# Outcome Analysis of Transperitoneal Laparoscopic Nephrectomy in Children: Experience from a Developing Country

Ghulam Mujtaba Zafar, Muhammad Zaheer, Fawad Humayun Akhtar and Sadia Ghias

Department of Paediatric Urology, Children's Hospital, The University of Child Health Sciences, Lahore, Pakistan.

## ABSTRACT

Objective: To analyse the outcome of laparoscopic nephrectomy among children.

**Study Design:** An observational study.

Place and Duration of the Study: Department of Paediatric Urology, Children's Hospital Lahore, from September 2021 to June 2023.

**Methodology:** During the study, 100 children aged 5-180 months were included. Data regarding age, gender, cause, side, intraoperative and postoperative outcomes such as number of ports, estimated blood loss, need of transfusion, operative time, hospital stay, analgaesia requirement and complications were recorded. Data were collected through proforma which were entered and analysed through computer software SPSS version 16.0.

**Results:** Among 100 children, 58.0% were males and the mean age was 79.54  $\pm$  4.427 months while the major cause of laparoscopic nephrectomy was PUJO (Pelvi-Ureteric Junction Obstruction) for 47.0% of children. The mean blood loss was 19.93  $\pm$  65.556 ml and the majority of the children (96.0%) did not require blood transfusion. The mean operative time was 125.31  $\pm$  43.365 minutes and the mean hospital stay was 2.82  $\pm$  1.258 days. Most of the children (90.0%) had no complications while 3.0% had ileus which was managed conservatively and 3.0% were converted to open surgery while 4.0% had wound infection.

**Conclusion:** Laparoscopic nephrectomy is an effective technique with regard to insignificant blood loss, operative time, hospital stay, and rate of complications.

Key Words: Laparoscopy, Nephrectomy, Children, Operative time, Hospital stay, Complications.

**How to cite this article:** Zafar GM, Zaheer M, Akhtar FH, Ghias S. Outcome Analysis of Transperitoneal Laparoscopic Nephrectomy in Children: Experience from a Developing Country. *J Coll Physicians Surg Pak* 2024; **34(11)**:1338-1342.

## INTRODUCTION

Nephrectomy is one of the most frequently utilised ablative surgeries carried out in the field of urology.<sup>1</sup> This procedure could be utilised to address both benign and malignant conditions that affect the kidney and upper urinary tract that may lead to impaired function of the nephron-ureteral units.<sup>2</sup> The nephrectomy was carried out for the first time by Gustav Simon in 1869, and since then, this procedure has been performed worldwide with continuous advancements over the years.<sup>3</sup> Nowadays, minimally invasive surgery is increasingly used, compared to open nephrectomy, especially in the paediatric population.<sup>4</sup>

Correspondence to: Dr. Muhammad Zaheer, Department of Paediatric Urology, Children's Hospital, The University of Child Health Sciences, Lahore, Pakistan E-mail: zaheeranjum210@gmail.com

Received: April 02, 2024; Revised: September 05, 2024; Accepted: October 04, 2024 DOI: https://doi.org/10.29271/jcpsp.2024.11.1338 Since, it is the first description of laparoscopic nephrectomy in adults by Clayman in 1990 and the first paediatric laparoscopic nephrectomy was reported by Ehrlich in 1992, this procedure has gained a wide acceptance.<sup>5</sup>

It has helped in decreasing morbidity due to minimal surgical trauma, smaller incisions, less postoperative pain, minimal need for blood transfusion, shorter hospital stay, faster recovery, early return to normal activities, and better cosmesis.<sup>6-8</sup> The most common indication of nephrectomy is to remove the kidneys that are non-functional because of vesico-ureteral reflux (VUR), pelvi-ureteric junction obstruction (PUJO), ectopic ureters or multi-cystic dysplastic kidney (MCDK).<sup>5</sup>

Several approaches can be utilised in laparoscopic nephrectomy, for example, transperitoneal and retroperitoneal in lateral or prone position. However, the selection of the certain approach depends upon the factors such as patient's surgical history, underlying pathology (malignant or benign), presence of systemic illness or associated anomalies as well as surgeon preference or experience. The transperitoneal approach offers a broader working area, direct visualisation of adjacent organs such as colon, liver, pancreas, and spleen as well as better manoeuverability when the distance between port sites is adequate. In the retroperitoneal technique, the short operative time, better function of bowel after surgery due to manipulation away from abdominal organs, and less hospital stays are the advantages of this approach. The disadvantages of this approach are that there is a narrower working area, making it more challenging to identify abdominal organs and requiring a longer learning curve.<sup>9-11</sup>

Data regarding the outcome of laparoscopic nephrectomy among children are relatively lacking in the Pakistani population. Therefore, the aim of this study was to analyse the outcome of transperitoneal laparoscopic nephrectomy in children.

#### **METHODOLOGY**

It was a prospective descriptive study carried out at the Department of Paediatric Urology, Children's Hospital, Lahore. Children who underwent laparoscopic nephrectomy between September 2021 and June 2023 were included in the study. Among them, 100 children aged 5-180 months were selected through a simple random sampling technique. Children with large Wilm's tumours (>5cm), horseshoe kidney, or duplex renal system were excluded.

Parents were counselled about the laparoscopic procedure and its outcomes. Written consents were taken from them before the procedure. Under general anaesthesia with ETT, the patient was placed in a semi-lateral position on the operating table and secured by strapping, along with padding of pressure points. Foley catheter was passed and surgical area was draped. The first optical port (10 mm size) was inserted at the peri-umbilical region using an open technique. Pneumoperitoneum was created by insufflating carbon dioxide  $(CO_2)$  at a pressure of 8-10 mm Hg and a flow rate of 2-3 liters/min. Two other working ports of 5 mm size each were introduced under camera vision on the ipsilateral side of surgery accordingly. If needed, a fourth port (5 mm) was inserted for retraction of the liver or spleen. First, the internal inspection of the peritoneal cavity and intraabdominal structures was performed. Then, the splenic flexure of the colon was mobilised in the case of left-sided nephrectomy, while the hepatic flexure was mobilised when exploring the right-sided kidney. Dissection was carried out between the colon and Gerota's fascia until the lower pole of the kidney and ureter were identified, which were dissected away to create a window below, allowing exposure of the psoas major muscle. This dissection plan was followed upward and medially to reach the renal hilum. Gerota's fascia was opened and the renal artery and vein were isolated and transected after being clipped with hem-o-lock separately.

The upper pole of the kidney was dissected with the preservation of the ipsilateral adrenal gland. The ureter was transected at the lower pole using an energy device, and the rest of the kidney was mobilised from its postero-lateral attachments. In the case of nephro-ureterectomy, the ureter was dissected down to its insertion at the bladder and then transected or ligated flush with the bladder. Haemostasis was checked, and a drain was placed. The specimen was placed in a customised Endo bag and retrieved through the extension of the periumbilical port incision in the midline or a separate Pfannenstiel incision for Wilms' tumour.

The child was started on oral feeds 4-6 hours postoperatively. The Foley catheter was removed on next day morning, and the child was mobilised. The drain was removed on the first day if there was no output or if its drainage was less than 20ml within 24 hours. The child was discharged on the next day with oral antibiotics for five days. Follow-up was done on the 10<sup>th</sup> day and one month after surgery.

Data regarding age, gender, cause of NFK, laterality, and intraoperative and postoperative outcomes such as number of ports, estimated blood loss, need for transfusion, operative time, hospital stay, analgaesia requirement, complications, and follow-up were recorded.

Data collected through proforma were entered and analysed using the computer software SPSS version 16.0. Frequencies and percentages were calculated and data were presented in tables. Continuous data were expressed as mean and SD. Formal permission was taken from the Hospital's Ethical Committee to conduct the study. Privacy and confidentiality were maintained at all costs in accordance with principles laid down in the Helsinki Declaration of Bioethics.

#### RESULTS

Table I demonstrates that among 100 children, 37 (37.0%) were aged 5-60 months 46 (46.0%) were aged 61-120 months, 17 (17.0%) children were aged 121-180 months. The mean age of the children was  $79.54 \pm 4.427$  months. Among these children, 58 (58.0%) were males and 42 (42.0%) were females. Out of 100 children who underwent laparoscopic nephrectomy, the major cause was PUJO 47 (47.0%), followed by stones 32 (32.0%), VUR 8 (8.0%), and tumour 5 (5.0%). There were 8 (8.0%) patients who presented with other causes such as multicystic dysplastic kidney, obstructed megaureter, and ureteric stricture (Table I).

#### Table I: Demographics of patients.

	Frequency	Percentage
A	riequency	rencentage
Age		
5-60 months	37	37.0
61-120 months	46	46.0
121-180 months	17	17.0
Total	100	100.0
Mean ± SD	79.54 ± 4.427	
Gender		
Male	58	58.0
Female	42	42.0
Total	100	100.0
Cause		
PUJO	47	47.0
Stone	32	32.0
VUR	8	8.0
Tumour	5	5.0
Others (MCDK, OMU, Ureteric stricture)	8	8.0
Total	100	100.0

	Frequency	Percentage
Side		
Right	41	41.0
Left	59	59.0
Total	100	100.0
Number of ports		
3 ports	76	76.0
4 ports	24	24.0
Total	100	100.0
Retrieval incision		
Peri-umbilical port site extension of	97	97.0
incision		
Sub-costal (converted to open) 3	3	3.0
Xanthogranulomatous pyelonephritis (2)		
Horseshoe kidney (1)		
Total	100	100.0
Estimated blood loss		
0-25 ml	95	95.0
26-150 ml	3	3.0
>150 ml	2	2.0
Total	100	100.0
Mean ± SD	$19.93 \pm 65.556$	
Need of transfusion		
No transfusion	96	96.0
1 pint transfused	4	4.0
Total	100	100.0

	Frequency	Percentage
Analgaesia requirement		
Controlled with paracetamol only	73	73.0
Nalbuphine added with paracetamol	27	27.0
Total	100	100.0
Complications		
No complications	90	90.0
lleus (managed conservatively)	3	3.0
Converted to open	3	3.0
(Xanthogranulomatous pyelonephritis = $2$ ,		
Horseshoe kidney = $1$ )		
Wound infection	4	4.0
Total	100	100.0

Among 41 (41.0%) children, the right-sided nephrectomy was involved while among 59 (59.0%) children, the left-sided nephrectomy was involved. Three ports were used in 76 (76.0%) children and four ports in 24 (34.0%) children (Table II).

Ninety-seven (97.0%) required periumbilical port site extension of incision while 3 (3.0%) children required subcostal incision (converted to open surgery). Majority (95, 95.0%) had an estimated blood loss of 0-25 ml and 3 (3.0%) had 26-150 ml, while 2(2.0%) children had >150 ml. The mean estimated blood loss was  $19.93 \pm 65.556$  ml.

Out of 100 children, 96 (96.0%) did not require transfusion while only 4(4.0%) children required blood transfusion.

Among these children, 14 (14.0%) had operative time <60 minutes, mainstream 82 (82.0%) had 60-150 minutes, and 4 (4.0%) children had operative time >150 minutes. The mean operative time was  $125.31 \pm 43.365$  minutes. Out of the 100 children, a major proportion, 93 (93.0%), had a hospital stay of 2 - 3 days while only 7 (7.0%) children stayed for more than 3 days. The mean hospital stay of children was  $2.82 \pm 1.258$  days. Seventy-three (73.0%) children were controlled with

paracetamol only while 27 (27.0%) children were administered with paracetamol + nalbuphine.

Most of the children, 90 (90.0%), had no complications, while 3 (3.0%) had ileus, which was managed conservatively. Wound infection was seen in 4 (4.0%), and 3 (3.0%) were converted to open surgery (Table III).

At one month follow-up, 100 (100.0%) children were found normal according to renal function tests and ultrasound. Majority of the children (96, 96.0%) had normal urine testing results, while 2 children (2.0%) each had results indicating pus cells and proteinuria.

#### DISCUSSION

Laparoscopic nephrectomy which is a minimally invasive surgical method for the removal of a kidney, has emerged as a preferred approach in the treatment of nonfunctioning kidneys in children. It is a widely used technique that offers several advantages such as faster recovery, reduced postoperative pain, shorter hospital stays, and better cosmetic outcomes when compared with the traditional open nephrectomy. Therefore, the current study was carried out to analyse the outcome of laparoscopic nephrectomy among the first 100 children treated at the authors' department. It was found that the majority of the children were aged 61-120 months while the mean age of children was  $79.54 \pm 4.427$  months. However, a similar study carried out by Igbal et al. highlighted that mean age of the children who experienced laparoscopic nephrectomy was 117.36 months.<sup>1</sup> Another study conducted by Molina *et al.* team demonstrated that the mean age of children at the time of surgical treatment was 46.5 ± 4.23 months.<sup>12</sup>

As far as the gender of the children is concerned, the study disclosed that most of the children (58.0%) were males and 42.0% were females. The findings of this study are comparable with a study undertaken by Ezomike *et al.* who asserted that mainstream (61.5%) of children were males and 38.5% were females.<sup>2</sup> Similar results were also reported in a study conducted by Iqbal *et al.* who confirmed that among children, 61.6% were males and 38.4% were females.<sup>1</sup>

During the study, the cause of the nonfunctioning renal unit was evaluated which revealed the major cause was PUJO (47.0%) followed by stones (32.0%), VUR (8.0%), and tumour (5.0%). There were 8.0% patients who presented with other causes such as MCDK, OMU, and ureteric stricture. However, a study conducted by El-Ghoneimi et al. highlighted that the main reason to perform laparoscopic nephrectomy was pretransplant arterial hypertension, haemolytic-uremic syndrome or nephrotic syndrome (51%) followed by non-functioning kidney caused by obstruction, reflux / ectopic ureter (38%), and multicystic dysplastic kidney (11%).<sup>13</sup> Another study performed by Menon et al. highlighted that major causes were multicystic dysplastic kidney (23.2%) and vesico-ureteric reflux (42.85%).<sup>14</sup> The findings of this study indicated that among the children, 41.0% of the nephrectomies were performed on the right side while 59.0% on the left side. The results of a study carried out by Ezomike *et al.* exhibited a similar scenario and also asserted that 41.0% of the nephrectomies were performed on the right side and 59.0% on the left side.<sup>2</sup> However, a study done by lqbal and *et al.* showed a different scenario that more than half (53.%) of the nephrectomies were done on the right side while 46.2% on left side.<sup>1</sup> Another study performed by Ku *et al.* confirmed that 55.0% of nephrectomies were performed on the right side and 45.0% on the left side.<sup>15</sup>

When the outcomes of laparoscopic nephrectomy were assessed among children, the study highlighted that among the majority of children (76.0%), 3 ports were used and the 4<sup>th</sup> port was required in 24.0% children only. A study undertaken by Miranda *et al.* also highlighted that among the patients 3 or 4 ports were utilised as per requirement.<sup>16</sup> The findings of this study further indicated that this technique was effective among 97.0% cases but 3.0% required conversion to open surgery due to xanthogranulomatous pyelonephritis and horseshoe kidney. However, the results of a study done by Ku *et al.* are better than this study which reported that laparoscopic nephrectomy was feasible among all children as none of the cases required conversion to open surgery.<sup>15</sup>

Blood loss during surgery is a critical factor that can have serious implications for children. It is important to mention here that majority of the children had blood loss between 0 - 25 ml, with a mean estimated blood loss was  $19.93 \pm 65.556$  ml, and 4.0% children required blood transfusion. The findings of this study are better than the studies carried out by Kaewwichian *et al.* and Nerli *et al.*, who elucidated that mean estimated blood loss was  $31.8 \text{ ml}^{17}$  and 25.0 ml,<sup>18</sup> respectively, however, none of the patients in both studies required blood transfusion. Different studies carried out by Bryks-Laszkowska *et al.*, Mei *et al.*, and Kozlov *et al.* demonstrated that there was insignificant blood loss during surgery.<sup>19-21</sup>

The operative time and hospital stay are the leading factors in assessing the outcome of surgical procedure. It was found during the study that mainstream of children had operative time between 60-150 minutes while the mean operative time was 125.31 ± 43.365 minutes. The findings of this study showed a better scenario than the study undertaken by Igbal et al. who stated that the mean operative time was 173 minutes.<sup>1</sup> However, a study done by Shankar et al. reported that the mean operative time among patients was only 65 minutes.<sup>22</sup> The findings of this study further highlighted that the mean hospital stay of children was  $2.82 \pm 1.258$  days. However, studies performed by Igbal et al. and Shankar et al. reported that mean hospital stay among patients was 3.4 days<sup>1</sup> and 4 days,<sup>22</sup> respectively. However, a study carried out by Davies and Najmaldin showed a better situation and reported that the mean hospital stay among patients was 2 days.<sup>23</sup>

Laparoscopic nephrectomy is considered a superior surgical technique with a relatively low rate of complications. It was found during the study that a major proportion of children (90.0%) had no complications except only 10.0% children mainly conversion to open surgery (3.0%) followed by prolonged ileus (3.0%) and wound infection (4.0%). Virtually, the findings of this study are comparable with a study carried out by lqbal *et al.*, who elucidated that mainstream (92.3%) of children had no complications except 7.7% children who converted to open surgery.<sup>1</sup> Another study done by Davies and Najmaldin also confirmed the efficacy of this technique and found that it was successful among all children except only one child who converted to open surgery due to poor laparoscopic viewing.<sup>23</sup> In a study by Shankar *et al.* reported that there were no intra- or post-operative complications.<sup>22</sup>

On follow-up of these children after one month postoperatively, the authors found that all children were having a normal renal function and ultrasound abdomen (normal contralateral kidney and no abdominal collection/haematoma). However, urine routine examination showed that 4.0% children had pus cells and proteinuria while it was normal in majority of the children (96.0%).

This is a single-centred study including a limited number of patients due to time constraints and all large tumours >5 cm, and patients with complex anatomy such as horseshoe and duplex renal systems were excluded.

# CONCLUSION

Laparoscopic nephrectomy is an effective technique with regard to insignificant blood loss, operative time, hospital stay and rate of complications. Further studies are needed on a larger scale to assess the outcome of laparoscopic nephrectomy among children.

# ETHICAL APPROVAL:

Ethical approval was obtained from the Institutional Review Board of the Children's Hospital University of Child Health Sciences (Approval No.: 729/CH-UCHS).

# PATIENTS' CONSENT:

Written consents were taken from the parents/relatives of the patients.

# **COMPETING INTEREST:**

The authors declared no conflict of interest.

## **AUTHORS' CONTRIBUTION:**

GMZ: Study design and proofreading. MZ: Literature search and data analysis. FHA: Interpretation of data and write-up. SG: Data collection.

All authors approved the final version of the manuscript to be published.

# REFERENCES

- Iqbal N, Ali SI, Iqbal S, Hasan A, Zareen N, Shabbir MU, *et al.* Laparoscopic nephrectomy in pediatrics: Experience from a new pediatric urology department. *ARC J Urol* 2019; **4(3)**:18-22. doi: 10.20431/2456-060X.0403004.
- Ezomike UO, Modekwe VI, Ekenze SO. Paediatric nephrectomy: Patterns, indications and outcome in a developing country. *Malawi Med J* 2018; **30(2)**:94-8. doi: 10.4314/mmj.v30i2.8.

- Alhaidari OI, Moazin MS, Alhussein RM, Alghaith AA, Almoaiqel FA, Kokandi AA, *et al.* Indications for pediatric nephrectomy: A retrospective hospital-based study on Saudi population. *IJMDC* 2019; **3(4)**:348-52. doi: 10.24911/ IJMDC.51-1545164607.
- Iaquinto M, Scarpa MG, De Castro R, Codrich D, Guida E, Cerrina A, et al. Laparoscopic heminephroureterectomy in infants weighing less than 10 kilograms: The two peculiar cases. World J Lap Surg 2020; 13(2):80-3. doi: 10.5005/jpjournals-10033-1410.
- Rivas Vila S, Lopez Pereira P, Martinez Urrutia MJ, Lobato Romera R, Amesty Morello V, Aguilera Bazan A. Laparoscopic nephrectomy in pediatric patients. In: Esposito C, Subramaniam R, Varlet F, Masieri L. Eds. Minimally invasive techniques in pediatric urology. Cham: Springer, 2022. doi: 10.1007/978-3-030-99280-4\_19.
- Sarhan OM. Laparoscopic nephrectomy in children: does the approach matter? J Pediat Urol 2021; 17(4):568.e1-7. doi: 10.1016/j.jpurol.2021.05.006.
- Babu R, Vikram, Shakir. Laparoscopic nephrectomy in children: A case report and review of our experience. *Sri Ramachandra J Med* 2007; 1(2):54-6.
- Coban S, Turkoglu AR, Guzelsoy M, Ozgunay SE, Unal D, Ozgunay T, et al. Transperitoneal laparoscopic nephrectomy of non-functional horseshoe kidney that could not be identified preoperatively in a child. *Ped Urol Case Rep* 2015; 2(3):18-24. doi: 10.14534/PUCR.20153 10305.
- Bhardwaj N. Retroperitoneal versus transperitoneal approach for nephrectomy in children: Anesthetic implications. J Anaesthesiol Clin Pharmacol 2015; 31(1): 25-6. doi: 10.4103/0970-9185.150523.
- Baez JJN, Luna CM, Mesples GF, Arias AJ, Courel JM. Laparoscopic transperitoneal and retroperitoneal nephrectomies in children: A change of practice. J Laparoendosc Adv Surg Tech 2010; 20(1):81-5. doi: 10. 1089=lap.2008.0401.
- De Carli C, Guerra LA. Simultaneous bilateral laparoscopic nephrectomy in a child with peritoneal catheter dialysis using a 4-port trans-abdominal technique. *Can Urol Assoc* J 2015; 9(1-2):59-61. doi: 10.5489/cuaj.2465.
- Molina CF, Bessa J Jr, Estevanato AG, Viana GS, Facincani I, Netto JMB. Applicability of laparoscopic nephrectomy in the treatment of multicystic dysplastic kidney: Sorting out surgical indication. *Cureus* 2018; 10(1):e2014. doi: 10.7759/cureus.2014.

- El-Ghoneimi A, Abou-Hashim H, Bonnard A, Verkauskas G, Macher MA, Huot O, *et al.*\_Retroperitoneal laparoscopic nephrectomy in children: At last the gold standard? *J Pediatr Urol* 2006; **6(4)**:357-63. doi: 10.1016/j.jpurol. 2006.04.005.
- Menon P, Handu AT, Rao KN, Arora S. Laparoscopic nephrectomy in children for benign conditions: indications and outcome. J Indian Assoc Pediatr Surg 2014; 19:22-7. doi: 10.4103/0971-9261.125953.
- Ku JH, Yeo WG, Kim HH, Choi H. Laparoscopic nephrectomy for renal diseases in children: Is there a learning curve? *J Pediatr Surg* 2005; **40(7)**:1173-6. doi: 10.1016/j.jpedsurg.2005.03.052.
- Miranda ML, Oliveira-Filho AG, Carvalho PT, Ungersbock E, Olimpio H, Bustorff-Silva JM. Laparoscopic upper-pole nephroureterectomy in infants. *Int Braz J Urol* 2007; **33(1)**:87-93. doi: 10.1590/S1677-55382007000100015.
- Kaewwichian W, Pacheerat K, Chotikawanich E. Laparoscopic nephrectomy in children: Experience at Srinagarind Hospital, Khon Kaen University. J Med Assoc Thai 2012; 95(11):34.
- Nerli RB, Vernekar R, Guntaka AK, Patil SM, Jali SM, Hiremath MB. Laparoscopic hemi/partial nephrectomy in children with ureteral duplication anomalies. *Pediatr Surg Int* 2011; **27(7)**:769-74. doi: 10.1007/s00383-011-2883-7.
- Bryks-Laszkowska A, Golebiewski A, Czauderna P. Laparoscopic single port surgery nephrectomy in a child – Initial experience. *Videosurgery Miniinv* 2012; **7(4)**:304-6. doi: 10.5114/wiitm.2011.30515.
- Mei H, Qi T, Li S, Pu J, Cao G, Tang S, et al. Transumbilical multiport laparoscopic nephroureterectomy for congenital renal dysplasia in children: Midterm follow-up from a single institution. Front Pediatr 2013; 1:1-5: doi: 10.3389/ fped.2013.00046.
- Kozlov Y, Kovalkov K, Baradieva P, Rasputin A, Chubko D. Comparison of single-port and multi-port laparoscopic methods of nephrectomy in young infants. *Adv Laparoscopy* 2017; **1(1)**:11-6. doi: 10.36959/367/433.
- Shankar G, Babu NM, Ramesh S, Srimurthy KR. Laparoscopic nephrectomy in children: Initial experience. *J Indian Assoc Pediatr Surg* 2006; **11**:223-6. doi: 10.4103/0971-9261.29605.
- Davies BW, Najmaldin AS. Transperitoneal laparoscopic nephrectomy in children. *J Endourol* 2009; **12(5)**. doi: 10. 1089/end.1998.12.437.

• • • • • • • • • • •