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Analysis of kidney transplantation results in patients
with chronic renal disease

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Introduction. The number of patients with chronic kidney disease has been steadily increasing throughout the world, which makes this pathology a pressing problem.

The purpose. The analysis of heterotopic kidney transplantation results.

Material and methods. The authors analyzed the experience of the clinical work arrangement, the results of operations, assessed the complication rate and the quality of life in 133 patients after heterotopic cadaveric kidney transplantation performed in the Grodno Regional Clinical Hospital in the period from 2013 to mid August of 2018.

Results. In the early postoperative period, complications occurred in 22 (13.5 %) patients, the postoperative mortality was 1.8% (3 patients). In the late postoperative period, the kidney explantation was performed in 4 (2.45%) patients, 6 patients died (3.7%) as a result of progressing comorbidities and complications (average at 15.6 ± 9.8 months after transplantation). A 5-year predicted patient survival after heterotopic kidney transplantation calculated by using the Kaplan-Meier' method was 94.5%.

Conclusions. Kidney transplantation in the Grodno Region, the results of operations, graft survival, quality of life and patient survival are comparable to international standards. A careful selection, examination, and preparation of patients for transplantation have a great effect on treatment outcomes.

Keywords: kidney transplantation, renal failure, postoperative complications, treatment outcomes

CHD, coronary heart disease

US, ultrasonography

CKD, chronic kidney disease

ECG, electrocardiography

Introduction

Worldwide, there has been a steady increase in the number of patients with a chronic kidney disease (CKD). This is due to the increasing number of patients with kidney pathology, on the one hand, and with the prevalence of diseases leading to CKD occurrence, such as diabetes, hypertension, chronic pyelonephritis, and other systemic diseases, on the other hand [1].

With the development of end-stage kidney disease, a renal replacement therapy becomes necessary to be performed. It may be of three types: a chronic program hemodialysis, peritoneal dialysis, and kidney transplantation. Kidney transplantation that provides the best long-term survival of patients with end-stage renal disease, having lower treatment costs compared to dialysis methods, has been recognized as one of the main achievements of medicine [2-4]. By completely eliminating uremia effects, transplantation provides an optimal level of medical and social rehabilitation and the longest life of the recipients; however, due to various obstacles, this method of replacement therapy cannot completely replace a dialysis treatment. Even in economically developed countries, transplantation faces such problems as the technical feasibility, immunosuppression consequences, a donor organ shortage, and insufficient professional training.

Kidney transplantation in the USSR was first performed by Yuri Y.Voronoy, a Soviet surgeon, on April 3, 1933. The first successful kidney transplantation was performed from one uniovular twins to another one by an American surgeon Joseph Murray in Boston on December 23, 1954. For over a half a century since then, transplantologists have gained a wide experience regarding the patient screening, organ preservation, and postoperative patient management; the surgical techniques have been considerably modernized and improved [5].

In Belarus, the first kidney transplantation was performed in the 4th Public Healthcare Clinical Hospital named after N.E.Savchenko on September 11, 1970. Improving the skills and gaining experience with every year, transplantology in Belarus has come to a new level. In Grodno, the Transplantation Department was established on the base of Grodno Regional

Clinical Hospital (GRCH) on January 1, 2013, and the first transplant was performed a month later, at night from February 2 to 3. As per mid-August 2018, 163 kidney transplantations were performed in GRCH.

The aim of the study was to analyze heterotopic kidney transplantation results obtained in our clinic, and to assess the quality of life of the patients before and after kidney transplantation.

Material and methods

From January 1, 2013, a Transplantation Department was opened on the basis of the GRCH, the Public Healthcare Institution, where the first kidney transplantation in the Grodno Region was performed. Later, from September 1, 2014, that structural unit became the part of the Department for Surgical Pancreatology, Hepatology, and Organ and Tissue Transplantation of GRCH. The Department capacity is 30 beds, including 20 surgical beds and 10 beds for transplant patients [5].

From the moment of the Transplantation Department opening on January 1, 2013, to mid-August, 2018, 163 heterotopic cadaveric kidney transplantations were performed by the staff of the hospital and the 1st Surgery Department of the Grodno State Medical University (GrSMU). The recipients were 93 men (57.1%) and 70 women (42.9%) at the age ranging from 18 to 72 years old (mean 44.66 ± 11.6 years old). The underlying pathology that led to the CKD development and the further placement patients on the waiting list for heterotopic cadaveric kidney transplantation included: chronic tubulo-interstitial nephritis in 118 patients (72.4%), diabetes in 16 (9.8%), polycystic kidney disease in 11 (6.75%), congenital anomalies of the urinary system in 6 (3.7%), systemic lupus erythematosus

in 5 (3.06%), urolithiasis in 2 (1.23%), and others (kidney amyloidosis, kidney hypoplasia, Alport syndrome) in 5 (3.06%).

Before transplantation, all patients underwent a renal replacement therapy, using hemodialysis in 130 patients (79.7%), or peritoneal dialysis in 33 (20.3%). The average period of dialysis therapy before transplantation was 24 months [13; 40], and the period of waiting for transplantation from the moment of patient's placement on the waiting list was 12 months [6; 24]. All patients having the indications for transplantation underwent a comprehensive examination in order to exclude absolute contraindications for surgery and specify the relative ones [6]. All potential recipients underwent mandatory routine tests: ABO blood grouping and Rhesus factor, HLA class I (HLA-A, B) and class II (HLA-DR) typing, regular testing for pre-existing HLA antibodies as often as once per 3 months, complete blood count and urinalysis (if there was urine output), blood biochemistry test to determine the concentrations of urea, creatinine, glucose, cholesterol, calcium, phosphorus, potassium, sodium, chlorine, and bilirubin; determination of transaminase, amylase and alkaline phosphatase activities; studying the hemostasis parameters: activated partial thromboplastin time, prothrombin time with the calculation of the international normalized ratio, a daily protein loss with urine (if there was urine output), bacteriology urine cultures for urea pathogenic flora and fungi (if there was urine output), bacteriology culture of sputum for aerobic activity, and optional culture for anaerobic microorganisms, fibrogastroduodenoscopy, electrocardiography (ECG), an exercise ECG test for patients over 50 years old and(or) for patients with diabetes mellitus, blood pressure profile, echocardiography, ultrasound examination (US) of the abdominal organs and kidneys, Doppler

ultrasonography of the iliac vessels, chest x-ray, virological testing: for Epstein–Barr virus by polymerase chain reaction to study for DNA of virus cells, for varicella-Zoster virus, the detection of toxoplasma, cytomegalovirus, herpes simplex virus type 1 and 2, hepatitis B virus antigen (hereinafter referred to as HBsAg) and anti-hepatitis-C-virus antibodies (hereinafter as anti-HCV) using the enzyme-linked immunosorbent assay (IgG and IgM); a complex of serological reactions to syphilis, testing for human immunodeficiency virus (HIV) antibodies, skin tuberculin test (Mantoux test); consultations by cardiologist, gastroenterologist (for patients with viral hepatitis B, and(or) C), endocrinologist (for patients with diabetes mellitus), dentist (oral cavity sanitation), elimination of chronic infection foci before transplantation.

The main homeostasis parameters of patients before surgery are presented in the Table.

Table. Homeostasis parameters before surgery

Parameter	M ± SD
Urinalysis	
pH	5.9 ± 1.2
Protein, g/L	0.5 ± 0.5
Density	1011.1 ± 4.2
Complete blood count	
Red blood cells, 10 ¹² /L	3.6 ± 0.6
Hemoglobin, g/L	111.1 ± 18.3
White blood cells, 10 ⁹ /L	7.8 ± 2.7
Erythrocyte sedimentation rate, mm/h	34.1 ± 15.2
Color indicator	1.0 ± 0.16
Hematocrit,%	33.4 ± 9.3
Platelets, 10 ⁹ /L	239.2 ± 63.6
Bands,%	6.3 ± 4.2
Segmented neutrophils,%	61.3 ± 11.3
Lymphocytes,%	22.1 ± 11.0
Monocytes,%	6.9 ± 3.5

Blood biochemistry	
Protein, g/L	68.8 ± 9.5
Urea, mmol/L	17.7 ± 7.0
Creatinine, µmol/L	620.2 ± 256.1
Glucose, mmol/L	5.1 ± 1.8
Total bilirubin, µmol/L	12.4 ± 3.0
Aspartate aminotransferase, U/L	45.0 ± 21.9
Alaninaminotransferase, U/L	48.7 ± 24.9
Amylase, U/L	113.8 ± 47.9
Na, mmol/L	137.9 ± 7.7
K, mmol/L	5.1 ± 0.8
Cl, mmol/L	98.4 ± 21.9
Coagulogram	
Activated partial thromboplastin time, s	32.1 ± 13.2
Prothrombin time, s	14.0 ± 3.1
Prothrombin complex activity, %	122.6 ± 27.7
International normalized ratio	1.7 ± 1.6
Fibrinogen, g/L	5.2 ± 2.5

No carriers of HIV infection or syphilis were seen among the recipients. Viral hepatitis C was found in 20 patients (12.3% of cases); viral hepatitis B was identified in 4 patients (2.5%).

All patients in need of kidney transplantation are generally entered in the Registry of the Republican Waiting List (Kidney Transplantation) designed to centralize and coordinate all the procedures related to transplantation where the list of the most suitable recipients for the existing donor organ is formed, as well as the most appropriate recipients are selected for transplantation. The process of selecting the most appropriate recipients is exercised by a computerized program based on the immunological analysis data (HLA- class I [HLA-A, B] and class II [HLA-DR] typing, testing for the pre-existing HLA antibodies, cross-match test), physiological

parameters, blood group, age parameters, period on the waiting list, priority by urgency status and by acceptable territorial location.

In this way, the most appropriate and compatible recipient is selected for an available donor kidney.

A positive pre-transplant test for pre-existing antibodies, i.e. panel reactive antibody (PRA), was seen in 11 of our patients (6.7%) and made $46 \pm 22\%$ (min 20%; max 80%).

For eliminating the chronic infection foci before kidney transplantation, 16 patients underwent nephrectomy (for urolithiasis with coral-shaped calculi in 3 cases, for polycystic kidney disease in 13 cases), 19 patients underwent laparoscopic cholecystectomy for cholelithiasis.

Organ donors for kidney transplantation were the Intensive Care Unit patients who had sustained brain injury incompatible with life and had an extremely unfavorable prognosis of their current severe condition due to a massive aneurysmal subarachnoid or intracerebral hemorrhage in 120 patients (73.6%), severe traumatic brain injury in 35 (21.5%), extensive ischemic cerebrovascular accident with cerebral edema and brain dislocation in 5 (3.1%), hypoxic and ischemic brain damage during prolonged cardiopulmonary resuscitation or asphyxia in 3 (1.8%). Among the renal graft donors, there were 95 men (58.3%) and 68 women (41.7%), the mean age of them being 47.4 ± 9.2 years old.

The following measures were taken to protect the organs in the body of a potential donor: ensuring a proper circulating blood volume, adequate hydration, stable hemodynamics, adequate diuresis; correct dosage of vasoactive substances were maintained, metabolic and cellular protectors were used, heparinization was provided, administering drugs with toxic effects was avoided.

A closed perfusion circuit was established at explantation. The abdominal aorta containing the mouth of the renal arteries was perfused with cooled (at a temperature from 0 to +4° C) preservative Custodiol solution through the catheter (intubation tube) and their surface was cooled with a frozen 0.9% sodium chloride solution. The kidneys were extensively mobilized, removed with the parts of aorta, inferior vena cava, with ureters, and placed in a preservative solution to be transported to the Transplantation Department in a melting ice system.

In most cases, cadaveric kidney heterotopic transplantation was performed into the right iliac region with an end-to-side anastomosis of the donor arteries and vein into the recipient external iliac artery and vein (Fig. 1).

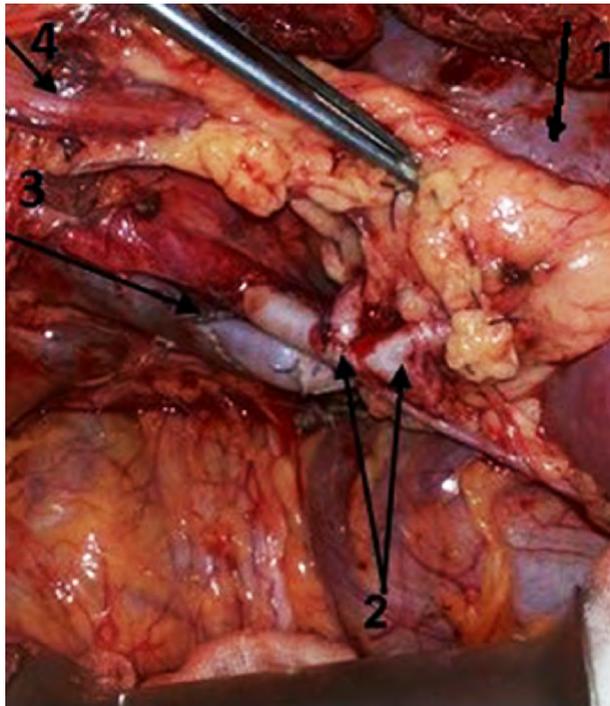


Fig. 1. Anastomosis of donor's arteries and vein: 1 - kidney; 2 - arterial anastomosis; 3 - venous anastomosis; 4 - ureter

The vein was anastomosed with four Prolen 5-0 sutures in an end-to-side fashion using a four-point technique, and the artery was anastomosed with a continuous blanket Prolen 6-0 suture using a "parachute" technique. After that, an areflux ureterovesical anastomosis was formed according to Litch–Gregoire technique with a Darwin mono 5-0 long-lasting monofilament absorbable suture. In 3 cases, transplantation was performed into the left iliac fossa due to the presence of a catheter for peritoneal dialysis and the scars from previous surgery on the right.

Generally, patients after kidney transplantation are followed-up by a staff nephrologist of GRCH. In the Nephrology Room, patients are consulted after surgery to have their graft function monitored and evaluated, have cytotoxic drugs prescribed within the preferential-coverage programs, to submit and register the applications for free immunosuppressive drugs; the doctors examine the patients to be hospitalized for considering their placement on a waiting list for a donor kidney, see potential donors to consider the live-related kidney transplantation, and the post-transplant patients who need inpatient treatment in GRCH.

Results and discussion

In the early postoperative period, complications developed in 22 patients (13.5%). Complications of the postoperative wound were seen in 10 patients (6.1%), including: the postoperative wound hematoma in 3 cases (1.8%) that occurred at 1-2 days after surgery, lymphocele that developed in 4 patients (2.45 %) after 5 ± 2 days post-surgery, seroma in 1 case (0.6%) at 4 days after surgery, and also a postoperative wound infiltration in 2 cases (1.2%) after 4–5 days.

Those complications were cured conservatively having a favorable outcome.

Due to the development of lymphocele with wound infection, one patient underwent a transplantectomy at 1.5 weeks after transplantation with further hemodialysis sessions being resumed.

One patient (0.6%) had bleeding that occurred in the graft bed area on day 2 after surgery, which required its revision and additional measures to achieve hemostasis.

Urinoma (a urinary fistula) developed in 5 patients (3.0%) after 5 ± 2 days, for which pylocystoanastomosis was formed in one case and reureteroneocystoanastomosis was made in 3 other patients, all had a favorable outcome. The stenosis of ureteroureteral anastomosis was identified in 1 case (0.6%), which correction necessitated performing reuretero-neocystoanastomosis [7].

In 1 patient (0.6%), an acute adhesive and intestinal obstruction developed on day 21 after kidney transplantation (the patient had a previous history of appendectomy and surgery for stomach injury). Viscerolysis and splinting of the small intestine with a nasointestinal tube were performed followed by abdominal cleansing and drainage, having favorable postoperative outcome.

Transplantectomy was performed in 3 patients, including 2 patients (1.2%) with the renal artery thrombosis that developed after 3 days, and 1 patient (0.6%) with the renal vein thrombosis that occurred 2 days after transplantation, with further resuming hemodialysis sessions.

According to the clinical protocol, the pharmacological management of patients in the postoperative period included an induction

immunosuppression with basiliximab (a preparation of a humanized anti-Tac monoclonal antibody) and a pulse therapy with methylprednisolone. Baseline therapy consisted of administering cyclosporin or tacrolimus (calcineurin inhibitors), mycophenolic acid (an inosine monophosphate dehydrogenase inhibitor) with following conversion to azathioprine; and prednisolone or methylprednisolone were also used. In addition, all patients were administered meropenem as a prophylactic antibiotic therapy, cotrimoxazole for the prevention of *Pneumocystis pneumonia*, ranitidine or omeprazole for gastroprotection, acetylsalicylic acid to prevent the thrombosis of vascular anastomoses, nystatin for fungal infection prevention, gancyclovir with the further conversion to valgancyclovir for cytomegalovirus infection prevention, symptomatic therapy was given when indicated.

In the early postoperative period, 3 patients died (1.8%). One female patient (0.6%) who had suffered from coronary heart disease (CHD) died of acute cardiovascular insufficiency after 5 days, despite intensive care therapy. This fact is consistent with available publications, indicating that deaths after kidney transplantation are often caused by cardiac pathology [8].

Another non-survival (0.6%) was the patient with overweight who was diagnosed with an acute renal graft rejection on day 7. An intensified immunosuppressive therapy failed to control the complication and that served an indication to perform a transplantectomy and further resume hemodialysis sessions. Later, the patient had an exacerbation of peptic ulcer disease of the duodenum with further developed recurrent bleeding from ulcers. After the conservative hemostatic and anti-ulcer therapy performed, and the unsuccessful attempts to achieve the endoscopic hemostasis for

recurrent bleeding, the indications for surgical treatment were considered. Laparotomy was performed followed by duodenotomy, which revealed the presence of two ulcers in the duodenal bulb occupying almost the entire semicircle of the duodenum. In one of the ulcers, a loose red blood clot with blood leakage was visualized. The volume of the intervention, namely, 2/3 resection of the stomach with Roux-en-Y reconstruction was chosen considering the size and localization of ulcers, a significant deformity in the duodenal bulb area, and the technical infeasibility to make an organ-saving surgery. However, despite the prophylactic anti-ulcer therapy, a decreased reparative potential associated with the administration of immunosuppressants, resulted in acute gastric ulcerations with recurrent bleeding from the ulcers. This was an indication to repeated endoscopic sessions of achieving hemostasis; and as they appeared ineffective, the gastrotomy of the stomach stump and suture of bleeding ulcers were indicated. The developed incompetence of the duodenal stump, due no regeneration process in that area after suture resorption, required repeated interventions with the duodenostomy and laparostomy placement. Despite the treatment, the patient died of multiple organ failure in the late postoperative period. The mortality rates associated with gastrointestinal bleeding in kidney transplant recipients have been reported to range from 8.3% to 40%, according to available data. We should mention that, according to some reports, obesity is a risk factor for the development of surgical and non-surgical complications after kidney transplantation [7–9].

The 3rd non-survived patient (0.6%) developed thrombosis of mesenteric vessels on the 8th postoperative day, further having an unfavorable outcome.

In the late postoperative period, transplantectomy was performed in 4 patients (2.45%) for recurrent allograft glomerulonephritis in 1 (at 5 months after transplantation), for ascending urinary tract infection in 1 (at 4 months after transplantation), and for graft dysfunction in 2 patients (at 1 and 1.5 months after transplantation). After transplantectomy, all patients were converted to hemodialysis sessions.

In the late postoperative period, 6 patients died (3.7%) of progressing comorbidities (coronary artery disease, atherosclerosis of the lower limbs, diabetes) and the developed complications (mean at 15.6 ± 9.8 months after transplantation).

An estimate of the predicted patient survival after surgery obtained by using the Kaplan-Meier methodology is presented in Fig. 2.

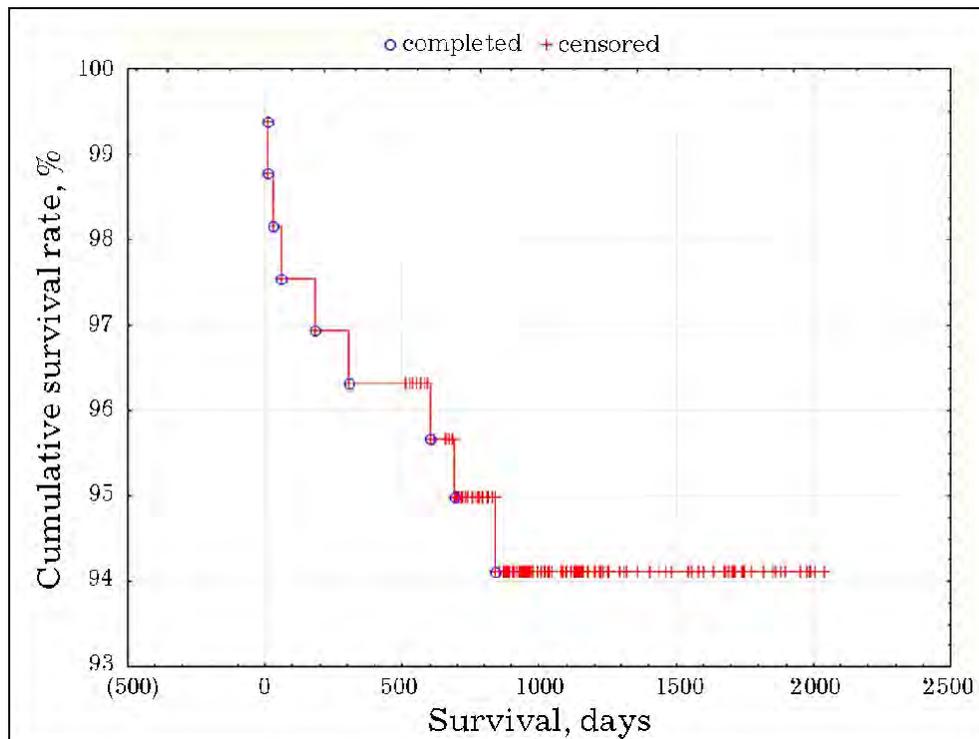


Fig. 2. Kaplan Meier Survival Analysis

According to the analysis by Kaplan–Meier methodology, a 5-year predicted patient survival after heterotopic kidney transplantation was 94.5%.

Here we give a clinical example of the preparation and the treatment of a kidney transplant recipient before the surgery. Patient T., 46 years old, was admitted to the GRCH Department of Surgical Pancreatology, Hepatology, and Transplantation on 29.11.2016. In September 2016, she had been diagnosed with bilateral adult polycystic kidney disease.

The time period of her being on hemodialysis had made 8 months. Upon admission, she was in a satisfactory condition. Magnetic resonance imaging (Fig. 3) showed that the patient had a pronounced bilateral polycystic disease of the liver and kidneys. The kidneys were normally located; the parenchyma on both sides was almost completely replaced by multiple thin-walled fluid masses of irregular shape, of various sizes, many of them having heterogeneous contents and levels in the lumen.

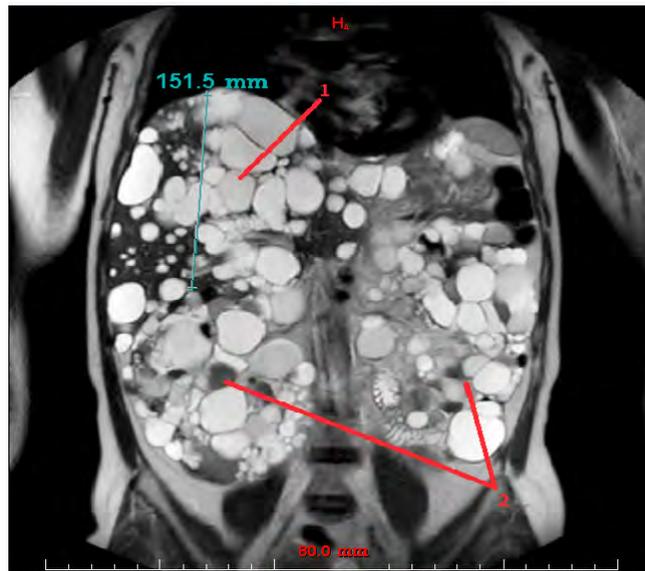


Fig. 3. Magnetic resonance imaging of the abdominal cavity: 1 - polycystic liver disease; 2 - polycystic kidney disease

For eliminating chronic infection foci, a right-sided nephrectomy was undertaken in the patient on 01.12.2016. That surgical intervention was performed under intubational anesthesia through a lumbotomy access. A polycystic altered kidney was isolated from the surrounding tissues by a blunt and sharp dissection (Fig. 4).



Fig. 4. Isolation of a polycystic altered kidney

The ureter was isolated, ligated, and cut off. The renal artery and vein were isolated and ligated separately. The kidney was removed (Fig. 5).



Fig. 5. Gross specimen: a removed polycystic altered kidney

On 27.02.2017, nephrectomy was performed on the left. The postoperative period was uneventful. The patient was discharged home in satisfactory condition on 10.03.2017.

On 11.05.2017, heterotopic cadaveric kidney transplantation was performed in the patient. The operation lasted for 2.2 hours; the patient stayed 8 days in hospital and was discharged home without complications in a satisfactory condition.

All patients after kidney transplantation in GRCH have been followed-up by a staff nephrologist and note an improvement in their quality of life. Many patients of working age with a transplanted kidney were able to return to work. Most of them have an active life position: 5 patients of childbearing age could become pregnant, bear and have a child, and one woman already gave birth to 2 children. Delivery in all those cases was undertaken by Caesarian section. In 2016, a woman with a transplanted kidney gave a natural birth for the first time in the Republic of Belarus.

Conclusions

1. Kidney transplantation is the only definitive method of chronic renal disease treatment eliminating uremia effects, ensuring an optimal level of medical and social rehabilitation, improving the quality of life and life expectancy of the recipients.

2. The analysis of our own clinical material indicates the successful results of the transplantation program implemented in the Grodno Region, which suggests the necessity of the transplantation development in the Regional centers.

Conflict of interests. Authors declare no conflict of interests.

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