus 62/2 = 31 for each. N for lap approach is 46 and for open approach is 16

Significant individual predictors of intraoperative HDI in the PCC group are depicted in Table 4. To further delineate significant predictors of intraoperative HDI in the PCC group, the median number of episodes of intraoperative HDI was compared by dichotomizing the PCC group into those patients undergoing laparoscopic vs open surgical approach (Figure 1). As expected, patients with PCC undergoing an open approach experienced a greater number of episodes

of intraoperative HDI than those undergoing a laparoscopic approach. The PCC group was again separated into two groups based on the median tumor size (4.1 cm) in this population (Figure 1). Patients with tumors larger than 4.1 cm (31 patients) were more prone to intraoperative HDI as compared with those patients with a tumor size less than 4.1 cm (31 patients).

TABLE 4. Significant Individual Predictors of Intraoperative Hemodynamic Instability for PCC Group

Predictor Variable	N	Estimated Coefficient	Standard Error (Estimated Coefficient)	95% Confidence Interval	P Value
Age (years)	62	0.044	0.020	0.005–0.083	.03
Tumor Size (cm)	62	0.403	0.107	0.189–0.617	< .001
Plasma Normetanephrine Levels (nM/L)	56	0.055	0.013	0.030–0.080	< .001
Plasma Metanephrine Levels (nM/L)	56	0.174	0.083	0.007–0.341	.04
Open Procedures	16	2.758	0.774	1.209–4.307	.001
Operative Time (min)	62	0.012	0.005	0.003–0.021	.01

N represents the number of patients with pheochromocytoma who had each variable entered into the regression analyses. Age, tumor size, number of procedures, and operative time were variables documented in the chart for each patient. For open procedures, only 16 patients had this type of procedure. Only 56/62 patients had preoperative plasma normetanephrine levels and preoperative metanephrine levels documented in MiChart.

Discussion

Our original hypothesis that patients with a pheochromocytoma would have more HDI was proven incorrect. It appeared that paraganglioma surgery was more often open and of longer duration than pheochromocytoma surgery (Table 2). This likely resulted in increased blood loss that led to more postoperative HDI in the paraganglioma group. However, the blood loss was likely not significant enough to result in intraoperative HDI but possibly only became apparent in the postoperative setting. Interestingly, when stratified by open approach, pheochromocytoma patients had more

instances of intraoperative HDI than paraganglioma patients, which may, in fact, be due to differences in norepinephrine and epinephrine secretion of the tumor types (Table 3). Our hypothesis that larger tumor size and use of open approach would result in increased episodes of HDI intraoperatively was supported (Figure 1). Contrary to what we hypothesized, it appeared there were no differences between the two types of tumors with regard to preoperative pharmacologic blockade in terms of dosing, type of medication, or length of the blockade. Our intent with this study was to compare two distinct patient populations with either

of these tumor types on the basis of demographics, tumor characteristics, and perioperative variables to identify significant differences that may warrant disease-specific monitoring or treatment.

Pre-operative blockade of α -adrenergic receptors and stabilization of blood pressures is critical in preventing HDI due to catecholamine secretion from intraoperative tumor manipulation.^{14,15} Patients are generally considered to be appropriately blocked and thus optimized for resection of their tumors when hemodynamic parameters are normalized (ie, SBP 90–140 mm Hg, DBP 60–90 mm Hg, Pulse < 100 bpm). The broad range of duration of preoperative blockade in our patient population can be attributed to occasional difficulties with surgical scheduling, issues of patient adherence to medication, and longer times required to achieve adequate blockade. Our study showed that the preoperative courses of patients in the two cohorts were largely the same. Patients with PCC or PG exhibited similar baseline blood pressure readings, underwent a similar duration of preoperative α -blockade, and required similar cumulative phenoxybenzamine dosages (Table 1).

Important differences were found between the two tumor groups when analyzing the intraoperative variables, with our results suggesting that patients undergoing PG resection were prone to greater blood loss and longer operations than those patients undergoing PCC resection (Table 2). While an open approach to resection was more often necessary in the PG cohort, both tumor groups experienced a similar number of episodes of intraoperative HDI. The intraoperative use of magnesium sulfate at the discretion of the anesthesiologist and other vasoactive medications were similar among the two tumor groups.¹²

Clinical practice guidelines currently recommend intensive postoperative monitoring for HDI in patients undergoing PCC or PG resection.^{16,17} However, postoperative morbidity and mortality in these patients remain uncommon.¹⁸ Recent research has attempted to identify tumor characteristics and patient factors that may better stratify patients into

high- and low-risk groups for more personalized postoperative management.¹⁹ In our study, patients in the PG cohort more frequently had hypertension and/or hypotension requiring medical intervention in the first 48 hours after surgery, and they required significantly longer postoperative hospital stays than the patients in the PCC cohort (Table 2). These results may suggest differing postoperative HDI risk profiles in patients with PG vs PCC; perhaps more frequent SICU admission and more intensive postoperative monitoring is warranted for patients undergoing PG resection. However, in our study it is difficult to assert whether HDI in the PG group is due to pathologic properties of these tumors, or rather, due to the greater operative blood loss and more frequent open procedures.

In an attempt to address this question, we performed the subgroup analysis, comparing perioperative hemodynamic parameters among the pheochromocytoma and paraganglioma groups stratified by operative approach. Interestingly, patients undergoing an open resection of PCC were more prone to HDI than their counterparts undergoing open resection of PG. Similar to our initial, overall comparison between the two tumor groups, patients undergoing laparoscopic PG resection were statistically more likely to have greater intraoperative blood loss and to experience HDI in the postoperative setting. These results provide some support to the idea that inherent pathologic, anatomic, or clinical differences between pheochromocytomas and paragangliomas may confer differing risks of per-operative HDI. The difference in postoperative HDI between the two groups as identified in our study may provide support for a disease-specific approach to PCC and PG resection.

Our study has some limitations. Due to the rarity of PG and the low sample size of patients in our single-institution study, we are limited in our ability to identify predictors of intraoperative HDI in the PG cohort. Also, the utilization of vasoactive agents and magnesium sulfate to control HDI may differ significantly between institutions,

which may not allow for generalized comparisons. To further address these limitations, an expanded multicenter study involving larger patient groups is warranted. In general, our study was additionally limited by its retrospective nature; therefore, prospective studies comparing perioperative HDI in PCC and PG groups would be useful. Finally, there is a potential confounding bias in the PG cohort. The more challenging anatomic locations of PGs make a laparoscopic approach less feasible. This is likely a contributing factor to the differences in surgical approach and operative blood loss in our study.

Recent retrospective studies have identified the potential of clinically useful variables that predict intraoperative HDI in PCC resection, including cumulative phenoxybenzamine dose, use of intraoperative magnesium and vasopressin, and preoperative SBP.^{6,20} Our results were in agreement with these studies; we identified that larger tumor size and open surgical approach predict HDI in PCC resection. To strengthen our conclusions, a larger PCC cohort allowing for valid multivariable regression models would be useful. Additionally, a larger PG cohort would allow for similar regression models to identify predictors of intraoperative HDI in this group and to compare and contrast predictors across the two tumor groups.

Conclusion

Patients undergoing PCC or PG resection had similar preoperative pharmacologic blockade requirements and experienced a similar number of episodes of intraoperative HDI. However, patients in the PG cohort were prone to more complicated operations with greater blood loss, required more frequent open procedures, and were more likely to have HDI in the postoperative period. When controlling for operative approach, patients with PCC undergoing an open approach had greater intraoperative HDI than PG patients undergoing an open approach. Therefore, PG patients are more likely to undergo an open approach than PCC patients and require intensive monitoring. However, when

PCC patients do require an open approach, they may need more intensive monitoring compared to PG patients who undergo open procedures. Conversely, patients with PG undergoing laparoscopic approach had greater intraoperative blood loss and postoperative HDI than patients with PCC undergoing a laparoscopic approach. Tumor size and operative approach appear to be predictive of intraoperative HDI in the PCC cohort.

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