## Title

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# International Multicentre Review of Perioperative Management and Outcome for Catecholamine-Producing Tumours

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## Abstract

**Background:** Surgery for catecholamine producing tumours can be complicated by intra- and postoperative haemodynamic instability. Prior to 1960, mortality rates ranged between 20 and 48%, but subsequently decreased substantially. However, in surgery for rare diseases, perioperative mortality may be difficult to determine accurately. Several perioperative management strategies have emerged but none evaluated in randomised trials. To assess this issue, contemporary perioperative management and outcome data from 21 centres were collected.

**Methods:** After local ethic board approval, 21 centres contributed outcome data from phaeochromocytoma and paraganglioma surgical patients. The data included the number of cases (with and without α-receptor blockade), surgical and anaesthetic techniques, complications and perioperative mortality.

**Results:** Across all centres, data from 1860 phaeochromocytoma and paraganglioma patients (343 without α-receptor blockade) were reported. The vast majority were performed using minimally invasive surgical techniques (79%) including 17% adrenal cortex sparing procedures. The overall cardiovascular complication rate was 5.0%: 5.9% (90/1517) in patients pretreated with an α-receptor blockade and 0.9% (3/343) for non-pretreated patients. Overall mortality was 0.5% (9/1860): 0.5% (8/1517) in pretreated and 0.3% (1/343) in non-pretreated patients.

**Conclusion:** There is substantial variability to the perioperative management of catecholamine producing tumours, yet the overall complication rate is low. This review provides an opportunity for systematic comparisons between practices with variable management strategies. Further studies are needed to better define optimal management approach. Reappraisal of international perioperative guidelines appears desirable.

## Introduction

Phaeochromocytoma and paraganglioma are rare diseases with an incidence of approximately 1 in 100.000 persons per year.[1] These tumours produce catecholamines, including epinephrine, norepinephrine, and dopamine, potentially leading to episodes of tachycardia, palpitations, diaphoresis, and extreme arterial hypertension. Over time, non-physiologic and excessive release of these hormones can lead to cardiovascular complications, decompensation and death. Surgical removal is the treatment of choice.[1–3] Intraoperative manipulation of the tumour can elicit hypertensive crises, which historically have been regarded as responsible for perioperative mortality rates of up to 48%.[1–3]

Over the last 60 years the perioperative mortality rate has dramatically decreased to a rate as low as 2 – 7%.[1–10] However, for rare diseases, overall mortality and morbidity are difficult to ascertain and are often derived from small single-institution case series.[1–10] It is even

more difficult to determine the factors contributing to the observed extraordinary reduction in mortality rates. The improvement in mortality has most often been attributed to the introduction of perioperative α-receptor blockade. However, many other advances in diagnostics, monitoring, surgery, and anaesthetic management have occurred concurently, and have also likely contributed to these improvements by allowing for earlier diagnosis, more precise tumour localization, less surgical trauma, improved monitoring and better intraoperative blood pressure control.[5, 11–20]

The clinical impact of these care elements on patient's outcomes has never been comprehensively investigated.[1–3, 21–23] In rare diseases such as catecholamine producing tumours, randomised controlled studies to examine individual interventions on clinical outcomes including mortality is unlikely to occur. With an expected mortality rate of 1% - 3%, several thousand patients would be needed for adequate power.

Precisely because of the relative infrequency of these tumors, evidence-based recommendations for best perioperative practice are highly desirable. Given the inability to conduct large randomised trials the Phaeochromocytoma and Paraganglioma initiative (PPI) was founded to establish an international multicentre retrospective data base and to permit analysis of aggregate case data from international centres with significant experience with this disease. The ultimate goal was to assess surgical approaches, perioperative anaesthetic management, and post-surgical outcomes, and to evaluate the need for, and effectiveness of, specific management strategies. To this end information of perioperative data from more than 1800 patients was collected.

## Methods

The PPI was initiated in 2015 and includes experts from Europe, North America, Asia and Australia. The aim was to summarise patient outcomes as well as contemporary anaesthetic and surgical techniques employed to manage surgical procedures for catecholamine producing tumours. To minimise the influence of management changes over time, procedures and data prior to the year 2000 were excluded. Most data for this study originated in the decade preceding completion of data collection on November 1, 2017.

Participating centres from 6 countries (Australia, Germany, Ireland, Japan, The Netherlands and the United States of America) collaboratively generated a single questionnaire to capture data from each centre. The centres were variably represented by physicians from Departments of Surgery, Anaesthesia, and Endocrinology. Each centre received approval from their respective institutional review boards (IRB) or ethics committees. In some centres, IRB or ethics approval was waived citing the use of de-identified summary data. Exclusevely, data from histologically verified tumours were included.

In addition to the key aim of describing perioperative management strategies, including surgical and anaesthetic techniques, the use of preoperative α-receptor blockade was specifically evaluated with respect to outcomes.

### Patients, Data Acquisition, and Perioperative Management

Collected data included the presence of either phaeochromocytoma or paraganglioma; the type of surgical approach; open laparotomy or endoscopic, minimally invasive surgery, and adrenal cortex sparing resection. The percentage of patients receiving preoperative α-receptor blockade and the various agents used was recorded.

Anaesthetic variables include information regarding centre use of routine central venous catheters and/or invasive arterial lines, the choice of drugs used for intraoperative blood pressure management, and the number of patients, who received combined epidural-general anaesthesia compared to general anaesthesia only.

### Outcome Analysis

The main outcome variables were intraoperative hypertensive crises, and perioperative morbidity and mortality. These complications were described overall and separately by use of preoperative preparation with α-adrenergic receptor blockers. The number of patients who intraoperatively experienced hypertensive crises defined as systolic blood pressure increase above 250 mmHg (each patient was counted as one regardless of the number of episodes). Procedural complications were counted only if they were related to catecholamine-producing tumor specific pathology (i.e., related to haemodynamic instability). Specifically, this included cardiac decompensation, myocardial infarction, symptomatic hypertension, transient or persistent cerebral ischaemia, orthostatic dysregulation, sustained hypotension, sustained arrhythmia, acute respiratory failure, hypoglycaemia or pulmonary embolism. Other perioperative morbidities, such as wound infection, postoperative nausea and vomiting, transfusion requirements were not included.

All intra- and postoperative death within 3 months of operation were assessed and briefly described for each patient.

### Data Analysis

We used descriptive statistics to display our data. Data are presented as percentages with 95% confidence intervals [CI]. We compared differences in the incidence of blood pressure episodes above 250 mmHg, morbidity and mortality between patients with or without α-receptor blockade using the chi-square-test. An analysis for confounding variables was not performed due to the small fraction and type of data that each individual centre was able to contribute to the completed data set. A p-value $< 0.05$ was considered significant. Data were analyzed using Statview software (Version 5.0.1, SAS Institute inc., Cary NC, USA).

## Results

### Characteristics of the Centres

Twenty-five centres were contacted and 21 centres provided data. Across all centres, a total of 1,860 patients were included. The number of patients included differed substantially across centres from 7 at Langen, Germany to 504 at Essen, Germany. Some of the centres could not retrieve a complete data set (Tables 1,2,3). One centre could not provide data about partial resections, one centre could not specify the type of α-receptor blockade used for

preoperative preparation, three centres could not determine the frequency of episodes with an intraoperative systolic blood pressure above 250 mmHg, and two centres could not provide the number of patients requiring postoperative intensive care treatment. For the centre with the largest group of patients without α-receptor blockade a separate table was provided to describe the groups of patients with or without α-receptor blockade (table 4).

### Surgical Approach and Preoperative Preparation

Most of the procedures were performed endoscopically with the exception of large tumours and patients that were scheduled for multi-visceral resections in addition to that for the catecholamine producing tumour (n=4, table 1).

α-receptor blockade was routinely used by many centres. Phenoxybenzamine was the predominant agent used (11 centres), followed by alternative α-receptor blocking drugs such as doxazosin (3 centres), prazosin (3 centres) and terazosin (1 centre) (table 1). Two centres did not use routine α-receptor blockade.

All resected tumours were histologically verified as either phaeochromocytoma or paraganglioma.

### Anaesthetic Approach

All procedures were performed under general anaesthesia. As opposed to minimally invasive surgical approaches, some of the open procedures received a combined epidural and general anaesthetic technique (7.2%). Anaesthetists monitored and controlled intra- and postoperative blood pressure with invasive blood pressure measurements in all of the centres. The preferred vasoactive drugs and the use of central venous catheters are summarised in table 2.

### Perioperative Morbidity and Mortality

Episodes of excessive blood pressure increases (systolic blood pressure > 250 mmHg) were noted and presented in relation to the presence or absence of α-receptor blockade (table 3). We tracked the rate of tumour related morbidities (table 3; figure 1). All surgeries with a fatal outcome are described briefly in table 5 (figure 2).

### Morbidity and Mortality with and without Preoperative α-Receptor Blockade

The incidence of episodes of intraoperative arterial systolic blood pressure peaks above 250 mmHg did not differ between patients with and without α-receptor blockade (5.2% [4.9–6.4] for patients with and 7.6% [4.7–10.5] for patients without α-receptor blockade; p=0.086).

The tumour specific complications related to haemodynamic instability occurred in 93 (4.9%) patients. The rate was significantly higher in patients with preoperative α-receptor blockade (5.9% [4.7–7.1]) compared to patients without α-receptor blockade (0.9% [−0.1–1.9]; figure 1; p<0.001). In detail, for patients receiving α-receptor blocking agents, the following medication or tumour related morbidities occurred: symptomatic hypotension (n=8), orthostatic dysregulation (n=24), stroke or transient ischaemic attack (n=7), sustained

arrythmia (n=18), cardiac decompensation (n=17), myocardial infarction (n=4), pulmonary embolism (n=1), acute respiratory failure (n=1), hypoglycaemia (n=3), and arterial hypertension (n=7). For patients without α-receptor blockade one patient developed sustained hypotension, one hypertension, and one stroke.

Mortality was not different for patients with (8 of 1517; 0.5% [0.14–0.88]) and without α-receptor blockade (1 of 343; 0.3% [−0.27–0.86]; figure 2; p=0.569).

## Discussion

For rare diseases such as phaeochromocytoma and paraganglioma, management guidelines are mainly based on clinical experience, and formal outcome data leading to an evidence-based management approach are often difficult to obtain. To compare the relative mortality rates of different management techniques in a randomised trial at an expected mortality rate of 1%, several thousand patients would be required. Such a trial is unrealistic to accomplish. Most of the currently available information stems from small single-institution case series with less than one hundred patients, or from similar single-institution case series collected over prolonged time periods of 40 years or more. The interpretation of results from such case series is complicated in the first instance by the small numbers of patients, and in the second by the changes in surgical and anaesthetic techniques over time. Furthermore, management strategies often reflect only the practice and expert opinions of a single centre. [6, 24, 25] Therefore, it was sought to collect data from international centres, and focused on a recent patient cohort, limiting patient selection to those occurring from the years 2000 – 2017.

In more than 80% of patients, surgery was performed using a minimally invasive approach (laparoscopically using the transabdominal approach and to a lesser extent retroperitoneoscopically). For specific endocrine syndromes such as von Hippel-Lindau disease or multiple endocrine neoplasia gland sparing techniques were used frequently (19% of all patients). This finding is similar to that of a previous large retrospective study from 2014, which focused on patients with multiple endocrine neoplasia type 2. [24]

Since most of the procedures were performed with a minimally invasive approach, general anaesthesia without an epidural catheter was employed in 94% of the patients. In a small number of patients receiving primarily open surgery, general anaesthesia was combined with epidural anaesthesia.

All centres used invasive arterial blood pressure measurement for continuous haemodynamic monitoring. Approximately half of the European centres (n=4) used a central venous catheter as their standard of care for administration of vasoactive medications, while American centres applied central venous catheters in selected patients only. The preferred vasopressor was norepinephrine followed by phenylephrine and the preferred vasodilators were sodium nitroprusside and urapidil.

The preferred medication regimen may be influenced by issues of drug demand and supply, particularly if such drugs are limited to use in a small patient population. Patients with rare diseases require only small quantities of specific medications such as sodium nitroprusside,

phentolamine or phenoxybenzamine, thus making their production commercially unattractive for pharmaceutical companies. Therefore, some of these drugs are either no longer produced or have to be imported at an excessively high cost influencing decisions regarding which drug to use.[26]

Perioperative α-receptor blockade was introduced approximately 60 years ago with the rationale to provide improved intraoperative haemodynamic control, particularly of anticipated hypertensive episodes. This concept still prevails, and the use of preoperative α-receptor blockade is regarded as standard of care for preoperative preparation in the 2014 guidelines for the management of patients with catecholamine producing tumours.[2, 3] However, as for many of the management recommendations for catecholamine producing tumours, its efficacy has never been proven, and the potential adverse effects of this recommendation have never been evaluated. Based on the findings provided by this study, consideration of the potential adverse effects of α-receptor blockade and a discussion regarding its routine use in the contemporary management of these tumours is warranted.[22, 23, 27–29] Most of the data of patients without an α-receptor blockade stem from one centre and the question occurs whether the two groups of patients from this centre differ in their characteristics. Therefore, additional information about the two groups of patients was provided (table 4) to allow a better interpretation of the data. There were no significant differences between the two groups.

Though it has been assumed that preoperative α-receptor blockade provides safety regarding the complications of intraoperative hypertensive episodes, such treatment is associated with preoperative symptoms including orthostatic hypotension, and the time needed for drug titration may unnecessarily delay surgery. It is evident from several case series and data from this study, that, despite the use of an α-receptor blockade, excessive hypertension still occurs intraoperatively. In addition, patients receiving preoperative α-receptor blockade often develop clinically significant hypotensive episodes that continue into the postoperative period.[22, 23, 28, 30] In this study, 31 out of 90 patients with α-receptor blockade with tumour-related complications needed treatment because of arterial hypotension. With all these peculiarities associated with catecholamine producing tumours and the management of patients with and without α-receptor blockade, surgery on patients with these tumours should be performed in centres with expertise and a continuous case load of these procedures.

A second important recommendation from the 2014 management guidelines is the requirement for continuous postoperative hemodynamic monitoring for 24 hours. Therefore, the practice of postoperative monitoring was evaluated and a wide variation among the centres was found. Two to 68% of patients were postoperatively admitted to an intensive care unit.[2, 3] It has to be acknowledged that these data are likely to be influenced to some extent by institutional practices that may include routine ICU, intermediate care unit, or recovery room admission for these patients. However, it can be emphasised that none of the fatal outcomes in this study appear to have been preventable by 24 hours of intensive care unit monitoring, as the patients died in the immediate perioperative period or more than 40 hours later.

The number of patients treated with and without perioperative α-receptor blockade including the specific type of the α-blocker used was assessed. Phenoxybenzamine was the preferred agent followed by doxazosin, prazosin and terazosin.

Although statistically not different, excessive hypertension with maximal systolic blood pressure peaks above 250 mmHg tended to occur more often in patients without preoperative α-receptor blockade. This finding reflects inclusion of initially misdiagnosed patients, who started surgery with a diagnosis of an incidentaloma (an adrenal tumour without any known hormone production), which was ultimately confirmed to be a catecholamine producing tumour in the group of patients without α-receptor blockade. At least 6 of these misdiagnosed patients developed systolic blood pressure increases above 250 mmHg until the team could respond properly. Therefore, these patients might have biased this number of patients with excessive hypertensive episodes for the untreated group.

During almost a century of experience with phaeochromocytoma and paraganglioma surgery, advances in the understanding and management of these tumours have led to a dramatic decrease in perioperative mortality. Undoubtedly, many improvements in surgery, diagnostic techniques and anaesthetic management have contributed to this development. Unfortunately, determining the significance of any single reason for this improvement seems impossible. In the case of preoperative α-receptor blockade as a continued paradigm of care, these data suggests that the benefits are likely largely historical given the current contemporary anaesthetic and surgical capabillities.[1–3, 5, 21, 23, 29]

The perioperative mortality rate in this cohort was 0.5%. Eight deaths occurred in patients who had received preoperative α-receptor blockade, and one death occurred in a patient without α-receptor blockade. How these deaths were related to the catecholamine producing tumour or the surgery or their comorbidities is difficult to discern retrospectively, as the etiologies included sepsis and multiple morbidities unrelated to the catecholamine producing tumour. For this reason, a brief description of each patient was provided and leaves the interpretation of any connection to preoperative α-receptor blockade or lack thereof up to the reader. Half of the patients appear to have had an uneventful surgical procedure and three of the patients seem to be related more to hypotension than hypertension. At least two of these patients with refractory hypotension occurred under α-receptor blockade.

There are several limitations of the study, including its retrospective design. The encountered management concepts are often institution specific and driven by local expert opinion and centre experience. However, strength of this analysis is the contribution of data from 21 international centres, demonstrating a range of management practices.

This study includes patients from a 17-year period, and even during this relatively narrow time frame, changes in techniques and knowledge may have occurred. The time period for the study was limited in part because of the major change in surgical approach to many of these patients that occurred at the end of the 1990's with the shift from open to minimally invasive, endoscopic surgery.[1–3, 7, 8] This shift had a major impact on duration of surgery and the associated surgical trauma and stimulus. Therefore, only patients in or after the year 2000 were included. [21]

Lastly, considering the variations in the pathology of catecholamine producing tumours and the different types and amounts of catecholamines produced, 1860 patients are still a relatively small number to make any definitive conclusions to be reached regarding treatment strategies and their individual impact on patient morbidity and mortality.

However, this study reports data from the largest number of patients to date and is nearly tenfold higher than previous reports upon which current guidelines and the most recent mortality estimates are based.

Overall, in the absence of a large longitudinal data set, management of patients with catecholamine producing tumours, including the use of α-receptor blockers, has become largely dogmatic; additional study will help clarify which patients, if any, truly benefit from each intervention. The ultimate aim of the phaeochromocytoma and paraganglioma initiative is to advance our knowledge of the behaviour and management of catecholamine producing tumours, and to provide stronger evidence on which to base future clinical practice recommendations. These data highlight the need for a prospective, collaborative, international database, and for ongoing critical re-assessment and discussion of the contemporary perioperative management of these patients. Critical re-assessment and discussion of current specific elements of preoperative preparation should develop our knowledge in this area of expertise and up-date existing guidelines that are based on concepts that can neither be proven nor rejected but resemble dogma without data.

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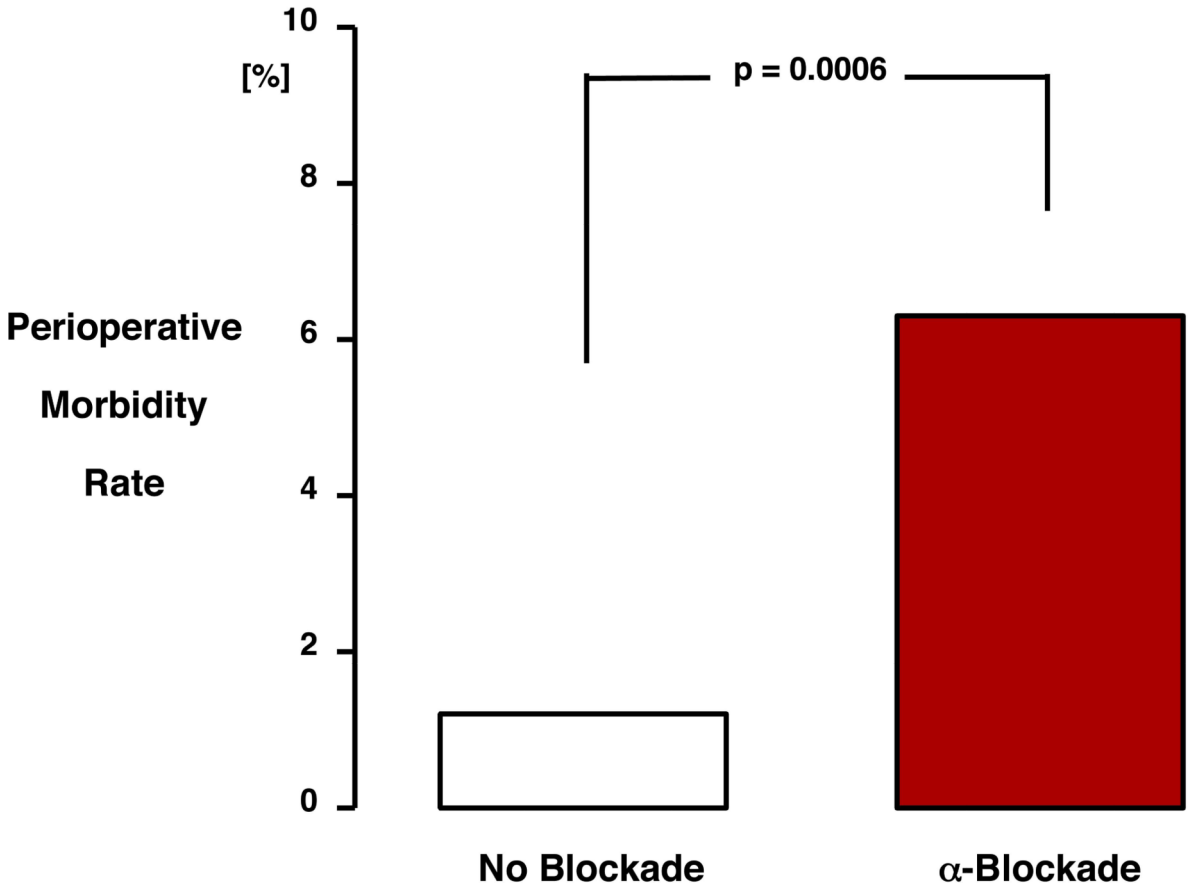


**Figure 1.**

Percentages of patients' complications, which are possibly related to intraoperative cardiovascular excesses, such as cardiac decompensation, myocardial infarction, stroke or sustained arrhythmias. White bars represent patients without α-receptor blockade, red bars patients with α-receptor blockade.

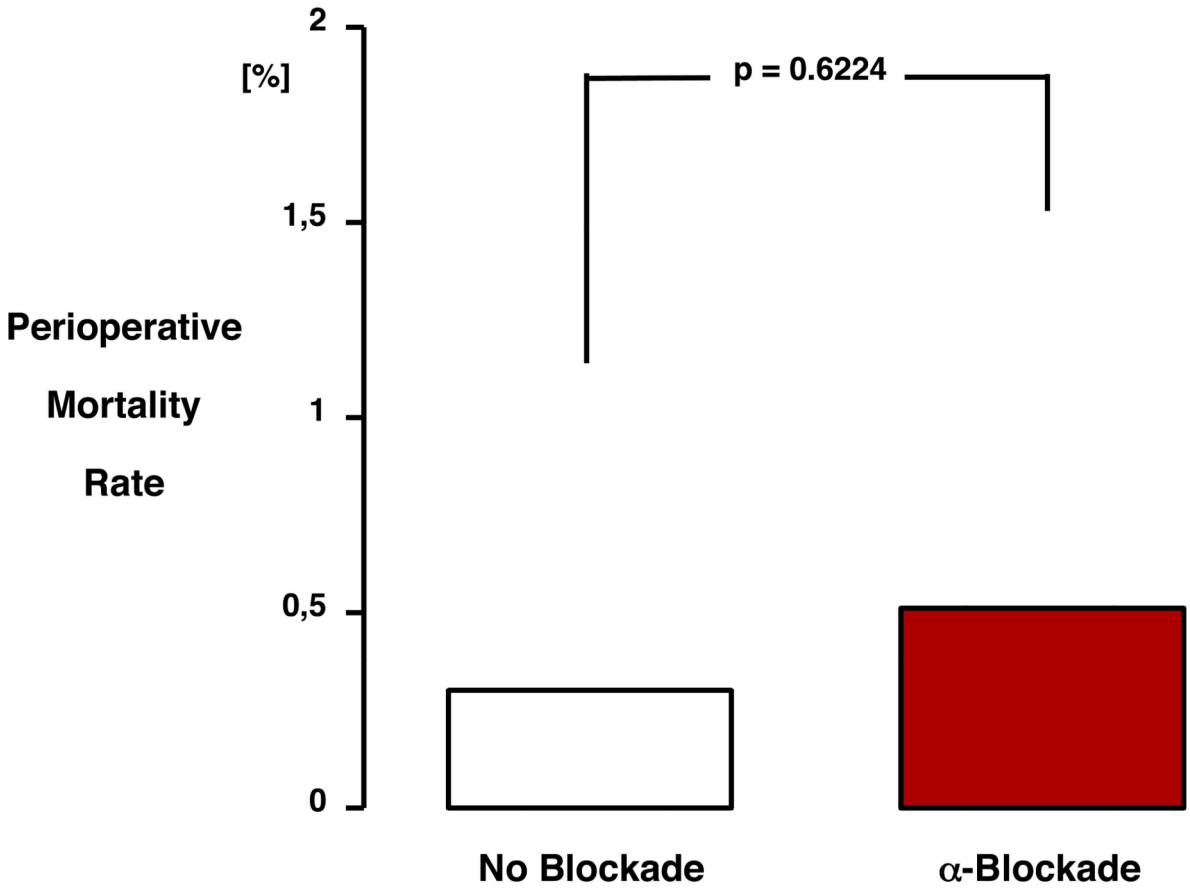


**Figure 2.**

Mortality rates of patients related to phaeochromocytoma or paraganglioma surgery. White bars represent patients without α-receptor blockade, red bars patients with α-receptor blockade. There was no significant difference in the mortality rate.

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**Table 1:**

Number of cases per center with phaeochromocytoma (Phaeo) or paraganglioma (Para), surgical technique (endoscopic or open, partial or complete), with and without α-receptor blockade and the use of phenoxybenzamine or alternative substances.

| Center | Evaluation | Cases (n) | Phaeo/Para (n/n) | endosc./open (n/n) | α-Bl/no Bl. | partial | phenox |
|---|---|---|---|---|---|---|---|
| Kliniken Essen-Mitte | 2001 – 2017 | 504 | 452 / 52 | 495 / 9 | 247 / 257 | 187 / 190 | 208 / 39 |
| Asklepios Klinik Langen | 2009 – 2013 | 7 | 3 / 4 | 6 / 1 | 1 / 6 | 0 / 3 | 0 / 1 |
| Amsterdam VUMC | 2012 – 2015 | 35 | no details | 33 / 2 | 35 / 0 | 0 / 0 | 10 / 25 |
| University Düsseldorf | 2001 – 2017 | 58 | 55 / 3 | 39 / 19 | 46 / 12 | 5 / 46 | 39 / 7 |
| Amsterdam AMC | 2008 – 2015 | 41 | 35 / 6 | 22 / 19 | 40 / 1 | 0 / 36 | 4 / 36 |
| San Francisco UCSF | 2000 – 2014 | 141 | 126 / 15 | 129 / 12 | 140 / 1 | 0 / 126 | 140 / 0 |
| University Galway | 2001 – 2015 | 17 | 16 / 1 | 9 / 8 | 17 / 0 | 0 / 16 | 14 / 3 |
| Tufts University Boston | 2005 – 2016 | 37 | 24 / 13 | 25 / 12 | 31 / 6 | 0 / 24 | 1 / 30 |
| Mayo Clinic Rochester | 2000 – 2016 | 258 | 210 / 48 | 161 / 97 | 247 / 11 | 0 / 210 | 240 / 7 |
| Royal Melbourne Hospital | 2000 – 2016 | 61 | 54 / 7 | 31 / 30 | 58 / 3 | 6 / 48 | 53 / 5 |
| Sapporo Medical University | 2006 – 2015 | 26 | 23 / 3 | 21 / 5 | 24 / 2 | 2 / 21 | 0 / 24 |
| Dresden University | 2008 – 2016 | 49 | 48 / 1 | 21 / 28 | 34 / 15 | no data | no data |
| University of Chicago | 2012 – 2016 | 27 | 25 / 2 | 26 / 1 | 26 / 1 | 1 / 24 | 18 / 8 |
| Vanderbilt University | 2002 – 2016 | 138 | 135 / 3 | 111 / 27 | 132 / 6 | 0 / 135 | 96 / 36 |
| Mass. General Hospital | 2002 – 2013 | 134 | 127 / 7 | 102 / 32 | 127 / 7 | 15 / 112 | 122 / 5 |
| Columbia University NY | 2006 – 2016 | 60 | 51 / 9 | 54 / 6 | 52 / 8 | 1 / 50 | 45 / 7 |
| Univ. Med. Center Groningen | 2001 – 2011 | 59 | 56 / 3 | 38 / 21 | 59 / 0 | 0 / 56 | 15 / 44 |
| Medical College of Wisconsin | 2010 – 2017 | 53 | 43 / 10 | 39 / 14 | 52 / 1 | 10 / 33 | 15 / 37 |
| Kl. München Bogenhausen | 2012 – 2017 | 10 | 10 / 0 | 9 / 1 | 7 / 3 | 0 / 10 | 7 / 0 |
| Portland OHSU | 2000 – 2017 | 80 | 72 / 8 | 59 / 21 | 77 / 3 | 5 / 67 | 51 / 25 |
| MDACC Univ. Texas | 2001 – 2017 | 65 | 61 / 4 | 37 / 28 | 65 / 0 | 10 / 51 | 31 / 34 |
| **Total** | | **1860** | **1626 / 199** | **1467 / 393** | **1517 / 343** | **242 / 1258** | **1108 / 348** |

**Table 2:**

Number of cases with phaeochromocytoma or paraganglioma, with (α-Bl) and without (no Bl.) α-receptor blockade. Cases were performed under general anaesthesia (GA) or combined general and regional anaesthesia (GA+RA). Preferred antihypertensive (Sodium-Nitroprusside = SNP), and antihypotensive drugs were listed and the use of central venous catheters (CVC).

| Center | Cases (n) | GA/GA+RA (n/n) | α-Bl/no Bl. | Antihypertensive Therapy | Antihypotensive Therapy | CVC |
|---|---|---|---|---|---|---|
| Kliniken Essen-Mitte | 504 | 504 / 0 | 247 / 257 | SNP | Norepinephrine | regularly |
| Asklepios Klinik Langen | 7 | 5 / 2 | 1 / 6 | SNP | Norepinephrine | regularly |
| Amsterdam VUMC | 35 | 33 / 2 | 35 / 0 | Urapidil | Phenylephrine, Norepinephrine | regularly |
| University Düsseldorf | 58 | 51 / 7 | 46 / 12 | SNP, Urapidil | Norepinephrine | regularly |
| Amsterdam AMC | 41 | 24 / 17 | 40 / 1 | Urapidil | Norepinephrine | individualized |
| San Francisco UCSF | 141 | 141 / 0 | 140 / 1 | SNP | Phenylephrine, Norepinephrine | individualized |
| University Galway | 17 | 9 / 8 | 17 / 0 | SNP, Urapidil | Norepinephrine | regularly |
| Tufts University Boston | 37 | 34 / 3 | 31 / 6 | SNP | Phenylephrine, Norepinephrine | individualized |
| Mayo Clinic Rochester | 258 | 258 / 0 | 247 / 11 | SNP, Nicardipine | Phenylephrine, Vasopressin | individualized |
| Royal Melbourne Hospital | 61 | 61 / 0 | 58 / 3 | Prazosin, Magnesium | Phenylephrine, Norepinephrine | individualized |
| Sapporo Medical University | 26 | 9 / 17 | 24 / 2 | Nicardipine, Nitroglycerin | Dopamine, Norepinephrine | regularly |
| Dresden University | 49 | 18 / 31 | 34 / 15 | Urapidil | Norepinephrine | individualized |
| University of Chicago | 27 | 26 / 1 | 26 / 1 | SNP | Phenylephrine | individualized |
| Vanderbilt University | 138 | 138 / 0 | 132 / 6 | SNP, Nicardipine | Norepinephrine, Phenylephrine | individualized |
| Mass. General Hospital | 134 | 124 / 10 | 127 / 7 | SNP, Phentolamine, Esmolol | Phenylephrine, Norepinephrine | individualized |
| Columbia University NY | 60 | 57 / 3 | 52 / 8 | Nicardipine | Phenylephrine | individualized |
| Univ. Med. Center Groningen | 59 | 59 / 0 | 59 / 0 | Phentolamine, Urapidil | Norepinephrine, Phenylephrine | individualized |
| Medical College of Wisconsin | 53 | 53 / 0 | 52 / 1 | SNP | Phenylephrine | individualized |
| Kl. München Bogenhausen | 10 | 9 / 1 | 7 / 3 | Urapidil | Norepinephrine | individualized |
| Portland OHSU | 80 | 64 / 16 | 77 / 3 | Phentolamine | Phenylephrine, Norepinephrine | regularly |
| MDACC Univ. Texas | 65 | 53 / 12 | 65 / 0 | SNP, Nicardipine | Norepinephrine, Phenylephrine | individualized |
| **Total** | **1860** | **1727 / 133** | **1517 / 343** | | | |

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**Table 3:**

Number of cases with phaeochromocytoma or paraganglioma, with and without α-receptor blockade and procedure related morbidity and mortality, postoperative intensive care stay (postop. ICU), and systolic blood pressure increase above 250 mmHg with (α) and without (no bl.) α-receptor blockade.

| Center | Cases (n) | α-Bl/no Bl. | postop. ICU | Morbidity (n; α-B/no B) | Mortality (n; α-B/no B) | 250 α | 250 no bl. |
|---|---|---|---|---|---|---|---|
| Kliniken Essen-Mitte | 504 | 247 / 257 | 24 | 3 / 2 | 1 / 0 | 16 / 231 | 23 / 234 |
| Asklepios Klinik Langen | 7 | 1 / 6 | 2 | 0 / 0 | 0 / 1 | 0 / 1 | 0 / 6 |
| Amsterdam VUMC | 35 | 35 / 0 | no data | 0 / 0 | 0 / 0 | no data | no data |
| University Düsseldorf | 58 | 46 / 12 | 18 | 2 / 0 | 0 / 0 | no data | no data |
| Amsterdam AMC | 41 | 40 / 1 | 10 | 9 / 0 | 0 / 0 | 6 / 34 | 0 /1 |
| San Francisco UCSF | 141 | 140 / 1 | 21 | 12 / 0 | 0 / 0 | no data | no data |
| University Galway | 17 | 17 / 0 | 1 | 1 / 0 | 0 / 0 | 0 / 17 | 0 / 0 |
| Tufts University Boston | 37 | 31 / 6 | 9 | 0 / 0 | 1 / 0 | 0 / 31 | 0 / 6 |
| Mayo Clinic Rochester | 258 | 247 / 11 | 87 | 3 / 0 | 1 / 0 | 9 / 238 | 0 / 11 |
| Royal Melbourne Hospital | 61 | 58 / 3 | 56 | 7 / 0 | 0 / 0 | no data | no data |
| Sapporo Medical University | 26 | 24 / 2 | 1 | 1 / 0 | 0 / 0 | 1 / 23 | 0 / 2 |
| Dresden University | 49 | 34 / 15 | no data | 0 / 0 | 0 / 0 | 4 / 30 | 1 / 14 |
| University of Chicago | 27 | 26 / 1 | 7 | 7 / 0 | 0 / 0 | 1 / 25 | 0 / 1 |
| Vanderbilt University | 138 | 132 / 6 | 2 | 5 / 0 | 0 / 0 | 6 / 126 | 0 / 6 |
| Mass. General Hospital | 134 | 127 / 7 | 36 | 8 / 0 | 2 / 0 | 8 / 119 | 0 / 7 |
| Columbia University NY | 60 | 52 / 8 | 14 | 14 / 1 | 0 / 0 | 6 / 46 | 1 / 7 |
| Univ. Med. Center Groningen | 59 | 59 / 0 | 22 | 3 / 0 | 2 / 0 | 2 / 57 | 0 / 0 |
| Medical College of Wisconsin | 53 | 52 / 1 | 19 | 1 / 0 | 0 / 0 | 3 / 49 | 0 / 1 |
| Kl. München Bogenhausen | 10 | 7 / 3 | 3 | 2 / 0 | 0 / 0 | 1 / 6 | 0 / 3 |
| Portland OHSU | 80 | 77 / 3 | 46 | 5 / 0 | 1 / 0 | 1 / 76 | 0 / 3 |
| MDACC Univ. Texas | 65 | 65 / 0 | 7 | 7 / 0 | 0 / 0 | 0 / 65 | 0 / 0 |
| **Total** | **1860** | **1517 / 343** | **385** | **90 / 3** | **8 / 1** | **64 / 1174** | **25 / 302** |

**Table 4:**

Characteristics of 504 patients (Kliniken Essen-Mitte) with (n=247) or without (n=257) α-receptor blockade, tumour size, time for surgery, and peak epinephrine and norepinephrine values (per cent upper limit of reference values) presented as mean and confidence interval (CI).

| | α-receptor blockade | no blockade | p-value |
|---|---|---|---|
| Height (cm) | 172 (170–174) | 172 (170–174) | 0.916 |
| Weight (kg) | 75 (72–78) | 75 (72–78) | 0.808 |
| Age (years) | 43 (41–48) | 42 (40–44) | 0.688 |
| Gender (female/male) | 118 / 129 | 139 / 118 | 0.156 |
| Typical Symptoms (yes/no) | 193 / 54 | 193 / 64 | 0.420 |
| Time for surgery (min) | 66 (59–73) | 62 (57–67) | 0.221 |
| Tumour Size (cm in diameter) | 3.6 (3.3–3.9) | 3.4 (3.2–3.6) | 0.191 |
| Epinephrine (%) | 668 (551–785) | 596 (472–720) | 0.404 |
| Norepinephrine (%) | 761 (504–1018) | 589 (476–702) | 0.213 |

**Table 5:**

Description of perioperative fatal outcomes with and without a-receptor blockade (POD=postoperative day; 0=day of surgery).

| Case | a-receptor blockade | POD | Case Description |
|---|---|---|---|
| **1** | **yes** | **5** | Patient died due to airway obstruction due to other malignant process in the body |
| **2** | **yes** | **7** | Patient died due to postoperative complications which involved respiratory insufficiency |
| **3** | **yes** | **11** | Patient underwent resection of 8 cm paraganglioma. Postoperative course complicated by persistent hypotension, myocardial infarction, heart failure, renal failure. He died due to cardiac arrest. |
| **4** | **yes** | **45** | Patient with GI-bleeding and bowel obstruction and an adrenal tumour underwent combined resection of the tumour and bowel surgery. The patient did well initially, but also suffered from COPD, dementia, coronar artery disease, arterial hypertension, diabetes, chronic kidney disease. The patient developed congestive heart failure and progressive renal failure and died ultimately from sepsis and pneumonia. |
| **5** | **yes** | **2** | Patient with vHL (posterior medullary haemangioblastoma and phaeochromocytoma) underwent adrenal surgery uneventfully. He was found unresponsive on POD 2 in asystole. Autopsie revealed cardiomegaly with left ventricular hypertrophy (no infarction), petechial lung haemorrhage, many haemangiomas, hepatic congestion, small pancreas tumour. Cause of death remained unclear. |
| **6** | **yes** | **0** | Patient with vHL and prolonged time until final diagnosis, developed severe cardiomegalie and congestive heart failure. Patient arrested after uneventful induction of anaesthesia. Prolonged resucitation could not lead to return of spontaneous circulation. |
| **7** | **yes** | **0** | Patient died to massive intraoperative bleeding and major difficulties to stabilize circulation. |
| **8** | **no** | **21** | Patient survived adrenal surgery uneventfully, but developed postoperative pneumonia and sepsis. |
| **9** | **yes** | **25** | Patient survived adrenal surgery uneventfully, but developed renal and respiratory failure, and sepsis postoperatively. |