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Advantages of selective ischemia and indocyanine green fluorescence navigation in laparoscopic partial nephrectomy: preliminary results

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SUMMARY
An important stage of the nephron-sparing surgery for the treatment of kidney tumors is the temporary creation of thermal ischemia, which can lead to a further decrease in kidney function, therefore this stage needs to be optimized. The aim of our work was to investigate the benefits of using segmental ischemia using intraoperative indocyanine green (ICG) navigation for kidney resection in patients with kidney tumors. The prospective study included 73 patients diagnosed with a kidney tumor who underwent partial nephrectomy (PN). Patients were divided into three groups, according to the use of the thermal ischemia method: total ischemia by clamping the main renal artery (n=33), segmental ischemia by clamping the segmental artery with the use of ICG navigation (n=26), and without it (n=16). Demographic, physiological, and perioperative data were analyzed for all patients. Before and on the fourth day after surgery, the glomerular filtration rate was evaluated according to the level of blood creatinine – eGFR (calculated glomerular filtration rate (eGFR). Multiple linear regression was used to model the effect of variables on change in eGFR. The data testify to the significant index difference in eGFR level change on the fourth postoperative day in the groups of total and segmental ischemia in favor of the latter (p=0.001). A decrease in eGRF was associated with the length of hospital stay (p=0.021). The data stratification in tumor size showed that it is the most important factor defining eGFR level change during total or segmental ischemia application. Renal tumor localization influences eGFR level change during the postoperative period for a maximum diameter of <40 mm tumors. However, for >40 mm diameter tumors, the statistically significant index of eGFR deviation was not found. At the same time, in the patient group with >40 mm tumors, there was a notable difference in eGFR deviation among the groups of total and segmental ischemia (about 15 mL/min/1.73 m^2). In the early postoperative period (up to 4 days) after partial nephrectomy using

selective warm ischemia, less pronounced eGFR deviations are observed compared to total warm ischemia. Tumor size and its localization are the risk factors for eGFR level decline in the early postoperative period. We did not find any statistically significant differences in intra- and early postoperative indexes for groups II and III patients where segmental ischemia was applied either with indocyanine green fluorescence imaging or without it.

РЕФЕРАТ

Переваги селективної ішемії з індоцианін зеленою флуоресцентною навігацією при резекції нирки: попередні результати. Молчанов Р.М., Гончарук О.О., Блюсс О.Б. У нефронзберігаючій хірургії лікування пухлин нирок важливим етапом операції є тимчасове створення теплової ішемії, яка може призвести до подальшого зниження функції нирки, у зв'язку з чим даний етап потребує оптимізації. Метою нашої роботи було дослідження переваг застосування сегментарної ішемії з використанням інтраопераційної навігації з індоціаніном зеленим (ІЦЗ) для резекції нирки у пацієнтів із пухлинами нирки. До проспективного дослідження було включено 73 пацієнти з діагнозом пухлини нирки, яким виконано оперативне втручання в обсязі резекції нирки. Пацієнти були розподілені на 3 групи, згідно з використанням методу теплової ішемії: тотальна ішемія шляхом перетискання основної ниркової артерії (n=33), сегментарна ішемія шляхом перетискання сегментарної артерії з використанням ІЦЗ навігації (n=26) та без неї (n=16). Для всіх пацієнтів проведено аналіз демографічних, фізіологічних та періопераційних даних. До і на четверту добу після оперативного втручання проводили оцінку швидкості клубочкової фільтрації за рівнем креатиніну крові – рШКФ (розрахована швидкість клубочкової фільтрації (eGFR). Для моделювання впливу вивчених параметрів зміну рШКФ використовувалася множинна лінійна регресія. Отримані дані свідчать про вірогідну різницю показників зміни рівня рШКФ на четверту добу після операції в групах тотальної та сегментарної ішемії на користь останньої (p=0,001). Зниження рШКФ було пов'язане з тривалістю перебування в лікарні (p=0,021). Стратифікація даних за розміром пухлини показала, що це є важливим фактором, що визначає зміну рівня рШКФ при застосуванні тотальної або сегментарної ішемії. Локалізація пухлини нирки впливає на зміну рівня рШКФ у післяопераційному періоді для пухлин з максимальним діаметром <40 мм. Однак для пухлин діаметром >40 мм статистично значущого показника відхилення рШКФ не виявлено. Водночас у групі пацієнтів із пухлинами >40 мм спостерігалася помітна різниця у відхиленні СКФ серед груп тотальної та сегментарної ішемії (близько 15 мл/хв/1,73 м^2). У ранньому післяопераційному періоді (до 4 діб) після резекції нирки із використанням селективної теплової ішемії спостерігаються менш виражені відхилення рШКФ порівняно з тотальною тепловою ішемією. Розмір пухлини та її локалізація є факторами ризику зниження рівня ШКФ у ранньому післяопераційному періоді. Не виявлено жодних статистично значущих відмінностей інтра- та ранніх післяопераційних показників у пацієнтів II та III груп, у яких застосовувалася сегментарна ішемія як з використанням ІЦЗ навігації так і без неї.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3% of global cancer diagnoses and is the cause of 2% of all cancer deaths (Quencer, 2021). The development of modern medical imaging methods allows for much earlier diagnosis of renal tumors. Some are benign or indolent tumors, which often do not need surgery treatment (Roussel et al., 2022), while RCC accounts for 85% of all kidney tumors (Pallagani et al., 2021). Among renal masses being accidentally detected during examination using modern imaging methods, up to 70% of RCC is diagnosed at the stage of T1, which significantly reduces deaths caused by this disease (Saad et al., 2019).

The opportunity to diagnose renal tumors at the early stage of their development significantly impacts its treatment strategy. Active use of partial nephrectomy [PN] as an alternative to radical one began after the results publication of several retrospective and one prospective research by Van Poppel et al. (2011) showing no cancer-specific survival differences between PN for the patients at the stage of T1-2 (Kim et al., 2012) and for renal masses ≤7 sm at the stage of T3 (12). According to EAU and NCCN recommendations, the general survival rate of patients suffering from renal mass at the stage of c/p T1 after PN does not differ from the survival rate after radical one. In this regard, the PN is recommended as the primary surgical treatment method for patients at the stage of T1 (Ljungberg et al., 2022; Motzer et al., 2022).

The advantage of nephron-sparing surgery is the decline of renal failure risk development and consequently reducing cardio-vascular and metabolic diseases. It reduces general mortality and improves long-term kidney function compared to radical nephrectomy (Daugherty et al., 2014; Weight et al., 2010).

PN implementation deals with the necessity of bleeding control during surgery. The traditional method implies renal artery clamping during resection. However, it may result in ischemia-reperfusion nephron injury, which is essential for a post-surgery acute renal failure during the early post-operative recovery phase or for a long-term chronic renal failure (Thompson et al., 2010; Xu et al., 2020). An alternative method of renal bleeding control is segmental ischemia, which implies the dissection and clamping of a renal artery that directly supplies the tumor itself or tumor-bearing kidney segment. While normal blood circulation is spared in the rest of the parenchyma, segmental renal artery clamping does not cause a considerable deviation in general kidney function (Gill et al., 2011; Lee et al., 2018). An alternative surgery variant when parenchymal ischemia is avoided is the 'off clamp' method which does not provide for the renal artery clamping. It leads to much less eGFR deviation than total warm kidney ischemia (Trehan, 2014).

The main problem of segmental renal artery clamping during resection is the necessity of renal artery segmental branch dissection that depends on individual anatomical peculiarities. The existence of additional renal arteries or early division of the main renal artery considerably simplifies segmental ischemia implementation. A deeper level of renal artery branching turns the process of segmental ischemia implementation into a rather complicated stage of surgery. In such cases, it is necessary to use methods that improve the process of identification and precise renal artery segmental branch separation. Among such methods, it is important to mention the dual-source computed tomography angiography that can be used during laparoscopic surgery (Shao et al., 2012).

Indocyanine green fluorescence imaging is one prospective method that helps effectively evaluate renal blood circulation during surgery. This method, combined with the laparoscopic technique, enables the control of real-time renal blood circulation and the ischemia zone during the renal artery and its branches clamping, simplifying PN implementation (Lee et al., 2018). So far, quite a little experience has been gained in indocyanine green imaging application during PN, and it needs further evaluation, development, and improvement.

The aim of the research was to investigate the advantages of segmental ischemia with intraoperative indocyanine green imaging in patients with kidney tumors.

MATERIALS AND METHODS

From 2018 till 2021 the prospective study included 73 patients with renal tumor diagnoses confirmed by CT scan with IV contrast data. All the patients were subjected to partial nephrectomy. The patients were divided into three groups based on the warm ischemia method application. Group #1 included 33 patients who were applied full ischemia with the main renal artery clamping. Group #2 and Group #3 included 24 and 16 patients, respectively who were applied segmental ischemia with segmental renal artery clamping using ICG navigation and without using it (respectively). The basis for dividing the patients into groups was renal blood circulation peculiarities that allowed for segmental ischemia application. In 2 patients, a transition from segmental to full warm ischemia was applied because of intense bleeding from the tumor bed.

All the patients were subjected to transperitoneal (laparoscopic) partial nephrectomy. The surgery was performed under general anesthesia. The patients were laid in a 45°angle position depending on the tumor side. The ports were located according to the laparoscopic nephrectomy standard position. After renal vessel dissection, the tumor-bearing segment of kidney was developed.

In case the tumor had intraparenchymal growth pattern its location was identified with the help of ultrasound scanning using the intraabdominal linear probe (7 MHz) inserted through the lower port. After the renal capsule dissection on the tumor border zone, the standard technique of renal artery clamping was used. Enucleoresection was applied within limits of the tumor capsule zone, leaving 1-2 mm of normal parenchymal area. In the process of tumor removal, intraparenchymal vessels were controlled by clipping (Absolock, Ethicon). After running suture application on the parenchyma in the tumor removal bed area, the clamps were removed from the arteries. The second row of stitches was used for the ultimate parenchyma suture.

The demographic information data of all the patients was collected as well as the severity of illness according to the Charlson comorbidity scale and ASA score. All the patients were subjected to a preoperational CT with IV contrast to specify tumor localization and size. The complexity of the tumor process was defined by the tumor size evaluation and by its localization in accordance with R.E.N.A.L. classification (Kutikov et al., 2009). Before the surgery and on the 4th postoperative day, the glomerular filtration rate estimation by the level of blood creatinine –eGFR (estimated Glomerular Filtration Rate) with MDRD formula (Modification of Diet in Renal Disease Study) was assessed (Borrego et al., 2020). The evaluation of the tumor characteristics was implemented following the routine procedure of the postoperative pathohistological study.

Descriptive statistics were calculated for all clinical characteristics. Continuous variables were summarized as medians (interquartile range) and categorical variables as frequencies (percentage). Multiple linear regression was used to model the effect of variables on change in eGFR. Two-sided p-values are reported for all statistical tests. Statistical analysis was performed using R version 3.5.1.

RESULTS AND DISCUSSION

The results of demographic, physiological, and perioperative data analysis are presented in Table 1.

TABLE 1. Data of the patients

Index	Group I (full ischemia) (n=33)	Group II (segmental ischemia ICG) (n=24)	Група III (segmental ischemia) (n=16)	p-value
Age (years)	54.5 [45.5;64.3]	59 [50.8;64.8]	58 [46.3;62]	0.545
Gender				
Female	19 (53%)	10 (42%)	6 (37%)	0.547
Male	17 (47%)	14 (58%)	10 (63%)	
BMI	27.8 [25.2;31]	27.7 [24.9;29.5]	27.3 [26;29.3]	0.828
ASA score				
1	0 (0%)	1 (4.2%)	0 (0%)	
2	25 (69.4%)	12 (50%)	8 (50%)	0.258
3	11 (30.6%)	11 (45.8%)	8 (50%)	
Charlson comorbidity index	2 [2;4]	4 [2.8;5]	2 [0.8;4.3]	0.164
Baseline eGFR (mL/min/1,73 m^2)	72.3 [62.7;92.6]	79.5 [59;88]	78.8 74.6;84.5]	0.583
Largest.tumour.size, mm	41 [33;53.3]	37 [27.8;51.8]	31.5 [23;55]	0.674
Tumor localization				
Intrarenal	10 (28%)	8 (33%)	4 (25%)	0.846
Extrarenal	26 (72%)	16 (67%)	12 (75%)	
Anterior	19 (53%)	9 (38%)	8 (50%)	0.196
Posterior	12 (33%)	5 (20%)	5 (31%)	
Lateral	5 (14%)	10 (42%)	3 (19%)	
Complexity of tumor localization				
Light	11 (31%)	9 (38%)	7 (44%)	0.919
Medium	19 (53%)	12 (50%)	7 (44%)	
Complex	6 (16%)	3 (12%)	2 (12%)	
Operative time (min)	150.5 [140;180]	170 [145;200.5]	145 [114;180]	0.563
Length of hospital stay (days)	5 [5-6]	5 [5-6]	5 [5-7]	0.706
Histology				
Benign	5 (14%)	9 (38%)	8 (50%)	0.06
Malignant	31 (86%)	15 (62%)	8 (50%)	

The median age of the patients was 54.5 [45.5;64.3], 59 [50.8;64.8] and 58 [46.3;62] in Groups I, II and III, respectively, ranging from 25 to 73. The BMI and Charlson Comorbidity Index were 27.8 [25.2;31], 27.7 [24.9;29.5], 27.3 [26;29.3], and 2 [2;4], 4 [2.8;5] and 2 [0.8;4.3], respectively. The maximum diameter of tumor according to CT scan data was 41 [33;53.3], 37 [27.8;51.8] and 31.5 [23;55] mm. For group division by the complexity of tumor localization R.E.N.A.L index was used classifying the tumor of 4-6 index as light, the one of 7-9 index as medium and the one of 10-12 as complex. Among the tumors the medium one prevailed 19 (53%), 12 (50%), 7 (44%), while light (31%); 9 (38%), 7 (44%) and complex 6 (16%), 3 (12%), 2 (12%) occurred more seldom respectively. At the same time the tumors of mostly extrarenal localization 26 (72%); 16 (67%), 12 (75%) and of anterior one 19 (53%); 9 (38%), 8 (50%) dominated. Baseline eGFR made 72.3 [62.7;92.6], 79.5 [59;88] and 78.8 [74.6;84.5] mL/min/1,73 m^2 in groups 1, 2 and 3 respectively.

The average operative time was 150.5 [140;180] and 170 [145;200.5], 145 [114;180] min. The median time of ischemia in group I was 19 [15.5-22] minutes, II – 22.5 [15-25], III – 20 [16-22]. The blood loss in group I was 238 [150-500], II – 180 [100-500], III – 195 [116-425].

In groups I and II, the malignant tumors prevailed – in 31 (86%) and 15 (62%) cases, respectively, while in group III both malignant and benign tumors were equally observed (8 incidents, 50%).

The statistical analysis found no statistically significant differences in demographic, physiological, and perioperative data among the groups under consideration (p>0.05).

Since one of the main purposes of selective renal ischemia application is the prevention of renal function reduction due to parenchymal ischemia, we used the multiple linear regression for modeling the characteristic influence on eGFR change, the results of which are presented in Table 2.

TABLE 2. Factors influencing eGFR

	Estimate	Std. Error	Pr(>|z|)	95% CI
Age at diagnosis	-0.166	0.197	0.403	-0.561 to 0.228
Gender Male vs Female	-4.027	4.265	0.349	-12.568 to 4.514
BMI	-0.12	0.486	0.806	-1.093 to 0.854
ASA score	-6.928	4.583	0.136	-16.106 to 2.25
Charlson.Comorbidity.Index	0.096	1.216	0.937	-2.338 to 2.53
Baseline.eGFR	-0.425	0.12	0.001	-0.665 to -0.184
Largest tumour size	-0.003	0.12	0.98	-0.244 to 0.238
Intrarenal vs extrarenal	-9.318	5.055	0.07	-19.442 to 0.805
Tumour site Posterior vs Anterior	-6.278	4.237	0.144	-14.763 to 2.207
Tumour site Lateral vs Anterior	4.057	5.044	0.425	-6.044 to 14.158
Renal degree	-5.006	3.899	0.204	-12.815 to 2.802
Operative time	0.008	0.022	0.716	-0.036 to 0.052
Length of hospital stay	-3.752	1.587	0.021	-6.93 to -0.574
Benign vs malignant	-1.901	5.172	0.715	-12.258 to 8.456
Warm ischemia time Partial vs Full	6.218	4.282	0.152	-2.357 to 14.793

The given data testify to the significant index difference in eGFR level change on the fourth postoperative day in the groups of total and segmental ischemia in favor of the latter. A decrease in eGRF was associated with the length of hospital stay.

The data stratification in tumor size showed that it is the most important factor defining eGFR level change during total or segmental ischemia application (Table 3, 4).

TABLE 3. Factors influencing eGFR (tumor size <40 mm, n=39)

	Estimate	Std. Error	Pr(>|z|)	95% CI
Age at diagnosis	-0.164	0.302	0.593	-0.788 to 0.46
Gender Male vs Female	-1.732	6.881	0.803	-15.933 to 12.469
BMI	0.524	0.842	0.54	-1.214 to 2.261
ASA score	-2.154	7.814	0.785	-18.281 to 13.973
Charlson Comorbidity Index	1.833	1.515	0.238	-1.294 to 4.96
Baseline eGFR	-0.242	0.156	0.135	-0.565 to 0.081
Intrarenal vs extrarenal	-7.559	6.274	0.24	-20.508 to 5.391
Tumour site Posterior vs Anterior	-15.853	5.643	0.01	-27.498 to -4.207
Tumour site Lateral vs Anterior	-8.831	8.245	0.295	-25.847 to 8.186
Renal degree	4.27	4.83	0.385	-5.699 to 14.239
Operative time	-0.016	0.024	0.508	-0.067 to 0.034
Length of hospital stay	-2.804	2.228	0.22	-7.403 to 1.795
Benign vs malignant	-2.564	6.362	0.69	-15.695 to 10.567
Warm ischemia time Partial vs Full	3.182	6.267	0.616	-9.752 to 16.116

According to the received data, renal tumor localization influences eGFR level change during the postoperative period for a maximum diameter of <40 mm tumors. However, for >40 mm diameter tumors, the statistically significant index of eGFR deviation was not found. At the same time, in the patient group with >40 mm tumors, there was a notable difference in eGFR deviation among the groups of total and segmental ischemia (about 15 mL/min/1.73 m^2). Moreover, judging by the confidence interval, the statistical significance was not identified only because of the insufficient number of patients.

Analogical trends were found in the subgroup analysis when comparing the patients of total ischemia application only with the patients of segmental ICG one. Thus, the eGFR deviation difference was also large (about 12 mL/min/1.73 m^2), but not statistically significant (p=0.202).

An important parameter defining the treatment strategy of patients with renal tumors is the tumor size and its localization. It is known that many accidentally found tumors of small size are benign or indolent, which often do not need surgical treatment. For these tumors, a tactic of active surveillance can be used (Roussel et al., 2022). Malignant tumor size growth increases the risk of tumor invasion and metastasis. It is supposed that the most important sign of malignancy is the size of a tumor. Due to this, renal tumors are usually divided into two categories: maximum diameter of less and more than 4 cm (Ballard et al., 2022). According to Asghar et al. (2021), benign tumors or tumors with low malignant potential are detected in 1 out of 8 patients with renal tumors of >4 cm diameter. In the case of benign tumor growth, there is a possibility of its influence on renal function capacity or the risk of complications of the tumor itself, like, for example, angiomyolipoma spontaneous rupture (Vaggers et al., 2021).

The results about tumor size and localization influence on the postoperative eGFR level reduction correspond with Carbonara et al. (2021) data. Based on retrospective analysis of 1019 robotic-assisted PN they established prolonged warm ischemia time results in higher frequency of postoperative complications, more pronounced eGFR level decline at the time of discharge from hospital and during future follow up in patients with >2 cm tumors and high R.E.N.A.L index. According to AUA, active surveillance is recommended for patients with renal masses of <2 cm diameter (Campbell et al., 2021).

TABLE 4. Factors influencing eGFR (tumor size >=40 mm, n=34)

	Estimate	Std. Error	Pr(>|z|)	95% CI
Age at diagnosis	0.149	0.355	0.679	-0.594 to 0.893
Gender Male vs Female	-9.485	8.234	0.264	-26.719 to 7.75
BMI	-0.247	0.765	0.751	-1.848 to 1.355
ASA.Score	-9.179	9.259	0.334	-28.56 to 10.201
Charlson Comorbidity Index	-2.926	2.784	0.307	-8.753 to 2.902
Baseline eGFR	-0.558	0.204	0.013	-0.986 to -0.13
Intrarenal vs extrarenal	-12.735	9.526	0.197	-32.674 to 7.204
Tumour.site Posterior vs Anterior	1.478	7.98	0.855	-15.223 to 18.18
Tumour.site Lateral vs Anterior	10.342	6.943	0.153	-4.191 to 24.874
Renal degree	-11.811	7.289	0.122	-27.068 to 3.445
Operative time	-0.003	0.092	0.97	-0.195 to 0.188
Length of hospital stay	-2.306	2.874	0.432	-8.322 to 3.71
Benign vs malignant	5.774	12.259	0.643	-19.884 to 31.432
Warm ischemia time Partial vs Full	15.143	7.779	0.067	-1.138 to 31.424

In accordance with our data, a significant influence of total ischemia compared with segmental one on eGFR level decline in the postoperative period is observed in >4 cm tumors. The received data correspond with the general tendency identified by Xu et al. (2020) in the meta-analysis of publications data about the advantages of segmental ischemia application. They found that the application of either selective or total ischemia depends on tumor size and localization as well as on methods of surgical treatment.

CONCLUSIONS

In the early postoperative period (up to 4 days) after partial nephrectomy using selective warm ischemia, less pronounced eGFR deviations are observed compared to total warm ischemia. Tumor size and its localization are the risk factors for eGFR level decline in the early postoperative period. We did not find any statistically significant differences in intra- and early postoperative indexes for groups II and III patients where segmental ischemia was applied either with indocyanine green fluorescence imaging or without it.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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