

## ANSWERING REVIEWERS



March 6, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7907-review.docx).

**Title:** Laparoendoscopic single-site, minimally-invasive or open surgery for adrenal tumors: selecting the optimal approach.

**Author:** Christopher B. Riedinger, Conrad M. Tobert, Brian R. Lane

**Name of Journal:** *World Journal of Clinical Urology*

**ESPS Manuscript NO:** 7907

Reviewer 00220901

- “On page 11, at first paragraph, the authors mentioned that MI-A is the surgical approach of choice for almost all benign adrenal tumors. However, I could not find any literature data regarding the recurrence rates after MI-A? Could recurrence rates be higher (especially in cortisol-secreting adenomas and pheochromocytomas) in MI-A when compared to other surgical modalities?

*Our review of the literature concluded that cortisol-secreting adenomas are best managed by MI-A, given its well-defined perioperative benefits over OS-A. Importantly, the incidence of local recurrence following open adrenalectomy for large adrenal tumors is unknown.(1) This prohibits a reliable historical comparison with MI-A. Regardless, recurrence appears to be an uncommon event following MI-A for this pathology. The largest relevant series, involving 163 cortisol-producing adenomas treated by MI-A at a single institution, demonstrated one instance of recurrence at mean follow-up: 70.9 months (range: 6 – 179 months).(2) That patient had a 7cm diagnosed as adrenal adenoma, but had malignant features as metastases were evident 6 months after resection (2). Similar results have been reported elsewhere in the literature.(2-4) There are few published studies documenting recurrence of this pathology.(1, 6-8) Palazzo et al.(1) reviewed 19 solid cortical tumors  $\geq 6$  cm without overt malignant preoperative or intraoperative characteristics. None of the 8 demonstrated to be cortical adenomas on histology demonstrated recurrence (mean follow-up: 34 months; range: 12 – 108 months). Three patients did experience recurrence, including two lesions of indeterminate pathology and one ACC. Brauckhoff et al.(6) reported two cases of large ( $\geq 5$  cm), apparently benign cortisol-producing adenomas with local malignant recurrence and peritoneal carcinomatosis. Overall, tumor recurrence is a rare event in true cortisol-secreting adenomas. This event is most often associated with indeterminate histopathology or ACC diagnosed after adrenalectomy. Given the paucity of reported cases of recurrence, we conclude that MI-A achieves durable oncologic*

*outcomes and should be considered the surgical modality of choice for cortisol-producing adenomas.*

*We have provided cited publications below to support these statements:*

- 1. Palazzo FF, Sebag F, Sierra M, Ippolito G, et al. Long-term outcome following laparoscopic adrenalectomy for large solid adrenal cortex tumors. World J Surg. 2006;30(5):893-8.*
- 2. Alesina PF, Hommeltenber S, Meier B, Petersenn S, et al. Posterior retroperitonesoscopic adrenalectomy for clinical and subclinical cushing's syndrome. World J Surg. 2010;34(6):1391-7.*
- 3. Mishra AK, Agarwal A, Gupta D, Agarwal G, et al. Outcome of adrenalectomy for cushing's syndrome: experience from a tertiary care center. World J Surg. 2007;31(7):1425-32.*
- 4. Walz MK, Peitgen K, Diesing D, Petersenn S, et al. Partial versus total adrenalectomy by the posterior retroperitoneoscopic approach: early and long-term results of 325 consecutive procedures in primary adrenal neoplasias. World J Surg. 2004;28(12):1323-9.*
- 5. Henry JF, Sebag F, Iacobone M, Mirallie E. Results of laparoscopic adrenalectomy for large potentially malignant tumors. World J Surg. 2002;26(8):1043-7.*
- 6. Brauckhoff M, Varhaug JE, Hauptmann S, Akslen LA, et al. Peritoneal carcinosis in apparently benign cortisol producing adrenal adenoma  $\geq 5$  cm in diameter: the need of regular postoperative surveillance. Exp Clin Endocrinol Diabetes. 2012;120(8):472-6.*
- 7. Iino K, Oki Y, Sasano H. A case of adrenocortical carcinoma associated with recurrence after laparoscopic surgery. Clin Endocrinol (Oxf). 2000;53(2):243-8.*
- 8. Hofle G, Gasser RW, Lhotta K, Janetschek G, et al. Adrenocortical carcinoma evolving after diagnosis of preclinical cushing's syndrome in an adrenal incidentaloma. A case report. Horm Res. 1998;50(4):237-42.*

*At this time, the available literature has demonstrated that recurrence rates following MI-A for pheochromocytomas are low (6-8%) and not significantly different from OS-A (1-5). However, these data have limited follow-up (21 – 102 months), which is likely inadequate to detect recurrence of a disease that usually presents years to decades later. Size remains a risk factor for malignancy, but numerous studies have demonstrated the feasibility of resecting large pheochromocytomas via MI-A.(2,4,6) Additionally, some literature suggests that tumor biology, rather than surgical approach, is more likely to determine the chance of cure in this disease.(7-8) The true rate of recurrence following LA will require longer follow-up than has currently been reported. Despite this limitation of the available data, many authors and guideline-producing societies have concluded that MI-A is an appropriate initial approach to pheochromocytomas without suspected malignancy.*

*We have provided cited publications below to support these statements.*

1. Society of American Gastrointestinal Endoscopic Surgeons (SAGES). Guidelines for the minimally invasive treatment of adrenal pathology. Los Angeles (CA): Society of American Gastrointestinal Endoscopic Surgeons (SAGES); 2013.
2. Carter YM, Mazeh H, Slippel RS, Chen H. Safety and feasibility of laparoscopic resection for large ( $\geq 6$  cm) pheochromocytomas without suspected malignancy. *Endocr Pract.* 2012;18(5):720-6.
3. Shen WT, Grogan R, Vriens M, Clark OH, Duh QY. One hundred two patients with pheochromocytoma treated at a single institution since the introduction of laparoscopic adrenalectomy. *Arch Surg.* 2010;145(9):893-7.
4. Perry KA, El Youssef R, Pham TH, Sheppard BC. Laparoscopic adrenalectomy for large unilateral pheochromocytoma: experience in a large academic medical center. *Surg Endosc.* 2010;24(6):1462-7.
5. Chen H, Sippel RS, Pacak K. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglionoma & medullary thyroid cancer. *Pancreas.* 2010;39(6):775-83.
6. Conzo G, Musella M, Corcione F, De Palma M, et al. Laparoscopic adrenalectomy, a safe procedure for pheochromocytoma. A retrospective review of clinical series. *Int J Surg.* 2013;11(2):152-6.
7. Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, et al. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. *J Clin Endocrinol Metab.* 2011;96:717-25.
8. Park J, Song C, Park M, Yoo S, et al. Predictive characteristics of malignant pheochromocytoma. *Korean J Urol.* 2011;52:241-6.

*We have included this in the Discussion section (page 9-10).*

**For pheochromocytomas, recurrence rates following MI-A are low (6-8%) and not significantly different from OS-A in reports that are somewhat limited by short follow-up durations (21 – 102 months) <sup>[50–54]</sup>. Most experts believe that size and tumor biology, rather than surgical approach, are more likely to determine the chance of cure in this disease <sup>[55,56]</sup>. Based on this literature, many authors and guideline-producing societies have concluded that MI-A is an appropriate initial approach to pheochromocytomas <sup>[50–57]</sup>. Recurrence of other benign adrenal tumors is extremely rare and is generally limited to tumors that are later discovered to be malignant based on metastasis after initially benign or indeterminate pathology.**

Reviewer 00725137

- “Since this is a review article, when discussing bilateral adrenalectomy, the authors could discuss the possibility RL-A offers to perform bilateral adrenalectomy with two surgical teams operating at the same time on the two sides of the patient, potentially reducing operative time and surgical stress.”

*This is an excellent point and we agree that it should be added to the Laparoscopic Adrenalectomy: Transperitoneal vs. Retroperitoneal section (page 7).*

*With RL-A, some have reported success with two surgical teams operating simultaneously to reduce operative time and surgical stress<sup>[28,29]</sup>.*

Reviewer 00736564

- “To make this article more valuable to our readers I would suggest writing a section which summarizes specifics of different hormonal diseases (e.g. pheochromocytoma, cushing syndrome, etc.) with recommendations or experience with different surgical approaches.”

*The literature demonstrates a consensus that MI-A is the approach of choice for functional adrenal tumors when ACC is not suspected.(1-5) Hall et al.(1) published a review article in 2010 that emphasized this issue while examining pertinent literature for different hormonal diseases. At this time, selecting amongst different MI-A approaches is based largely upon surgeon familiarity and experience, rather than comparative studies demonstrating superiority of one approach over another for specific functional tumors, which are lacking. We do not feel that there is sufficient data to support specific recommendations regarding which form of MI-A to use for different functional adenomas.*

*We have provided cited publications below to support these statements.*

1. Society of American Gastrointestinal Endoscopic Surgeons (SAGES). Guidelines for the minimally invasive treatment of adrenal pathology. Los Angeles (CA): Society of American Gastrointestinal Endoscopic Surgeons (SAGES); 2013.
2. Hall DW, Raman JD. Has laparoscopy impacted the indications for adrenalectomy? *Curr Urol Rep* 2010;11:132-7.
3. Broome JT, Gauger P. Surgical techniques for adrenal tumors. *Minerva Endocrinol.* 2009;34(2):185-93.
4. Kuruba R, Gallagher SF. Current management of adrenal tumors. *Curr Opin Oncol.* 2008;20(1):34-46.
5. Melman L, Matthews BD. Current trends in laparoscopic solid organ surgery: spleen, adrenal, pancreas and liver. *Surg Clin N Am* 2008;1033-46.

*We have included this in the Discussion section (page 9):*

*At this time, selecting amongst different MI-A approaches should be determined by surgeon familiarity and experience, as there is inadequate evidence to demonstrate superiority of any one MI-A approach for a specific benign adrenal pathology*

- “Regarding patient body habitus, it would be valuable to include information/recommendations for which approach to use and why, as well as what the intraoperative and postoperative specifics of morbidly obese patients are.”

*There are few published studies comparing different MI-A approaches in obese patients. Epelboym et al. (1) analyzed 81 RL-A and 130 TL-A procedures in obese patients. They found that operative time (90 vs 130 min;  $p<0.001$ ) and estimated blood loss (0 vs 50 mL;  $p<0.001$ ) were significantly less for RL-A, but failed to demonstrate significant differences*

*for length of stay, overall mortality, incidence and severity of postoperative complications, and rates of readmission. Aksoy et al. (2) compared 42 retroperitoneal RAL-A and 57 RL-A procedures in obese patients. They found no difference in perioperative outcomes between these two approaches. We do not feel that there is sufficient data to support specific recommendations regarding which form of MI-A to use for obese patients. However, we will include the above data in our manuscript to highlight the current state of the literature and its limitations.*

*We have provided cited publications below to support these statements.*

1. *Epelboym I, Digesu CS, Johnston MG, Chabot JA, et al. Expanding the indications for laparoscopic retroperitoneal adrenalectomy: experience with 81 resections. J Surg Res. 2013;*
2. *Aksoy E, Taskin HE, Aliyev S, Mitchell J, et al. Robotic versus laparoscopic adrenalectomy in obese patients. Surg Endosc. 2013;27(4)1233-6.*

*We have included this in the Discussion section (page 13):*

***Two studies have been published comparing different MI-A approaches in this patient subgroup. Epelboym et al.<sup>[23]</sup> analyzed 81 RL-A and 130 TL-A procedures in obese patients. They found that operative time (90 vs 130 min;  $p<0.001$ ) and estimated blood loss (0 vs 50 mL;  $p<0.001$ ) were significantly less for RL-A, but failed to demonstrate significant differences for length of stay, overall mortality, incidence and severity of postoperative complications, and rates of readmission. Aksoy et al.<sup>[32]</sup> compared 42 retroperitoneal RAL-A and 57 RL-A procedures in obese patients. They found no difference in perioperative outcomes between these two approaches. Given the paucity of studies comparing MI-A approaches in obese patients, we cannot provide specific recommendations at this time as to which approach is best.***

Thank you again for considering our manuscript for publication in the *World Journal of Clinical Urology*.

Sincerely yours,

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