

Fluorescence ureteral angiography with indocyanine green for the prevention of urological complications in kidney transplantation

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Abstract

Background. *Some of the most common complications following kidney transplantation are urological complications. According to the literature, local tissue ischemia plays a crucial role in their development. Numerous studies have confirmed the effectiveness and safety of fluorescence imaging with indocyanine green (ICG) for assessing organ perfusion. However, this technique has not yet been widely integrated into kidney transplantation practice.*

Objective. Improving kidney transplantation outcomes through the implementation of a fluorescent ureteral angiography protocol with ICG for the prevention of urological complications.

Material and method. This retrospective study analyzed the treatment outcomes in 294 kidney transplant recipients. Group I included 233 patients who underwent transplantation between 2018 and 2021. Neoureterocystoanastomosis was performed in all cases using Barry's extravesical anti-reflux technique. The incidence and risk factors for urological complications were assessed. Based on these findings, a fluorescence-guided approach to forming the neoureterocystoanastomosis was developed and implemented into clinical practice. If fluorescence imaging confirmed satisfactory ureteral perfusion, the anastomosis was performed using the standard method. If fluorescence findings were unfavourable, an excessive ureteral length was resected within the well-perfused zone, and a non-tunneled anastomosis was performed. Group II included 61 kidney transplant recipients operated on between 2022 and 2023, who underwent transplantation using this fluorescence-guided method.

Results. The incidence of urological complications in Group I was 12.0% (28/233). No significant correlation was identified between complications and potential risk factors. In seven cases in Group II, unfavourable fluorescence findings required extended ureteral resection and non-tunneled anastomosis. A comparative analysis demonstrated that the use of fluorescence angiography reduced the risk of urological complications three-fold (12% vs. 3.3%, $p=0.045$).

Conclusions. Fluorescence angiography of the transplanted kidney ureter is a safe and effective imaging technique that contributes to preventing urological complications. This approach ensures anastomosis

formation within well-perfused tissues, reducing postoperative risks and improving transplant outcomes.

Keywords: kidney transplantation, urological complications, fluorescence angiography, indocyanine green

Conflict of interests Authors declare no conflict of interest

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BMI, body mass index

CI, confidence interval

DBD, donation after brain death

DCD, donation after cardiac death

ICG, indocyanine green

ICU, Intensive Care Unit

Introduction

Currently, urological complications are among the most common complications of kidney transplantation. According to some studies, their incidence reaches 30% [1, 2]. The group of medical conditions under consideration significantly prolongs the recipient's recovery period, in some cases reducing their quality of life in the long term. Despite the fact that urological complications themselves rarely become a direct cause of the graft loss, in presence of immunosuppressive therapy they are associated with the development of severe infectious complications, which increase both the likelihood of organ death, and also mortality rates among the recipients [3]. The group under consideration in this study

includes complications such as the extravasation of urine as a result of neoureterocystoanastomosis failure and ureteral stricture.

It is generally accepted that the extravasation of urine develops in the early postoperative period; its prevalence reaches 9.3% [4]. It may occur due to technical errors during surgery, leading to a break of the anastomosis integrity or contributing to the development of local ischemia [5]. Among the most likely causes, there is an excessive skeletonization of the ureter, the cutting through the anastomotic sutures due to an excessive traction, and various injuries to the organ during its harvesting, preservation, or at "back table" stage. It is believed that rough and excessive dissection in the area of the so-called golden triangle significantly increases the risk of urine extravasation, leading to damage to the vessels that branch off at the graft gate and directly supply the ureter with blood [6].

The formation of ureteral strictures, making up to 15%, is somewhat more common among postoperative complications [7]. Considering the timing of their development, they can be classified as early or late. Late strictures are associated with the inflammatory process developing as a result of bacterial and viral infections. The causes for the formation of early strictures are similar to those in the development of the extravasation of urine [8]. From a technical point of view, the development of neoureterocystoanastomotic stricture is often associated with using the continuous suture, which contributes to the ureteral wall ischemia or its lumen stenosis.

Thus, according to the literature, tissue ischemia plays a key role in the development of the urological complications under study. Due to the peculiarities of the blood supply, the distal parts of the ureter are at the greatest risk of ischemia [9]. Many studies have proven the effectiveness and safety of using fluorescent visualization with indocyanine green

(ICG) to assess the blood supply to various abdominal organs at risk of ischemia due to the peculiarities of surgical interventions [10, 11]. However, currently, the experience of using this technology in kidney transplantation is small. In this regard, the goal of our study was to improve the kidney transplantation outcomes by developing and implementing into practice a protocol for fluorescent angiography of the renal graft ureter.

Objectives

- To determine risk factors for the development of urological complications after kidney transplantation
- To develop and implement into clinical practice an algorithm for the formation of neoureterocystoanastomosis using fluorescence angiography with ICG, to evaluate its sensitivity and specificity in assessing the distal ureter ischemia.
- To conduct a comparative analysis of the incidence of urological complications using a standard approach and the fluorescent angiography of the ureter with ICG.

Material and methods

The retrospective study analyzed the treatment outcomes of 294 patients who underwent kidney allotransplantation at the Moscow Multidisciplinary Scientific and Clinical Center n.a. S.P. Botkin from 2018 to 2023. Group I included 233 patients who underwent surgery from 2018 to 2021. There were 114 men (48.9%) and 119 women (51.1%). The median age of the patients was 45 (30;58) years, the median body mass index (BMI) was 25.7 (22.3;28.1) kg/m². In all cases, the kidney transplant was performed from a deceased donor: in 214 cases from a donor with confirmed brain death, in 19 cases from a donor with

irreversible cardiac arrest. The median age of donors was 52 (23;69) years, median BMI was 29.3 (24.8;35.3) kg/m². Among donors with confirmed brain death, 105 (49.1%) were classified as expanded criteria donors. In 14 cases (6%), the renal graft had 2 or more arteries. The median time of static cold preservation was 12.4 (10.1;14.7) hours, the median time of secondary warm ischemia was 40 (30;45) minutes.

Standard technique for performing neoureterocystoanastomosis

In all cases of group I, neoureterocystoanastomosis was performed according to the extravesical Barry's antireflux method (Fig. 1). Two apertures at a distance of 2 cm from each other were formed in the muscular membrane of the urinary bladder mucosa towards the pubic symphysis. The ureter of the renal graft was passed through the submucosal tunnel, followed by performing its anastomosis with urinary bladder mucosa, using interrupted sutures PDS 6-0 with the obligatory placement of an internal double-j stent for 14 days. The openings in the detrusor were sutured with separate interrupted sutures.



Fig. 1. Extravesical technique for forming neoureterocystoanastomosis

In retrospective study group I the incidence and risk factors for the development of urological complications were analyzed. Based on the analysis results, an algorithm for the formation of

neoureterocystoanastomosis using fluorescent angiography with ICG was developed and implemented in clinical practice.

Formation of neoureterocystoanastomosis using fluorescein angiography

Fluorescein angiography was performed using the IMAGE1 S™ RUBINA imaging system (Karl Storz SE & Co. KG, Germany). After reperfusion of the renal graft, ICG was administered intravenously at a calculated dose of 0.2 mg/kg. The fluorescence of the drug in the ureter tissue was recorded in the mode of the near infrared light overlay on white light. In case of a positive result, namely the satisfactory fluorescence of the ureter along its entire length (Fig. 2), the neoureterocystoanastomosis was performed using the standard technique described above. In case of a negative result, when hypoperfusion of the distal ureter was recorded (Fig. 3), the ischemic area was excised within the satisfactorily blood-supplied zone, and an anastomosis was formed with the urinary bladder by using the tunnel-free technique.



Fig. 2. Intraoperative photograph. Favourable fluorescence angiography result: the ureteral fluorescence intensity is the same throughout the entire length



Fig. 3. Intraoperative photograph. Unfavourable fluorescein angiography result: the fluorescence intensity of the distal ureter is reduced (indicated by the arrow)

In each case, the resected portion of the ureter was sent for routine histological examination, where the ischemia degree was assessed. The results of fluorescein angiography and histological examination were subsequently compared; and the sensitivity and specificity of the developed technique were determined with respect to ischemia.

Fluorescein angiography was used in 61 recipients operated on from 2022 to 2023 and comprising study group II. There were 24 men (39.3%) and 37 women (60.7%). The median age was 49 (31;67) years, the median BMI was 27.8 (20;30.4) kg/m². In 58 cases, the organs were obtained from donors with confirmed brain death, and in 3 cases, from donors with irreversible cardiac death. The median donor age was 54 (21;67) years, the median BMI was 32.7 (25.8;38.6) kg/m². Among donors with confirmed brain death, 25 (43.1%) were classified as expanded criteria donors. In 4 cases (6.6%) the renal graft had 2 or more arteries. The median time of static cold preservation was 13.1 (11.3;15.1) hours, the median time of secondary warm ischemia was 35 (33;40)

minutes. No statistically significant differences ($p>0.05$) were found between the groups in the main baseline characteristics of recipients, donors, and perioperative parameters (Table 1).

Table 1. Comparative characteristics of the study groups I

Parameter	Group I (n=233)	Group II (ICG) (n=61)	p
Characteristics of recipients			
Recipient age, years	45 (30;58)	49 (31;67)	0.53
Male recipient, n (%)	114 (48.9%)	24 (39.3%)	0.107
Recipient BMI, kg/m ²	25.7 (22.3;28.1)	27.8 (20;30.4)	0.325
Hemoglobin, g/L	106.5 (102.2;110.9)	110.5 (95.8;116.4)	0.29
Length of stay on dialysis, months	21 (19;26)	19 (15;24)	0.267
Perioperative parameters			
Cold preservation time, h	12.4 (10.1;14.7)	13.1 (11.3;15.1)	0.29
Surgery duration, h	3.8 (2.7;5.5)	4.3 (3.1;5.9)	0.457
Secondary warm ischemia time, min	40 (30;45)	35 (33;40)	0.28
Donor characteristics			
Donor age, years	52 (23;69)	54 (21;67)	0.433
Male, n (%)	124 (53.2%)	28 (45.9%)	0.31
Donor BMI, kg/m ²	29.3 (24.8;35.3)	32.7 (25.8;38.6)	0.225
Donor length of stay in the ICU, h	43 (36;63)	39 (34;58)	0.101
Norepinephrine dose > 1000 ng/mL or 2 vasopressors, n (%)	13 (34.7%)	7 (41.1%)	0.64
Serum creatinine, μ mol/L	125.4 (97.1;163.8)	134.9 (89;171.2)	0.21
Donor:			
Donation after cardiac death	19	3	0.84
Expanded criteria donor	105	25	0.43
Standard criteria donor	109	33	0.54
Number of arteries in the graft			
1	219 (93.9%)	57 (93.5%)	0.997
2 or more	14 (6.1%)	4 (6.5%)	

Note: ICU, Intensive Care Unit

To stratify urological complications after kidney transplantation, a simplified letter classification (A–E) was used based on the extent of intervention required and the potential threat to the graft. Class A corresponded to asymptomatic changes that required no treatment; Class B implied mild complications that could be pharmacologically treated; Class C meant complications that required minimal intervention (catheterization, stent placement); Class D qualified complications that

required an invasive intervention under anesthesia (e.g., surgical revision of the anastomosis); Class E comprised severe complications that were life-threatening or could lead to a graft loss.

Statistical processing and data analysis

Statistical data processing was performed using IBM SPSS Statistics for Windows software, version 26.0 (IBM Corp., Armonk, NY, USA). To compare two groups of quantitative variables with normal distribution (depending on the equality of variances), the Student's t-test or Welch's t-test was used. In case of abnormal distribution of quantitative variables, the Mann-Whitney U-test (for two groups) and Kruskal-Wallis test (for three or more groups) were used. Qualitative variables were compared by using Pearson's χ^2 -test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. Recipient and graft survival rates were estimated using the Kaplan-Meier method. To estimate the diagnostic value of the proposed method, the sensitivity, specificity, positive and negative predictive values were calculated.

Results

In group I, the incidence of urological complications of kidney transplantation was 12.0% (28/233). In 3/28 cases (10.7%), class B complications occurred, which were the extravasation of urine, and were treated conservatively by placing a urethral catheter. Class C complications, which required nephrostomy and stent placement in the graft ureter, occurred in 7/28 patients (25%) and were strictures. In 18/28 cases (64.3%), urological complications were class D and required repeated surgical interventions with the formation of a reneoureterocystoanastomosis: they were a failure of the ureterovesical anastomosis in 6 cases and a stricture of the graft ureter in 12 cases. At

the first stage of the study, we analyzed factors that could influence the development of urological complications, but no statistically significant relationship was found for any of them (Table 2).

Table 2. Risk factors for the development of urological complications of kidney transplantation

Parameter	Without complications (level A) n=214	Presence of urological complications (level B–D) n=28	p
Recipient risk factors			
Recipient age, years	45 (36;48)	46 (34;49)	0.53
Male recipients, n (%)	105 (49.0%)	9 (47.3%)	0.107
Recipient BMI, kg/m ²	25.4 (22.1;28.4)	26.8 (23.9;28.2)	0.325
Length stay on dialysis, months	21 (19;26)	24 (23;28)	0.29
Hemoglobin, g/l	106.3 (102.6;110.4)	104.8 (100.7;107.6)	0.267
Donor risk factors			
Donor BMI, kg/m ²	27.6 (23.3;28.2)	31.7 (25.4;36.8)	0.345
Donor age, years	49 (36;63)	53 (41;66)	0.3
Donor:			
Donation after cardiac death	10	9	0.745
Expanded criteria donor	64	41	0.41
Standard criteria donor	47	62	0.62
Number of arteries in the graft:			
1	108	111	0.76
2	6	8	
Perioperative risk factors			
Cold preservation time, h	12.4 (10.1;14.7)	12.1 (9.9;13.8)	0.12
Secondary warm ischemia time, min	35 (35;40)	40 (35;45)	0.23

At the second stage, we analyzed the safety and effectiveness of the developed protocol for the formation of neoureterocystoanastomosis using fluorescent angiography. According to the histological examination results, the distal ureter ischemia (Fig. 4) was detected in 12 of 63 cases (19.0%), while in 11 cases ICG fluorescein angiography correctly identified the perfusion impairment. In 2 cases, angiography erroneously

indicated ischemia in the absence of its histological confirmation, which was regarded as a false-positive result.

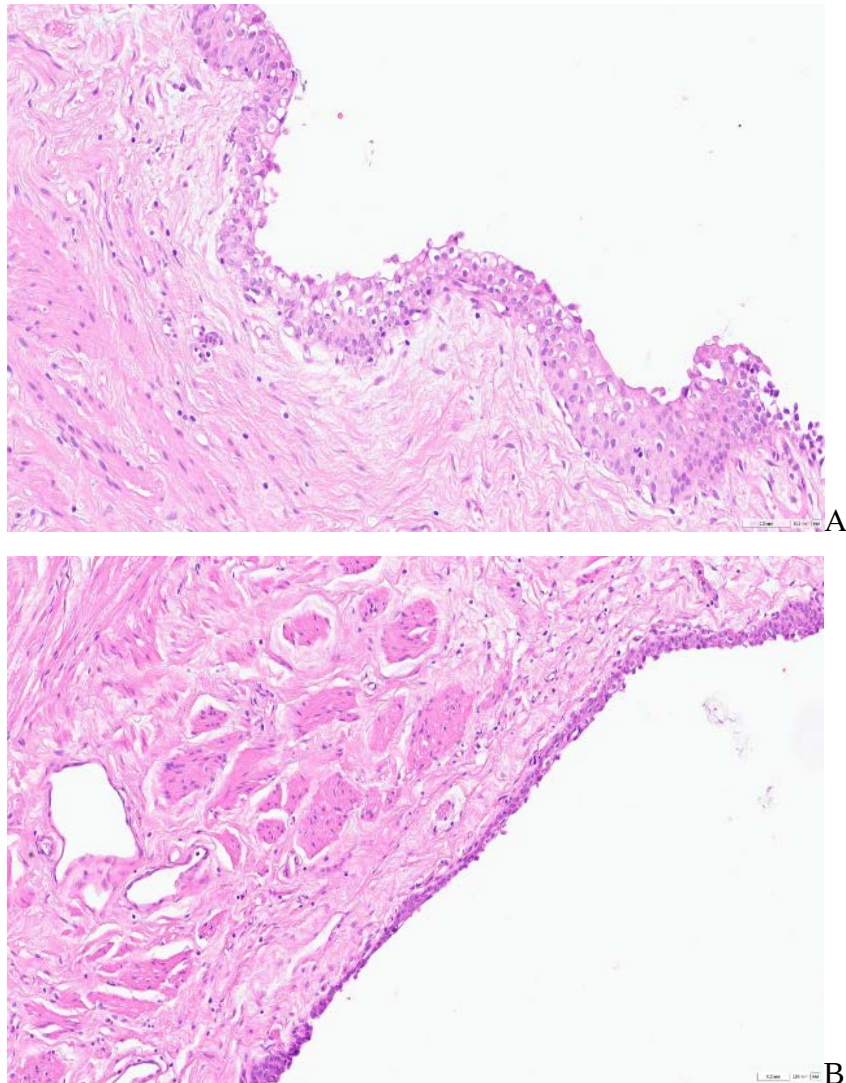


Fig. 4. Microphotography. Histological examination of the resected portion of the graft ureter. A, the ureter edge with intact epithelium and slight swelling of the mucous membrane (corresponds to a favourable result); B, the ureter edge with flattened epithelium, pronounced swelling of the mucous membrane, uneven filling of blood vessels (corresponds to a unfavourable result)

Thus, the sensitivity and specificity of the technique in relation to ureteral ischemia were 91.7% and 96.1%, the positive predictive value was 84.6%, and the negative predictive value was 98%. Based on the

negative results of fluorescein angiography, 7 cases of group II required the resection of the ureter over a large length and formation of the anastomosis without an antireflux tunnel. In a comparative clinical study, the use of fluorescein angiography led to a three-fold decrease in the risk of developing all urological complications in group II: 28 (12%) compared to 2 (3.3%), $p=0.045$. In one case, a stricture of the neoureterocystoanastomosis was diagnosed, which was treated by endourological intervention; in the other, a stricture developed, requiring an open surgical reconstruction. For other parameters of the early and late postoperative period, including the graft function, hospital length of stay, the incidence of graft rejection and other surgical complications, no statistically significant differences were found ($p>0.05$). The results of the study clinical stage are presented in Table 3.

Table 3. Comparative analysis of kidney transplantation results in relation to the use of ureteral fluorescence angiography

Parameter	Group I (n=233)	Group II (ICG) (n=61)	p
Length of stay in the Intensive Care Unit, days	2 (1;8)	3 (2;7)	0.65
Hospital length of stay, days	23 (17;35)	24 (15;29)	0.76
Incidence of delayed renal graft function, n (%)	95 (40.7%)	26 (42.6%)	0.1
Other surgical complications, n (%)	80 (34.3%)	21 (36.0%)	0.106
Rejection incidence, n (%)	15 (6.4%)	7 (11.4%)	0.383
Incidence of urological complications (class B–D), n (%)	28 (12%)	2 (3.3%)	0.045
Mean plasma creatinine level at discharge, $\mu\text{mol/L}$	158.9 (95% CI [153.1–164.7])	164.7 (95% CI [158.4–171.0])	0.365
Mean creatinine level after 12 months, $\mu\text{mol/L}$	125.4 (95% CI [120.3–130.7])	130.6 (95% CI [125–136.2])	0.74
Median follow-up period for recipients, months	42 (29;46)	21 (18;23)	<0.001

Note: CI – confidence interval

We calculated one-year recipient and graft survival rates for both groups. In group I, they made was 94.8% (95% CI [93.3–96.3]) and

93.6% (95% CI [92–95.2]), respectively; and in group II, they made 96.6% (95% CI [94.2–99]) and 91.8% (95% CI [88.3–95.3]) (Fig. 5, 6).

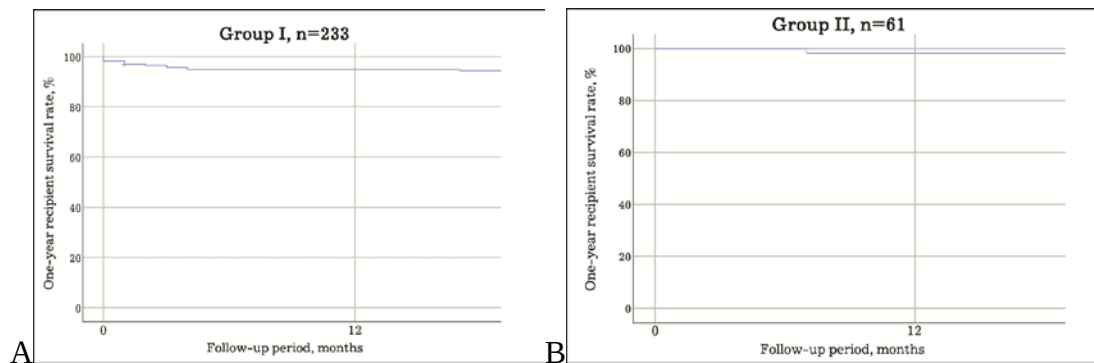


Fig. 5. One-year recipient survival rate. A, group I; B, group II

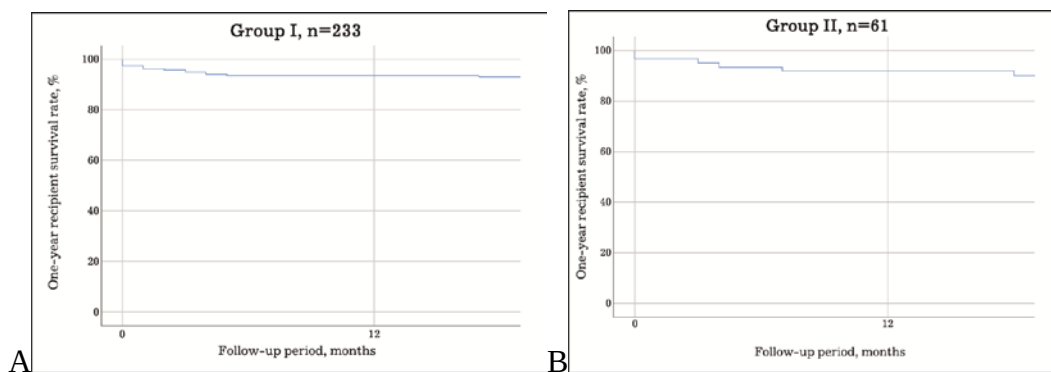


Fig. 6. One-year graft survival rate. A, group I; B, group II

Discussion

Currently, kidney transplantation is the gold standard of renal replacement therapy for patients with stage 5 chronic kidney disease [12]. This method has a number of advantages, but is associated with the development of typical complications that can lead to the graft loss, the need to return to dialysis, and even to a severe disability of the recipient. These typical complications include a graft rejection, intolerance to immunosuppressive therapy, arterial and venous thrombosis, vascular stenosis. In addition, there is a high risk of developing a wound infection in the presence of immunosuppression or severe lymphorrhea [13]. Urological complications are also not inferior in their incidence to those listed above. The implementation of new technologies contributing to

increased precision and delicacy of surgeon's work, definitely has a positive effect on the results of the interventions performed [14]. Thus, in our sample size of 294 recipients, the development of urological complications was observed in 30 patients (10.2%), in whom 9 anastomotic failures (3.1%) and 21 strictures (7.1%) were detected. Strictures among our patients were more than 2 times more common than urinary leaks.

Most authors note the peculiarities of the surgical technique of performing a neoureterocystoanastomosis and local tissue ischemia as key factors increasing the risk of developing strictures during kidney transplantation. None of the studied characteristics of the donor, recipient or the postoperative period peculiarities reached a statistical significance for our sample size in terms of the development of urological complications. Thus, taking into account the literature data and our personal experience, we came to the conclusion that the key factor in preventing the development of the medical conditions under consideration is the formation of a neoureterocystoanastomosis within well-perfused tissues. Based on this, we proposed an approach to select the most favorable option for forming an anastomosis of the donor ureter and the recipient's bladder in group II. However, a number of studies that included a comparative analysis of various techniques for performing a neoureterocystoanastomosis during kidney transplantation noted an increased incidence of pyelonephritis when using techniques without antireflux protection [15]. This complication poses a serious threat to the graft functioning and can lead to its loss, and in some cases to a fatal outcome. However, according to our study, the one-year recipient and graft survival rates were comparable in two groups.

We should note that, according to a number of publications, the formation of a neoureterocystoanastomosis with antireflux protection can

increase the risk of developing stenosis, which in turn requires additional interventions and can worsen the functional results of transplantation [16]. Thus, both options have advantages and certain limitations, and the choice of a specific approach, in our opinion, should be predetermined by a clinical situation and the experience of the operating surgeon. In addition, the literature describes a technique for pyeloureteral anastomosis using the recipient's native ureter [17]. This option can be considered optimal in cases where the length or blood supply of the donor ureter is significantly limited, but we are inclined to consider this technique burdensome due to the need for ipsilateral nephrectomy in most recipients.

Evaluation of the intensity of bleeding from the ureteral stump does not always allow one to adequately judge the absence of ischemia in the area selected for anastomosis formation. Figure 3 shows an intraoperative photo using fluorescent ICG visualization. The hypoperfusion zone of the distal ureter is clearly visible, where the anastomosis formation is unacceptable, but no differences from healthy tissues had been revealed during the previously conducted visual assessment. ICG application technology for the purpose of visualizing blood supply and preventing tissue ischemia of certain organs during surgical interventions is widely used throughout the world. However, there is relatively little data on the use of fluorescent ICG visualization in kidney transplantation, in particular for the purpose of preventing urological complications. We found 4 studies devoted to this method: 3 small prospective studies and 1 large retrospective study [18–21]. P. Kanammit et al. (2021) used ICG in a series of cadaveric kidney transplants. The study included 10 recipients, the blood supply to the distal sections of their graft ureters was visualized using ICG; then they were resected and sent for histological examination. Based on the analysis of 31 specimens, the authors found that the sensitivity of the proposed method was 100%, and the specificity was

92.6%. Of particular interest is the work of A.L.H. Gerken et al. (2022) from the Clinical University of Mannheim. The study retrospectively collected a large sample size, presented 196 visualizations of the ureteral blood supply, and demonstrated the effectiveness of the method in visualizing of ureter perfusion. However, no study has statistically proven the advantage of ICG visualization over the classical principle of assessing the blood supply to the ureter.

In our study, the technique under consideration proved to be an effective approach to visualizing the blood supply to the ureter, which in each case was confirmed by the morphological study results. According to our data, the sensitivity of the method under consideration is 91.7%, and the specificity is 96.1%. The formation of neoureterocystoanastomosis within well-perfused tissues made it possible to reduce the incidence of urological complications after kidney transplantation from 12% to 3.3% ($p=0.045$).

Conclusion

Thus, fluorescein angiography of the transplanted kidney ureter is an effective and safe method for preventing urological complications, allowing the formation of neoureterocystoanastomosis within the limits of satisfactorily blood-supplied tissues.

Based on the study results we have made the following conclusions:

1. No statistically significant associations were found among the analyzed potential risk factors for the development of urological complications.
2. The algorithm we have developed for fluorescent angiography of the renal graft ureter before performing a

neoureterocystoanastomosis allows us to determine the degree of its blood supply with a sensitivity of 91.7% and a specificity of 96.1 %.

3. The use of fluorescein angiography before performing neoureterocystoanastomosis during kidney transplantation makes it possible to reduce the rate of urological complications of this surgery from 12 to 3.3% ($p=0.045$).

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