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후복막강의 부신경절종의 크기가 환자의  
수술 중 혈압 불안정 예측인자로 중  
요하다.

Mass size is Important to Predict Fluctuation of Blood  
Pressure during Surgery in Patients with Paraganglioma  
of Retroperitoneum.

울 산 대 학 교 대 학 원  
의 학 과  
윤지형

Mass size is Important to Predict  
Fluctuation of Blood Pressure  
during Surgery in Patients with  
Paraganglioma of Retroperitoneum.

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이 논문을 의학 석사학위 논문으로 제출함.

2022 년 2 월

울 산 대 학 교 대 학 원  
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윤지형의 의학석사 학위 논문을 인준함

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2022년 2월

## 감사의 글

어느새 2년간의 석사 과정이 끝나고 학위 논문을 제출하게 되었습니다. 본 석사 학위논문 작성에 도움을 주신 분들께 감사의 글을 올립니다.

주제선정 과정 및 논문 작성 전반에 도움을 많이 주신 박성찬 지도 교수님께 진심으로 감사드립니다.

논문에 대해 조언 및 격려를 해 주신 심사위원장 김성철 교수님, 심사위원 권택민 교수님께도 깊은 감사를 올립니다.

논문 작성 과정에서 무한한 신뢰와 응원을 준 반려자 이영숙에게도 고마움과 사랑을 전합니다.

## 국문요약

**목적:** 방광을 포함한 후복막에서 발생하는 부신경절종은 매우 희귀하여 주로 증례나 연속물로 보고되고 있다. 부신경절종은 부신에 발생하는 갈색세포종과 같은 조직학적 소견을 보이나, 부신 이외에 발생하는 종양을 뜻한다. 부신의 갈색세포종에서는 수술 시 발생하는 불안정한 혈압에 관한 연구가 어느정도 되어 있으나, 부신경절종은 드문 종양으로 증례가 많지 않아 이에 대한 연구가 없다. 저자는 본 연구에서 후복막 부위의 부신경절종 수술 시 혈압 불안정에 영향을 미치는 인자들을 찾아보고자 하였다.

**방법:** 2006년 3월부터 2021년 5월까지 조직검사로 확인된 32명의 부신경절종 환자를 후향적으로 조사하였으며, 그 중에서 방광을 포함한 후복막 부위의 부신경절종을 가진 24명의 환자에서 수술 시 불안정한 혈압에 영향을 미치는 위험인자들을 분석하였다. 불안정한 혈압의 정의는 종양 제거 중에 수축기 혈압 200mmHg 이상 또는 80mmHg 이하인 이벤트가 있는 경우로 정하였다. 예측력은 receiver operating characteristic (ROC) 곡선의 곡선하면적 (area under the curve, AUC)으로 평가하였다.

**결과:** 32명의 부신경절종 환자에서 각 종양의 위치는 후복막강 19명, 방광 5명, 중이 2명, 종격 2명, 목 2명, 척추 1명, 그리고 십이지장 1명으로 나타났다.

방광을 포함한 후복막 부위의 24명의 환자 중에서 7명 (29.2%)의 환자에서 통증, 혈압 불안정, 촉진되는 종양 등의 수술 전 증상이 있었다. 수술 시 불안정한 혈압은 11명 (45.8%)의 환자에서 관찰되었다. 불안정한 혈압이 있는 군 (n=11)과 없는 군 (n=13) 사이에서 종양 크기가 가장 유의한 차이를 보였다 (P=0.007). 종양 크기에 따른 수술적 합병증의 예측에 대한 곡선하면적 (AUC)는 0.808 이었다. (4.25 cm에서 민감도 72.7%, 특이도 76.9%)

**결론:** 방광을 포함한 후복막 부위의 부신경절종 환자에서 종양 크기가 수술 시 불안정한 혈압에 유의한 영향을 미쳤다. 부신경절종이 의심되는 4.2 cm 이상의 후복막 부위의 종양 수술 시 불안정한 혈압의 발생을 조심해야 하겠다.

## **GLOSSARY**

**UB:** urinary bladder

**CT:** computed tomography

**TURB:** transurethral resection of the bladder

**AUC:** area under the curve

**ROC:** receiver operating characteristic

**MIBG:** metaiodobenzylguanidine

**PET-CT:** positron emission tomography - computed tomography



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## INTRODUCTION

Paraganglioma, known as extra-adrenal pheochromocytoma, can be located in the retroperitoneum, thorax, head, neck, urinary bladder (UB), etc.(1). It is a sporadic tumor and comprises 18% of pheochromocytomas with 10% in the bladder(2). Paraganglioma of the UB comprises approximately 0.06% of bladder tumors(2, 3).

Paragangliomas produce catecholamines such as epinephrine, norepinephrine, metanephrine, and dopamine. Thus, they can induce severe hypertension, tachycardia, and even death. The classic triad of clinical symptoms are palpitation, headache, diaphoresis, however, anxiety, panic attack, syncope, abdominal pain, and weight loss can appear in some cases(4, 5). In addition, paraganglioma of the UB also induces hematuria and urinary attack –, which are due to catecholamine release caused by micturition or distension of the bladder(3, 6). These symptoms can help in the diagnosis of paraganglioma, but some patients do not have symptoms in some cases; thus, preoperative diagnosis is difficult. Then, the incidental discovery of paraganglioma is becoming common with the widespread use of computed tomography (CT)(7, 8).

The only curative treatment for paraganglioma is surgical resection(9). However, surgical manipulation of paragangliomas can induce a massive release of catecholamines leading to the fluctuation of blood pressure, arrhythmia, myocardial infarction, and stroke(10). Thus, preoperative medication of combined  $\alpha$ - and  $\beta$ -adrenergic blocker therapy is necessary to control hypertension and prevent intraoperative fluctuation of blood pressure. Intraoperative hypertension could be treated with nitroprusside(9, 11).

To date, the risk factors for fluctuation of blood pressure during surgery, are unknown. To our knowledge, this study is the first to evaluate risk factors for intraoperative fluctuation of blood pressure in patients with retroperitoneal paragangliomas.

## MATERIALS AND METHODS

### *Study design and patients*

We conducted a retrospective chart review of 32 patients who had a pathological diagnosis of extra-adrenal paraganglioma between March 2006 and May 2021. We analyzed the risk factors impacting surgical complications such as massive bleeding or fluctuation of blood pressure in 24 patients with retroperitoneal paragangliomas including 5 UB paragangliomas. The mean patients age was  $63.8 \pm 11.4$  years. The male:female ratio was 13:11. The mean systolic and diastolic blood pressure were  $128.1 \pm 15.4$  mmHg and  $76.8 \pm 8.6$  mmHg, respectively (**Table 1**). There was preoperative hypertension in 11 patients (45.8%). The follow-up period was  $55.2 \pm 48.2$  months.

For the UB paragangliomas, transurethral resection of bladder (TURB) using bipolar current was performed for UB paragangliomas in three patients, robot-assisted partial cystectomy was performed in one patient and open partial cystectomy was performed in one patient with end stage renal disease. For the retroperitoneal masses, laparoscopic and open resections were performed in five and 14 patients, respectively. Complications included massive bleeding (requirement for transfusion of blood) or fluctuation of blood pressure during surgery. Fluctuation of blood pressure was defined as systolic blood pressure  $> 180$  mmHg during the excision of the mass(12, 13). Thereafter, we compared the clinical features of patients with and without fluctuation of blood pressure.

**Table 1.** Clinical characteristics of the patients with retroperitoneal paraganglioma

Retroperitoneal paraganglioma including urinary bladder	
(n=24)	
Sex (male : female)	13:11
Age, years	63.8 ± 11.4
Body mass index, kg/m <sup>2</sup>	24.3 ± 3.8
History of hypertension, n (%)	11 (45.8)
Preoperative blood pressure	
Systolic, mmHg (mean ± SD)	128.1 ± 15.4
Diastolic, mmHg (mean ± SD)	76.8 ± 8.6
Follow-up period, months	55.2 ± 48.2

SD: standard deviation

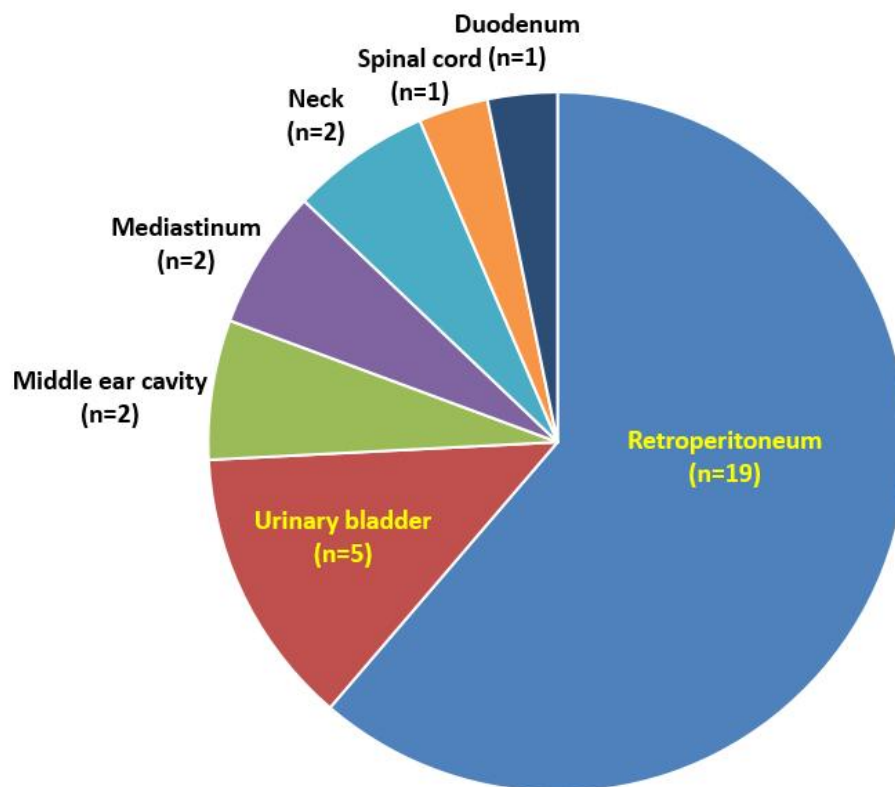
### ***Ethics statement and statistical analyses***

This study was approved by our institution review board (UUH-2021-12-009). Statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (IBM Corporation, Armonk, NY, USA). The Wilcoxon signed-rank test, Mann–Whitney U test, and chi-square trend test were used to evaluate the significance of differences between the groups. All statistical analyses were two-sided, and  $p < 0.05$  was considered statistically significant. The predictive power was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

## RESULTS

There were 32 patients with paraganglioma. Regarding tumor locations, there were 19 retroperitoneal, five UB, two middle-ear cavity, two mediastinal, two neck, one spinal cord, and one duodenal paraganglioma (**Fig. 1**). Of these, we analyzed the 24 patients (75%) with retroperitoneal and UB paragangliomas.

**Fig. 1. Tumor locations of the 32 paragangliomas**





There was fluctuation of blood pressure in 11 (45.8%) of the 24 patients. Four patients experienced massive bleeding during the surgery; however, there were no unusual clinical courses after surgery. Seven (29.2%) of the 24 patients had preoperative symptoms such as pain, fluctuation of blood pressure, and palpable mass (Table 2). There was no recurrence or disease specific mortality in all 24 patients for an average of 55.2 months after follow-up.

**Table 2.** Clinical outcomes in patients with retroperitoneal paragangliomas

	Retroperitoneal paraganglioma including urinary bladder (n=24)
Preoperative symptoms, n (%)	7 (29.2)
Pain	4 (16.7)
Fluctuation of blood pressure	2 (8.3)
Palpable mass	1 (4.2)
Mass size, cm	
Mean $\pm$ SD	4.1 $\pm$ 3.2
Range	0.6 - 11.5
Events during surgery, n (%)	
Massive bleeding	4* (16.7)
Fluctuation of blood pressure	11 (45.8)
Recurrence, n	0
Disease specific death, n	0

\* Four patients had elevated blood pressure and massive bleeding during surgery.

SD: standard deviation

Between patients with (n=11) and without (n=13) fluctuation of blood pressure, there was a significant difference in mass size ( $5.9 \pm 3.4$  cm vs  $2.6 \pm 2.1$  cm,  $p = 0.007$ ). The mass location also significantly differed between the two groups ( $p = 0.018$ ). However, the mean size of the bladder mass was significantly smaller than that of the retroperitoneal mass except for the bladder ( $1.59 \pm 1.2$  cm vs  $4.8 \pm 3.2$  cm,  $p = 0.002$ ). There was no difference in age, sex, height, weight, blood pressure, hypertension history, or presence of preoperative symptoms between the two groups (Table 3).

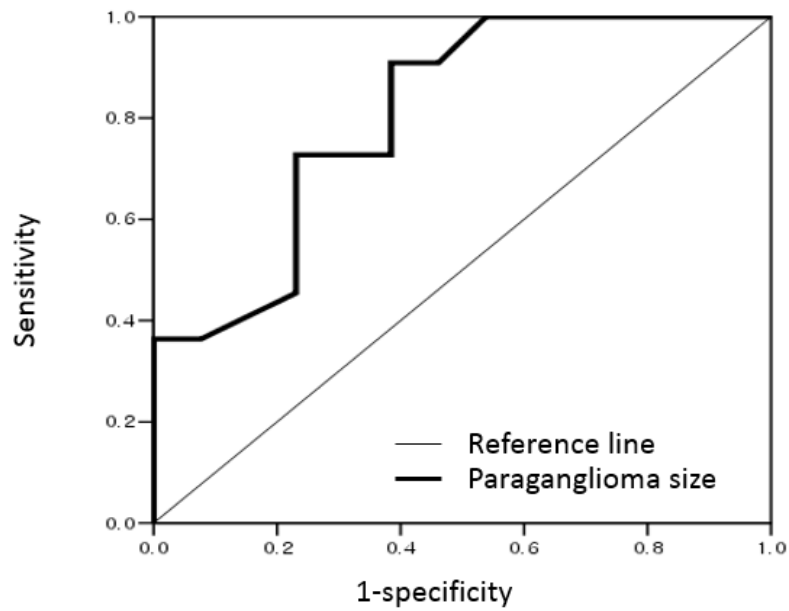
**Table 3.** Comparison of risk factors between the groups with and without fluctuation of blood pressure during surgery

	No complicated events (n=13)	Fluctuation of blood pressure (n=11)	P-value
Age, years (mean $\pm$ SD)	62.7 $\pm$ 11.3	65.0 $\pm$ 12.0	0.635
Sex (male : female)	8 : 5	5 : 6	0.454
Height, cm (mean $\pm$ SD)	163.0 $\pm$ 7.2	161.4 $\pm$ 9.1	0.623
Weight, kg (mean $\pm$ SD)	64.3 $\pm$ 10.4	62.7 $\pm$ 11.9	0.747
Blood pressure			
Systolic, mmHg (mean $\pm$ SD)	129.2 $\pm$ 17.0	126.8 $\pm$ 13.8	0.714
Diastolic, mmHg (mean $\pm$ SD)	76.2 $\pm$ 7.2	77.5 $\pm$ 10.3	0.727
Hypertension history, n (%)	6 (46.2)	5 (45.5)	0.698
Preoperative symptoms, n (%)	2 (15.4)	5 (45.5)	0.142
Mass location, n (%)			0.018
Bladder	5 (38.5)	0 (0)	
Retroperitoneum	8 (66.7)	11 (100)	
Mass size, cm (mean $\pm$ SD)	2.6 $\pm$ 2.1	5.9 $\pm$ 3.4	0.007

SD: standard deviation

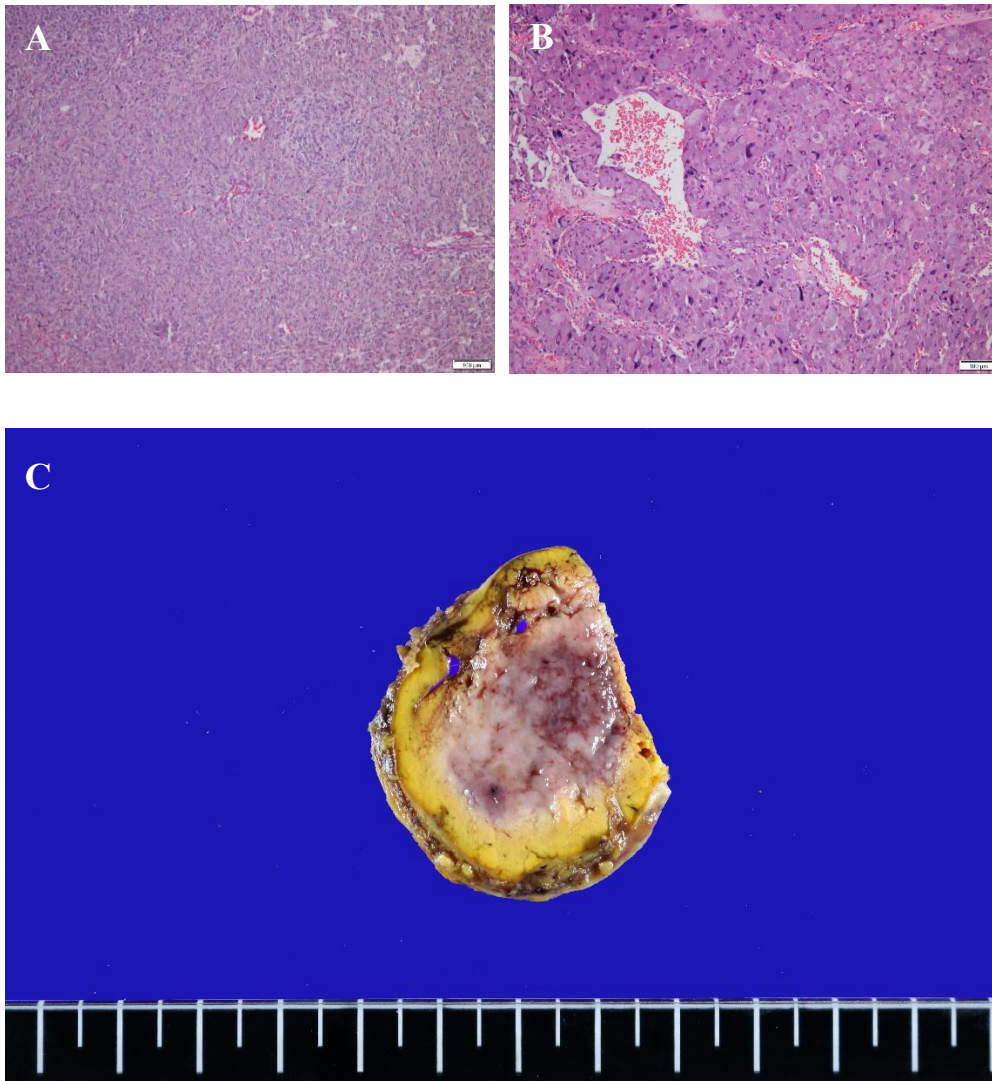
ROC analysis showed that the AUC for predicting surgical complications according to mass size was 0.808 (**Fig. 2**). At cutoff mass size of 4.25 cm, the sensitivity and the specificity were 72.7% and 76.9%, respectively.

**Fig. 2.** Receiver operating curves for predicting fluctuation of blood pressure during surgery according to mass size. The area under the curve was 0.808. At cutoff mass size of 4.25 cm, the sensitivity and the specificity were 72.7% and 76.9%, respectively.



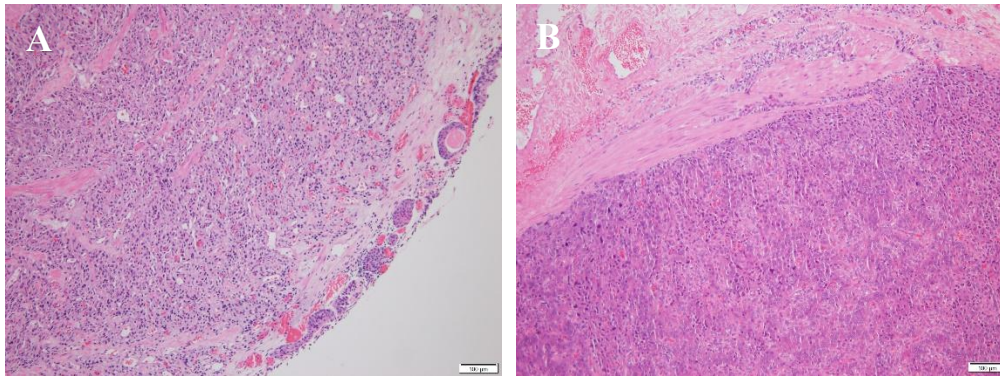
Histopathology of paraganglioma typically shows well-defined nests (Zellballen) composed of chief cells and Bizarre nuclei (**Fig 3**). Paraganglioma in UB can invade the muscle layer, although the tumor is benign (**Fig 4**).

**Fig. 3.** Histopathology of retroperitoneal paraganglioma A) In low field magnification, well-defined nests (Zellballen) composed of chief cells with abundant basophilic granular cytoplasm can be seen. B) Bizarre nuclei can be seen but are unrelated to malignancy. C) Gross findings: the cut surface of the mass was yellowish-brown, diffusely multifocally necrotic, and surrounded by a thin fibrous capsule, which was grossly intact.





**Fig. 4.** Histopathology of paraganglioma of the urinary bladder A) Small cells with hyperchromatic nuclei and scant cytoplasm markedly infiltrated the subepithelial layer of the bladder. B) Neoplastic cells infiltrating the adjacent muscle layer of the bladder can be seen.



## DISCUSSION

Paraganglioma can present with various features such as pain, hypertension, and palpitation like pheochromocytoma. In this study, most patients had no symptoms, and the paraganglioma was incidentally found with CT or during surgery. Moreover, only seven patients underwent preoperative blood and urine evaluation for catecholamine to diagnose paraganglioma. Moreover, for patients with pheochromocytoma, an adrenal mass is usually diagnosed imaging studies; thereafter, biochemical testing is performed in all patients with adrenal mass before surgery(14). This difficulty in diagnosing paraganglioma before surgery unlike for pheochromocytoma, has made the un-predicting risk of complications such as fluctuation of blood pressure and massive bleeding during surgery(8). Therefore, to prevent these complications, we evaluate preoperative risk factors for fluctuation of blood pressure in patients with retroperitoneal paragangliomas, because predicting fluctuation of blood pressure is essential. According to the results in the current study, all patients with symptoms had retroperitoneal paraganglioma. In addition, events during surgery occurred only in cases of retroperitoneal paraganglioma. However, it seems that this difference was not due to the location, but the size of the paraganglioma. Thus, history taking is important, when paraganglioma is suspected, especially if a huge mass (> 4.2 cm) is noted. Thereafter endocrinologic evaluation and treatment before surgery are required. Functional imaging such as MIBG scan and PET-CT is also helpful(15, 16). Moreover, preoperative combined  $\alpha$ - and  $\beta$ -adrenergic blocker therapy can reduce the fluctuation of blood pressure during surgery(4, 17). Furthermore, in these patients, operators should be careful during surgical manipulation.

There were a few limitations to this study. First, the number of patients was small because paraganglioma is notably rare. Therefore, multicenter studies are required for more accurate results. Second, the current study was retrospective. However, a prospective study of paraganglioma would be complex because the diagnosis of paraganglioma is difficult and incidental. Third, the sizes of UB paraganglioma in the current study were small, as such we could not confirm if the huge UB paraganglioma could induce intraoperative events. However, there are some case reports on this subject. Kurose et al. reported on a 32-mm UB paraganglioma(18). At TURB initiation, the patient's systolic

blood pressure was 120 mmHg but was acutely elevated to over 200 mmHg, and the tumor easily bled. Falcao et al. also reported a UB paraganglioma that underwent by transurethral resection with blood pressure elevation(19).

Considering recent developments, robotic surgery may be helpful depending on the operator. This should help reduce fluctuation of blood pressure and severe complications. There are a few similar studies on risk factors for fluctuation of blood pressure during pheochromocytoma surgery. In those studies, risk factors aware large tumor size and high urine catecholamine levels(12, 20). Since pheochromocytoma and paraganglioma are histologically the same tumors, it is expected that they show similar patterns. Thus, urine catecholamines should be considered in further studies.

## **CONCLUSION**

Mass size impacted fluctuation of blood pressure during surgery in patients with retroperitoneal paraganglioma. Caution is required regarding fluctuation of blood pressure during the resection of a retroperitoneal mass exceeding 4.2 cm suspected as paraganglioma.

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## **ABSTRACT IN ENGLISH**

**Purpose:** Paragangliomas of the urinary bladder (UB) and retroperitoneum are notably rare tumors and have only been recorded as case report or case series. We aimed to investigate factors related to surgical complications such as fluctuation of blood pressure during surgery in patients with paraganglioma.

**Materials and Methods:** Our retrospective chart review included 32 patients who had a pathological diagnosis of paraganglioma between March 2006 and May 2021, in single center. We analyzed the risk factors impacting fluctuation of blood pressure in 24 patients with retroperitoneal paragangliomas including UB. Fluctuation of blood pressure was defined as systolic blood pressure > 180 mmHg during excision of the mass. The predictive power of risk factor was assessed by the area under of the receiver operating characteristic (ROC) curve (AUC).

**Results:** There were 19 retroperitoneal, 5 UB, 2 middle-ear cavity, 2 mediastinal, 2 neck, 1 spinal cord and 1 duodenal paraganglioma. Seven (29.2%) of the 24 patients had preoperative symptoms such as pain, fluctuation of blood pressure, and palpable mass. Fluctuation of blood pressure during surgery occurred in 11 patients (45.8%). There was a significant difference in mass size between groups with (n=11) and without (n=12) fluctuation of blood pressure (p=0.007). The AUC for predicting surgical complications according to mass size was 0.808 (cutoff size 4.25 cm, sensitivity 72.7%, specificity 76.9%).

**Conclusions:** Mass size impacted fluctuation of blood pressure during surgery in patients with retroperitoneal paraganglioma. Surgeons have to be watchful regarding of fluctuation of blood pressure during resection of retroperitoneal masses exceeding 4.25 cm, which are suspected as paraganglioma.