



Robotic adrenalectomy in patients with pheochromocytoma: a systematic review

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Abstract: Pheochromocytomas (PHEOs) are neural crest cell tumors producing catecholamines. PHEOs need to be early diagnosed and adequately managed. Adrenalectomy is the gold standard treatment of these type of tumors. There has been major improvement of surgical technologies with the development of laparoscopic and robotic systems these past several years. We conducted a review of the literature to evaluate the robotic approach for adrenalectomy for patients with PHEO.

Keywords: Pheochromocytoma; adrenalectomy; robotics; laparoscopy; morbidity; hemodynamic instability

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Introduction

Pheochromocytoma (PHEO) is a rare catecholamine producing neuroendocrine tumor that can be adrenal or extra adrenal in its origin. It manifests itself by various symptoms such as sweating, headaches, palpitations and hypertension. The estimated incidence of PHEO ranges from 0.05% to 0.1% in the general population. However, it is higher in the hypertensive population (1). PHEO occurs mostly in young patients (40–50 years old) with a slight predilection for women and is diagnosed by measuring elevated levels of metanephrines (catecholamine metabolites) in blood or urine. Then when a biochemical diagnostic is set, imaging techniques such as CT or MRI are used to localize the adrenal tumor(s). CT and MRI have a high sensitivity (between 93–100%), but they lack specificity (50–90%), implicating various false negatives (2). Thus, the use of functional imaging using MIBG scintigraphy and/or DOPA PET is a relevant tool to diagnose and localize PHEOs.

Adrenalectomy is the gold standard treatment of PHEOs. Several different techniques of adrenalectomy

have been described: open transperitoneal adrenalectomy, laparoscopic lateral transperitoneal adrenalectomy, posterior retroperitoneal adrenalectomy and robotic surgery. Open transperitoneal adrenalectomy has been considered for a long time as the gold standard when treating adrenal diseases. However, since the 1990's, laparoscopic and robotic techniques have emerged and replaced open approaches. In 2020, almost all PHEOs can be resected using a laparoscopic and/or robotic approach, while laparotomy remains to be used in large or malignant tumors with adjacent organs invasion. The goal of this manuscript was to review all available studies evaluating the use of the robotic system to perform an adrenalectomy when treating patients with PHEO.

Methods

A systematic review using PubMed database was used to search for relevant English language studies comparing laparoscopic to robotic adrenalectomy (RA) in patients with PHEO. We also searched for articles addressing the

specificities of treating PHEOs. One author independently searched the literature on November 3rd, 2019 for pertinent studies using several keywords such as “robotic”, “pheochromocytoma”, “laparoscopic”. We excluded case reports, articles not focused on surgical management and articles that had less than 5 patients. A total of 21 articles met our inclusion criteria. The principles of Helsinki declaration were followed in this review

RA versus laparoscopic adrenalectomy (LA): feasibility and safety

The robotic system was first introduced for cardiac surgeries in the late nineties. It has since expanded its use to many other types of surgeries including adrenalectomies. Robotic technology increases surgeon's control, has a superior instrument dexterity, wristed articulation and a 3D visualization.

Several articles in the literature demonstrate that RA is as feasible and safe than RA.

It was shown that there was a need to perform 20 cases to obtain a similar outcome than with a laparoscopic approach (3). This means that after a learning curve of 20 robotic cases there is no difference as regards to operative time between the RA group and the LA group. This study also demonstrated that the robotic system was an advantage in certain specific situations such as in obese patients and patients with larger tumors (>55 mm). Karabulut *et al.* supported these findings in their study: intraoperative time was similar in their study when comparing LA and RA, whereas the tumor's volume was larger for the robotic approach (4).

As regards to operating time, studies tend to have conflicting results. Indeed, Brunaud *et al.* and Morino *et al.* showed that there was a longer operative time when using the robot compared to the laparoscopic approach (3,5). However, these findings tend to be put in perspective since several other studies did not have the same results. Indeed, several studies did not find a significant difference between RA and LA as regards of operative time (4,6,7). Furthermore, Greilsamer *et al.* showed in a recent prospective study, including 303 patients, that mean operative time decreased from 99 to 77 min ($P < 0.001$) between the first and last 100 patients. Studies since 2012 have not shown a significant difference as concerns of operative time between RA and LA, and moreover, recent studies suggest a lesser operative time than earlier studies on this matter and a decrease of operative time with

experience. This could suggest that with the widespread use of the robot and robotic experience, it seems to be no difference between RA and LA.

There is no unique complication related to a robotic approach. In Chai *et al.* systematic review regrouping 6 studies, there was no particular complication directly associated with the use of the robot (8). Based on the available data to this day, we can solely affirm that there is no difference in terms of mortality or morbidity between RA and LA.

To sum up, robotic surgery is as safe and feasible than a laparoscopic procedure. However, because of its financial burden for the hospital and its long training process, the value of robotic system needs to be put in perspective when performing operations that are already performed safely and rapidly with a laparoscopic approach.

RA and PHEO

There is limited data on the use of the robotic system in patients with PHEO. We only found one study with a prospective database analyzed retrospectively. Indeed, Aliyev *et al.* (9) conducted a study comparing perioperative outcomes and the efficacy of RA versus RA for PHEOs. In this study, 25 patients underwent 26 RA, and 40 patients underwent 42 LA procedures for PHEO. They compared blood loss, operative time, tumor size and intraoperative hemodynamic parameters. There was no difference in terms of blood loss, and intraoperative hemodynamic parameters. Furthermore, there was a lower pain score on postoperative day 1 and a shorter hospital stay in the RA group, and it seemed there was an advantage with the use of the robotic system regarding operative time. There were no significant differences in terms of morbidity and mortality between the two groups. Nonetheless, there were several limitations to that study including the nonrandomized design and the sample size. To establish the role of robotic surgery in patients with PHEO there is a need to conceive prospective randomized studies in larger population (Table 1).

Robot-assisted laparoscopic partial or total adrenalectomy for PHEO?

The traditional surgical treatment of PHEO is total adrenalectomy. However, in the recent years, adrenal sparing surgery has increased to avoid side effects of adrenal insufficiency and steroid replacement. Indeed, some adrenal tumors can be bilateral, such as in hereditary syndromes.

Table 1 Comparison of perioperative outcomes between RA and LA for patients with adrenalectomies for pheochromocytoma

Variable	Operative time		EBL (mL)		Conversion		Complication		Hospital stay		Greatest intraoperative BP (mean)		Lowest intraoperative BP (mean)	
	LA	RA	LA	RA	LA	RA	LA	RA	LA	RA	LA	RA	LA	RA
Aliyev 2013	178	149	43	36	3	1	4	0	1,7	1,2	132	127	77	75
Gupa 2014	176	161	176	92	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Asher 2011	163	NA	161	NA	1	NA	0	NA	NA	NA	NA	NA	NA	NA

RA, robotic adrenalectomy; LA, laparoscopic adrenalectomy; EBL, estimated blood loss; NA, non available data.

Treatment of these bilateral masses would be total bilateral adrenalectomy and would result in life-long steroid supplementation. To avoid this life-long supplementation which is not exempt of sides effects and the risk of potential adrenal insufficiency, adrenal sparing surgery has expanded. And thus, this trend of partial adrenalectomy has also spread to those with a normal contralateral gland supported by the benefits it carries.

Kaye *et al.* in their systematic review of partial adrenalectomy outcomes, showed that adrenal sparing surgery is mostly done in Conn's disease, closely followed by PHEO (10). They state in that review that the position of the tumor is an important criterion for deciding whether to use an adrenal sparing approach. Still in this review, it was demonstrated that perioperative outcomes were similar in partial and total adrenalectomy.

Hereditary PHEO has a high recurrence rate with a multifocal nature. In Kaye's systematic review, there were no articles showing that partial adrenalectomies were unsafe to treat hereditary PHEO (10).

Gupta *et al.* evaluated in their 2014 study perioperative functional and short- term oncological outcomes of partial adrenalectomy in patients with multiple PHEO (11). They included 8 patients and performed 10 procedures for ipsilateral PHEOs. Of those 10 procedures, 6 were robot assisted and 4 by laparoscopy. There were no perioperative complications, and at follow-up at 12 months, every patient had resolution of their symptoms and only one required steroid replacement. However, these results need to be put in perspective: several limitations exist; it was again a retrospective study with a small population.

Asher *et al.* evaluated robot assisted laparoscopic partial adrenalectomies for PHEO (RALPA) (12). They performed 15 RALPA in 12 consecutive patients. Blood loss, tumor size, intraoperative hemodynamic parameters and operative time were reviewed. They recognize that technical

considerations, such as the position of the patient on the operating table and the exposition of the adrenal glands, are crucial to correctly dissect the glands and there so put to use the advantage of the robotic approach during the resection of the tumor.

Concerning blood loss, operative time and hemodynamic parameters it was shown that these factors decreased with the robotic approach comparing to an open approach. This study has also several limitations: small sample, retrospective and the non-randomized design. Furthermore, there was no comparison between a robotic approach and a laparoscopic approach. This is why we can only affirm that minimally invasive surgical resection should be considered as a safe and feasible approach in patients with PHEO. There is a need to evaluate with large population prospective randomized studies the use of robot assisted technology in partial adrenalectomy versus laparoscopic partial adrenalectomy in patients with PHEO.

Robotic approach and malignant PHEO

Malignant PHEO is a rare catecholamine cancer deriving from chromaffin cells of the adrenal medulla (13). Surgical management of malignant PHEO consists of adrenalectomy or debulking surgery (14). There are different types of surgeries possible: open surgery, laparoscopic and robotic surgery. Goffredo *et al.* in their 2015 study, analyzed patterns of use of minimally invasive surgery (MIS) (laparoscopic and robotic surgeries) for malignant PHEOs in the United States and compared short term outcomes of MIS to open adrenalectomy. They observed no difference in the number of lymph nodes harvested, 30-day mortality or readmissions rates compared to the open surgery group (15). They also observed that malignant tumors were smaller in the MIS group. However, they collected their data on a large database, providing source to coding errors.

They also could not discriminate the minimally invasive procedures: how did the robot influence this minimally invasive approach? Moreover, they only compared short term outcomes and further studies on long term outcomes and robotic use are required.

Preoperative fluid and hypotensive drug administration

Pre-operative blockade of alpha-1 receptors is increasingly employed in an attempt to reduce the risk of hypertensive episodes, especially during manipulation of the tumor (16). Operative resections carry a high intraoperative risk of releasing massively catecholamines into the blood circulation. It was shown that there are three perioperative phases that are associated with a high risk of hemodynamic instability: endotracheal intubation, creation of the pneumoperitoneum and manipulation of the adrenal gland (16,17). Alpha adrenergic blockade has been routinely accepted as preoperative medical management to reduce intraoperative hemodynamic instability (18). Other regimen using calcium channel blockers or other medications for preoperative medical preparation have also been proposed more recently (16). However, the most vivid criticism regarding the routine use of preoperative medical preparation is that there is no longer a significant relationship between preinduction blood pressure normalization after preoperative medical preparation and post-operative morbidity (19). Indeed, Lentschener *et al.* condemned the lack of evidence based when proning preoperative medical management (20). Preoperative hypotensive drugs were first used in the late fifties. Golstein *et al.* observed from 1957 to 1996, in 108 PHEOs a decrease in complications from 69% to 3% with the use of alpha blockers (19). However, they did not incorporate the major surgical improvements (laparoscopy, preoperative localization, PET imaging) that occurred during that period and anesthetic management. A recent meta-analysis confirmed the lack of evidence for preoperative α -blockade in surgery for pheochromocytoma (21). It was shown in several studies the impact of robotic use in the precision of tumors' resections. With this new robotic technology that allows to have a superior instrumental dexterity, and so to be more precise in surgical dissections: how can the robot help surgeons and anesthesiologists manage intraoperative hemodynamic instability? More studies need to be performed to evaluate the role of a robotic approach in intraoperative hemodynamic instability episodes and postoperative complications. There has not yet any data on

the role of the robotic approach and its utility as regards to the management of hemodynamic instability, this matter should be one of the major concerns going forward.

Conclusions

Introduction of robot technology has had a major impact on the surgeon's operating technique, with a better control and greater dexterity. Many studies have described the utility of the robot versus laparoscopic on adrenalectomies. However, there is a lack of articles when specifically addressing the subject on adrenalectomies for patients with PHEOs. Studies need to be performed to evaluate the use of the robot on performing adrenalectomies for patients with PHEO.

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