Peer Review File

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Reviewer A

Nice overview of a large series of pheochromocytoma patients operated under blockade.

Some questions remain;

Comment 1: It is unclear why 156 patients were prepared as pheochomocytoma and only 97 patients were confirmed. It is also unclear how 9 patients were operated without knowledge it concerned pheochromocytoma; please explain.

Reply 1:

The criterion for the diagnosis of pheochromocytoma was histopathological examination.

In 156 patients, pheochromocytoma was suspected on the basis of preoperative tests of methoxycatecholamines and imaging tests. The level of methoxycatecholamines in the 24-hour urine collection exceeded the reference range, hence the patients were treated as suspected pheochromocytoma.

In 97 of them the diagnosis was confirmed by postoperative histopathological examination. In the remaining cases, the adrenal tumor in the postoperative examination turned out to be adrenal cortical adenoma in most cases (29 patients) followed by adrenal cortical nodular hyperplasia (14 patients). They were excluded from the study.

In 9 patients, preoperative laboratory and imaging tests did not indicate a suspected pheochromocytoma. The diagnosis was made only on the postoperative histopathological examination. The results of methoxycatecholamines in the 24-hour urine collection and a routine panel of laboratory tests were within the normal range. Patients also did not report symptoms. The indication for surgery in their case was the tumor diameter. Due to the lack of preoperative preparation, they were not included in the study

Changes in the text 1:

We have modified our text (see Page 5, line 88-89 and Page 6, line 92-94)

Comment 2: The overproduction of normetanefrine or metanefrines is possibly also a risk factor for instability during surgery; why are the data on hormonal outcomes used as > 10 above the upper limit and not in absolute values.

Reply 2: In our work, we also analyzed the absolute values of methoxycatecholamines

and did not show that they were a risk factor for hemodynamic instability. We decided to show it in a similar way to Gaujoux et al. (2015). He showed in multivariate analysis that ten-fold increase in urinary metanephrine or normetanephrine was linked to an odds ratio of 15.63 (95% CI 3.74-65.21). We have not observed such a phenomenon. We can of course show the changes as absolute values.

	Univariate logistic regression (OR, 95% CI, p-value)
Urine metanephrine level (mg/24 h)	1.17, 0.92-1.47, 0.1974
Urine normetanephrine level (mg/24 h)	1.09, 0.98-1.22, 0.1299
Urine methoxytyramine level (mg/24 h)	1.18, 0.45-3.11, 0.7379

Changes in the text 2: We have modified Table 3.

Comment 3: Data on intraoperative hypotension are not included, although the hypotension was associated with postoperative problems. Please explain.
Reply 3: We did not collect data on hypotension during surgery. We have data on the intraoperative need to use vasopressors during surgery, which indirectly proves the occurrence of episodes of hypotension.
We showed that episodes of hypotension requiring intraoperative use of vasopressors were an independent risk factor for both all-cause and cardiovascular morbidity.

We examined also postoperative hypotension and it was treated as a complication.

Changes in the text 3: no changes

Comment 4: The discussion is a bit too long with repeating arguments.
Reply 4: Thank you for your comment. The discussion has been shortened
Changes in the text 4: We have modified our text (Discussion, Page 11-14)

Reviewer B
This is an interesting article correlating hemodynamic instability with size of the adenoma and diabetic patients and postoperative morbidity with intraoperative use of vasopressors.
The authors acknowledge an important limitation regarding a retrospective study over 17 years.
To be detailed by the authors:

Comment 1: Definition for diabetes mellitus: were all diabetic patients requiring

insulin injections?

Reply 1: The WHO definition of type 2 diabetes has been used. In our group of patients, 15
required intensive insulin therapy and 21 were taking oral antidiabetic drugs

Changes in the text 1: no changes

Comment 2: Bleeding was a significant complication in this series (more than in the literature: see Hauch A, et al. Ann Surg Oncol (2015) 22:103–110), opening some questions:

- Who did surgery: dedicated trained endocrine surgeons?
- Did bleeding occurrence change over time (17 years)?
- To what extent did bleeding influence hemodynamic instability during surgery
- Please separate patients requiring blood transfusion// no transfusion and specify bleeding in these 2 groups respectively (in order to answer the abovementioned question)

Reply 2:

Procedures were performed by experienced laparoscopic surgeons with extensive expertise in adrenal surgery (>50 cases per surgeon).

In the perioperative period, 8 (8.3%) patients required transfusion of blood products.

The bleeding that occurred was related to: the location of the tumor near the hilum of the kidney, damage to the aortic wall; damage to the tumor capsule; spleen damage; a large cystic tumor with additional vascularization.

The amount of bleeding changed over the course of the study. The last one occurred in 2016.

Since then, there has been no need to transfuse blood products.

Hauch et al showed on large cohort of patients (n = 7,829) a bleeding rate equal to 5.7%. However, the group differed from the one presented by us. The author included all adrenalectomies in the analysis, we only analysed pheochromocytomas.

		Blood transfusion	
		Yes (n=8)	**No (n=88)**
Intraoperative blood loss (mL)	**Mean (SD)**	**822.5 (945.0)**	**88.4 (108.5)**
	Median (IQR)	**600.0 (225.0-950.0)**	**50.0 (25.0-100.0)**
Hemodynamic instability	**n (%)**	**6 (75.0%)**	**35 (39.8%)**

Changes in the text 2: We have modified our text (see Page 7, line 123-124).

We included the issue of blood transfusion in the discussion (Hauch A, et al. Ann Surg Oncol (2015) 22: 103–110) (Page 13, line 262-266)

Comment 3: In some patients, starting pneumoperitoneum itself can lead to a high blood pressure despite adequate preparation: did it happen in your series? (see Naranjo J et al. J Cardiothor Vascular Anesth (2017)31:1427–1439).

Reply 3: In some patients, despite the appropriate preoperative preparation, both during the induction of anesthesia and surgical manipulations before the adrenal vein clipping, episodes of increased blood pressure occur. Another moment reported by some authors is the onset of pneumoperitoneum.

In our study, we did not notice a similar relationship but we raised this topic in the discussion.

Changes in the text 3:

We have modified our text (see Page 13 line 272-274)