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KIDNEY AUTOTRANSPLANTATION: A METHOD FOR TREATING URETERAL LESIONS IN UROLOGICAL AND ONCOLOGICAL PRACTICE

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The first successful kidney autotransplantation was performed in 1902. The technique has undergone several changes since then. The indications and surgical technique are presented in this literature review. Kidney autotransplantation is the treatment of choice for preserving renal function. Three clinical observations on the use of kidney autotransplantation in urological and oncological practice are described: a patient after iatrogenic ureteral injury and two patients with primary retroperitoneal tumor. Literature analysis and clinical observations from urological and oncological practice show that kidney autotransplantation could be safely used for strictly selected indications.

Keywords: kidney autotransplantation, ureteral injury, primary retroperitoneal tumors.

The history of kidney autotransplantation dates back to 1902. At the Vienna Medical Society Meeting, Hungarian surgeon Emerich (Imre) Ullmann, reported the first case of renal autotransplantation performed in a dog. In the same year, he performed the first autotransplantation of a kidney to a dog, using the recipient's carotid artery and jugular vein for vascular implantation. The operation technique was as follows: carotid artery and vein were ligated cranially, magnesium medical tubes were inserted into the proximal part of the vessels, to which a kidney, removed without flushing the vascular bed, wrapped in a napkin soaked in warm saline solution, was attached. The transplanted organ produced urine for 5 days. A few months later, Ullmann presented the first xenotransplantation of a kidney from a dog to the neck of a goat. In 1912, Nobel laureate A. Carrel, who developed the vascular anastomosis technique, repeated Ullmann's experiments. At that time, scientists and clinicians were not aware of the problems of ischemia-reperfusion injury. For more than 50 years, autotransplantation was not a hot topic, but during this time, researchers tested various kidney allotransplantation techniques using femoral and forearm vessels, as well as orthotopic position, alloimmunity mechanisms were discovered and the first successful kidney transplantation from a living donor into heterotopic (iliac fossa) position was performed [1, 2].

In 1956, Brazilian C. Freire performed this operation for the first time on a man with renal artery aneurysm, although an early thrombosis forced him to perform nephrectomy [3].

Only in 1961, R. Schackmann and W. Dampster successfully performed the same operation for the first time to preserve renal function in a patient suffering from renal artery stenosis and secondary arterial hypertension [4]. After the surgery, the patient's blood pressure normalized and did not require prescription of hypotensive therapy. This disease was previously considered incurable or treated by nephrectomy. In 1964, K. Ota performed renal autotransplantation in a 39-year-old patient for renal artery repair due to congenital vascular renal hypertension and complete obliteration of the right renal artery (Fig. 1, b) [5]. Autotransplantation of the right kidney into the left iliac fossa with microsurgical correction of the vessels was performed; the right renal artery was dilated using a venous graft patch.

American James Hardy performed autotransplantation of the right kidney to the right iliac region in 1963 due to proximal ureteral stricture resulting from traumatic injury (Fig. 1, a). Notably, J. Hardy used moderate whole-body hypothermia (32–36 °C) rather than graft to minimize ischemic injury [1, 2].

Rapid development of clinical transplantology in the 1970s gave impetus to the development of the topic of kidney autotransplantation. In 1970, J. Whitsell described a series of experiments on heterotopic autotransplantation in dogs without ureteral transection and a clinical case of successful treatment of a patient with extended (2.5 cm) arterial stenosis of the only right kidney. The renal vessels were reimplanted into the common iliac vessels, and the ureter was arched on the mesentery of the small intestine (Fig. 1, c) [6]. The first kidney autotransplantation for a malignant tumor was performed by famous pioneer of transplantology, R. Calne in 1971. A patient with bilateral renal tumor lesion with 1/3 of the right kidney parenchyma intact (according to selective angiogram) underwent left-sided nephrectomy with

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subtotal ex vivo extracorporeal nephrectomy resection and its implantation into the iliac area [3, 7]. In 1972 C. Linke and A. May were the first to describe the use of kidney autotransplantation to treat urological pathology (Fig. 1, e), more specifically, retroperitoneal fibrosis causing atrophy and extended ureteral stenosis [8]. Preoperative retrograde pyeloureterogram demonstrated bilateral hydroureteronephrosis with external compression and medial deviation of both ureters. Subsequently, a multistage correction of ureteral compression was performed, culminating in a right-sided renal autotransplantation.

Thus, the range of indications for kidney autotransplantation has been formed, including various vascular lesions of the renal pedicle, ureter and renal parenchyma of an infectious-inflammatory, metabolic, fibrotic, dysplastic and neoplastic nature (Table).

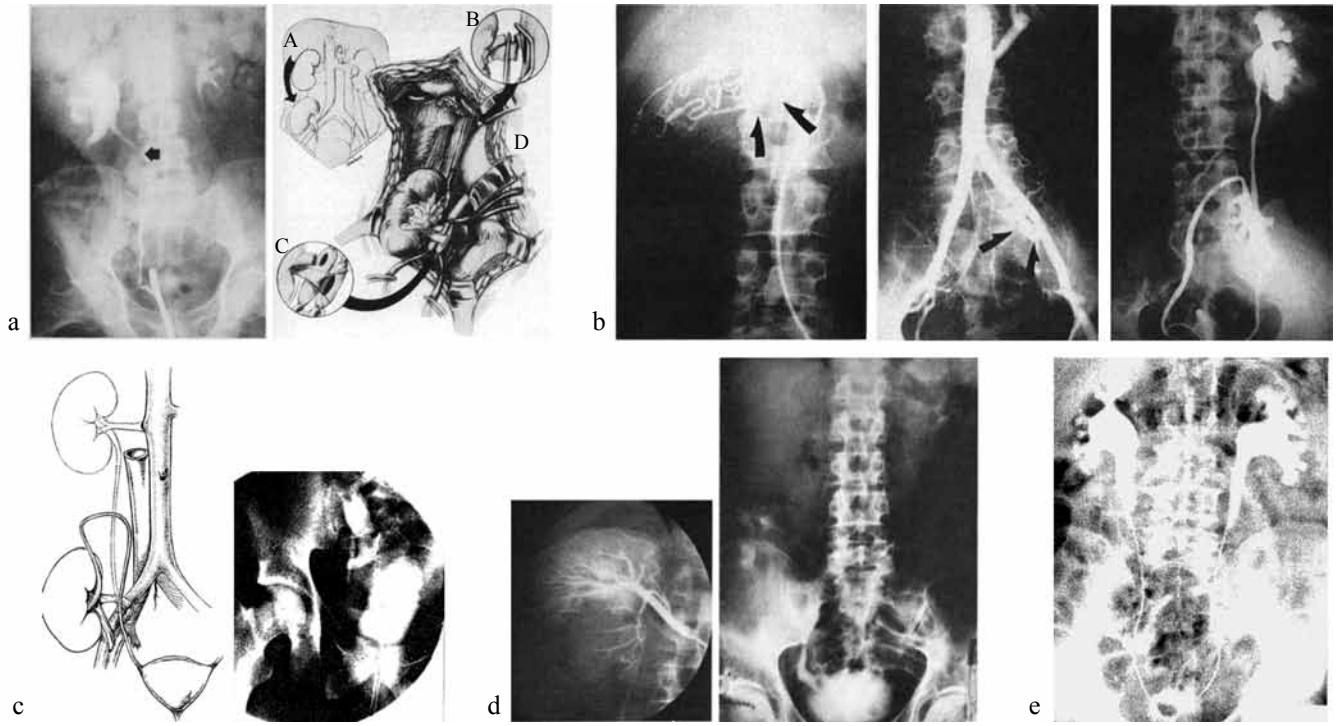

Fig. 1. a, left to right: right ureteral stricture diagnosed by right-sided retrograde pyeloureterogram (through nephrostomy tube) and retrograde urethrogram. Operation scheme; b, left to right: arrows indicate complete obliteration of the right renal artery. Aortogram – arrows point to the right renal artery, after microsurgical correction. Retrograde pyelogram; c, left to right: positions of the repositioned kidney and course of the ureter – diagram, cystoureteropyelogram; d, bilateral renal tumor lesion. Left to right: selective angiogram. After left-sided nephrectomy and subtotal extracorporeal nephrectomy and 1/3 kidney autotransplantation; e, Preoperative retrograde pyeloureterogram

Table

Indications for kidney autotransplantation

Vascular	Renal artery aneurysm
	Atherosclerosis of the renal artery and aorta (wall stenosis or dissection)
	Fibromuscular dysplasia
	Renal vein aneurysms
	Nutcracker syndrome (aortomesenteric compression of the left renal vein)
	Large saccular aneurysm of the renal artery
	Midaortic syndrome
Urological (main)	Extended ureteral strictures
	Ureteral avulsion
	Idiopathic retroperitoneal fibrosis
Oncological	Complex intraorganic lesion
	Bilateral tumor lesion
	Prior to radiotherapy
	Retroperitoneal sarcomas

VASCULAR INDICATIONS

Until recently, vascular pathology was the most common indication for kidney autotransplantation (Table). Currently, modern endovascular technologies have replaced autotransplantation in the treatment of arterial hypertension due to renal artery disease, having clear advantages – low invasiveness and possibility of repeated intervention without significant trauma to the patient. The same technologies are almost routinely used in the treatment of venous renal hypertension. But in some cases, for example, in large sized sac-shaped renal artery aneurysm, autografting is still the method of choice [2, 9].

Midaortic syndrome (a rare abdominal aortic coarctation syndrome) deserves special attention. This is a rare vascular pathology of various etiological nature, leading to narrowing of the descending aorta at the level of the L6 thoracic to L1 lumbar vertebrae. It is caused by congenital or acquired arteritis (Takayasu disease), neurofibromatosis, and fibromuscular dysplasia. Midaortic syndrome often leads to renovascular hypertension and decreased renal function. When endovascular intervention is ineffective, abdominal aortic bypass with bilateral orthotopic renal autografting becomes the method of choice [10].

UROLOGICAL INDICATIONS

Urological pathology is currently the main indication for kidney autotransplantation (Table). It is performed when ureteral prosthesis is necessary and plastic surgeries such as ureteroneocystostomy, ureteroureterostomy, pyelocystostomy, ipsilateral ureteroureterostomy, lower nephropexy, Boari surgery or psoas hitch are not possible due to tissue deficiency [11]. An alternative solution might be to replace the affected ureter with a section of the small intestine. However, the use of the small intestine leads to higher chances of complications of varying severity. Persistent urinary tract infection, unregulated metabolic acidosis, excessive mucus production, and adhesions can occur in combination in almost a third of patients, carrying additional risks of loss of kidney function and sepsis. In addition, the use of the small intestine may be limited by adhesions in the abdomen and retroperitoneum due to previous interventions [12].

The widespread use of endoscopic methods of lithoextraction and endourological treatment of uroteric tumors in recent decades has increased the number of extended lesions and proximal ureteric ruptures [13]. This leads to the need to perform temporary urinary diversion (nephrostomy) to preserve kidney function and provide multistage treatment. In such cases, kidney autotransplantation can be considered as a method allowing to solve the problem of urinary tract restoration in the shortest possible time and avoid complications associated with additional urinary derivation from the damaged kidney and subsequent delayed reconstructive intervention [11, 14].

Idiopathic retroperitoneal fibrosis (autoimmune periaortitis) is a rare disease with an annual incidence of 0.1–0.3 cases per 100,000 people, involving the abdominal aorta, iliac vessels and adjacent retroperitoneal space with frequent involvement of the middle and lower thirds of both ureters, leading to obstruction and terminal renal failure. The disease is caused by a chronic fibro-inflammatory process in which Ig4-secreting plasma cells are involved, and often requires differential diagnosis from retroperitoneal malignancies [15, 16]. If conservative treatment, including immunosuppressive therapy, progression of urinary tract obstruction is ineffective, bilateral kidney autotransplantation in heterotopic position allows to save a functioning renal parenchyma, preventing progression of chronic kidney disease [8].

ONCOLOGIC INDICATIONS

In the last decade, improvements in surgical techniques and complex, including chemotherapeutic, treatment of cancer patients, and increase in prognosis of patients' recurrence-free survival, has led to the development of the concept of "organ-sparing" surgical treatment of malignant tumors. A new sub-specialty, onconeurology, has appeared. The tasks of this subspecialty are: solving problems related to acute kidney injury and chronic renal failure in cancer patients, assessing nephrotoxic risks of antitumor therapy, both conventional chemotherapy and the latest molecular targeted therapy, treatment of renal manifestation of paraneoplastic process, treatment of patients who underwent nephrectomy for renal cancer, aspects of renal replacement therapy amidst active treatment of oncological process, possibility of performing kidney transplantation in patients who have undergone oncological treatment, treatment of oncological pathology in patients after kidney transplantation [17, 18]. The cornerstone of onco-nephrology is the concept of "nephron-sparing" treatment (Table). The importance of this approach is due to the fact that acute kidney injury or chronic kidney failure leads to a significantly increased risk of mortality in cancer patients from non-oncological causes, primarily from cardiovascular pathology [19, 20].

Organ-sparing treatment improves life expectancy in patients whose tumor has not spread beyond the kidney [21]. This is particularly important in patients with tumor lesions in one kidney, where all efforts should be focused on preserving the organ in order to avoid the need for chronic renal replacement therapy. Under such conditions, kidney autotransplantation with ex-vivo resection or tumor enucleation appears to be a feasible technique; this operation has significantly lost its popularity in the last decade [22]. This is due to the fact that minimally invasive nephron-sparing surgery in malignant kidney tumors, such as laparoscopic or robotic partial nephrecto-

my with superselective ischemic parenchyma, as well as ablative techniques, provide equivalent cancer-specific survival compared with radical nephrectomy [23].

Autografting with ex vivo tumor resection can be used in cases with complex intraorgan lesions involving the renal collar and/or the pelvicalyceal system, where resection carries risks of major blood loss or ischemia of the remaining, unaffected part of the renal parenchyma [24]. This operation can also be applied to multiple bilateral renal tumor lesions when organ-sparing treatment is absolutely obvious, but the standard approach to resection with bilateral local thermal ischemia carries a high risk of acute renal injury in the early postoperative period and chronic renal failure in the long term [7, 25].

On the other hand, autotransplantation for a kidney tumor can lead to a rather large range of complications, including bleeding (3.3–5% of cases), urinary tract infections (7.4%), renal vein thrombosis (4.1%), and loss of graft function (12.3%). Although it is necessary to take into account that patients with initially more anatomically complex spread of tumor process fall into the autotransplantation group [26].

Bolling described a casuistic case of kidney autotransplantation in a patient suffering from Ewing tumor arising from the 9th–11th ribs on the left side. In order to avoid radiation damage, the kidney was moved to the left iliac region before radiotherapy was started [27].

In 2010, V. Bonsal reported on the first removal of retroperitoneal liposarcoma in a block with the ureter, followed by kidney autografting into the iliac area to restore urine passage [28].

Surgical intervention is the main method of treatment for locally disseminated retroperitoneal sarcomas. Neither radiotherapy nor chemotherapeutic combination therapy significantly improves tumor prognosis and control. The need for multivisceral surgery in the removal of retroperitoneal sarcomas is due to the principles of radicalism in the removal of malignant tumors. However, the modern and reasonable desire to perform organ-sparing operations has led to the need to find a more rational, but also technically complex, surgical approach [29]. Statistically, up to 40% of surgical interventions performed for retroperitoneal sarcomas are combined with unilateral and sometimes bilateral nephrectomy. S. Mussi presents that there are 78.5% and 45.8% cases of kidney and ureter involvement in the tumoral process, respectively, but infiltrative damage occurs at a much smaller frequency – 10.7% and 12.5%, and in other cases, the involvement has a compressive nature, which is especially characteristic of liposarcoma. The noninfiltrative nature of the growth of fatty sarcoma makes it more likely to perform surgery, while maintaining the mass of functioning nephrons [30].

The use of transplantation and extracorporeal surgical techniques in complicated retroperitoneal anatomicotopographic conditions expands the possibilities of organ-sparing treatment without reducing the radical nature of the intervention. Prolonged involvement of the ureter in giant retroperitoneal sarcomas may require its removal en bloc with surrounding tumor tissues. It is almost impossible to compensate for the ureteral length deficit in such cases using standard urological approaches. Performing autotransplantation in the heterotypic position as a second step after tumor removal allows preserving the kidney function and urinary tract integrity [28, 31].

When retroperitoneal sarcoma spreads to the upper regions of retroperitoneal space, at the level of cavarenal segment of the inferior vena cava, the involvement of renal vascular pedicle and the difficulty of intraoperative differentiation of tumor tissue from parainephral tissue can lead to the need for tumor nephrectomy [32, 33]. In such cases, ex vivo dissection of the kidney from the surrounding tumor tissues followed by its autotransplantation is possible to preserve kidney function [28].

In Russia and in post-Soviet states, the use of kidney autotransplantation in oncological diseases was actively studied by A.E. Zotikov [34], I.B. Schepotin [35] and R.I. Rasulov [36].

TECHNICAL PECULIARITIES OF AUTOTRANSPLANTATION

The kidney autotransplantation technique does not differ fundamentally from that of allogeneic kidney transplantation, but there are a number of gray areas that require special attention.

The main condition for preserving the functioning renal parenchyma in autotransplantation is to minimize its ischemic injury. Controlled hypothermia is used as the first line of defense against hypoxic damage in organ transplantation. As a rule, organs are cooled to a temperature of 0 to +4 °C. Cooling reduces cellular metabolism and oxygen demand. However, at this temperature, a certain level of metabolism is preserved in human cells, which eventually leads to apoptosis and necrosis [37]. Therefore, the use of local hypothermia is indicated even at the tumor conglomerate explantation stage, when, due to traction at its extraction and mobilization stage, it is possible to kink the renal pedicle with blockage of organ blood flow. The use of pharmaco-cold protection during the ex vivo phase is also considered absolutely necessary. Kidney autotransplantation does not imply long periods of cold ischemia. Flushing of the vascular bed with 500.0 ml saline cooled to +4 °C with addition of 10,000 IU of heparin is considered sufficient for preservation of the renal autograft within 2–4 hours. On the other hand, the use of special preserving solutions (HTK, UW, IGL, etc.), which are now widely available, allows prolonging the cold ischemia time up to 24 hours without significant damage [38].

The most important factor for successful kidney autotransplantation is to obtain a renal artery and vein of

sufficient length and diameter c. Often prolonged compression of these vessels by tumor tissue leads to wall thinning and reduced diameter, which can lead to vascular complications after kidney reimplantation, both in the early and late postoperative period [39]. Marking the renal vessels during removal of the tumor-kidney block allows cutting off the vessels most proximally to obtain sufficient length and quickly find them in the conglomerate for rapid cannulation and perfusion with a preservative solution, minimizing warm ischemia time [39, 36].

At the stage of extracorporeal kidney dissection, it is necessary to use a precision surgical technique with the use of surgical binocular loupes (recommended magnification 2.5). This makes it possible to maximally protect important anatomical structures of the renal collar from damage during dissection, and to assess possible invasion into the collar and capsule of the removed kidney [36].

The choice of heterotopic position for kidney transplantation is not accidental. This position has certain surgical advantages that minimize complications compared with orthotopic autotransplantation. As a rule, the vessels of a renal autograft are somewhat shorter and thinner than those of an allograft. To prevent kinking and twisting of arterial and venous anastomoses, it is necessary to maintain some mobility in the anastomosis area. Wide mobilization of the external iliac vein, in some cases with intersection of the internal iliac vein, mobilization of the external iliac artery throughout, or use of the internal iliac artery, if its atherosclerotic lesion is excluded, can help avoid blood flow disturbances in the kidney and choose the optimal graft position in the iliac fossa [40, 41].

It should be noted that in patients with large-volume malignancies, balance in the blood coagulation system is shifted towards hypercoagulation. The use of anticoagulant therapy from day 1 after autotransplantation can reduce the likelihood of thrombosis in the vascular anastomoses area and in the renal microcirculatory bed [42, 43].

The second advantage of the heterotopic position is associated with the possibility of restoring urine passage in the transplanted kidney. The vast majority of urological complications following a kidney transplant surgery are associated with impaired blood supply to the ureter and pelvis. Since the autograft ureter is fed only from the renal vessels, there is always a risk of ischemization of its distal parts. Shortening the ureter usually solves this problem. Proximity to the bladder also allows any available repair options to be performed if the ureter length proves insufficient [44, 45].

CLINICAL CASE 1

Male patient Z., 29 years old, was admitted in October 2013 at the Lopatkin Research Institute of Urology and Interventional Radiology in Moscow with complaints of a left nephrostomy tube. In his medical history, 12 months before admission to our clinic, the patient had undergone an attempt of contact ureterolithotripsy on the left for a stone in the upper third of the left ureter, which resulted in iatrogenic detachment of the left ureter. The patient was placed with a percutaneous puncture nephrostomy tube on the left side.

When examined at the Research Institute of Urology, the secretory function of the left kidney was found to have reduced by 23% according to the radioisotope study, and the kidney function on the right side was satisfactory. According to ultrasound and multi-slice computed tomography (MSCT), the right kidney measured 12.5 × 6 cm, the parenchyma was 1.5 cm thick, there was no enlargement of the pelvicalyceal system. The type of blood supply was trunk. The left kidney was 11.8 × 5.8 cm, parenchyma was 1.5 cm thick, there was no enlargement of the pelvicalyceal system, a nephrostomy tube was visualized in the lumen of the pelvis. The type of blood supply was arterial. Left antegrade pyelography (Fig. 2, a) showed that the contrast medium was filling the pelvicalyceal system of the left kidney. No contrast agent was delivered to the left ureter from the pelvis.

Fig. 2. a, antegrade pyelography (left); b, retrograde ureterography (left); c, d, renal MSCT with intravenous bolus contrast enhancement

During retrograde ureterography on the left, ureteral catheter was inserted 3 cm above the orifice of the left ureter, where an insurmountable obstacle was encountered. No contrast agent is delivered above 3 cm of the left ureter from its orifice (Fig 2, b).

Given the patient's young age, the intact function of the left kidney, and technical capabilities of the clinic, he underwent open autotransplantation of the left kidney. The left kidney with an artery and a vein was removed. Access to the left iliac fossa was performed. The artery and vein of the left kidney were anastomosed with the iliac artery and vein. The left ureter was modeled from the bladder according to the Boari technique and anastomosed on the inner stent No. 6 with the left renal pelvis. The operation lasted for 145 minutes; blood loss was 250 mL. The postoperative period was smooth. The patient was discharged on day 14 after surgery. Internal stent and nephrostomy tube were removed 8 weeks after the operation. Control computed tomography revealed that the left kidney was located in the left iliac region, passage of the contrast agent from the left kidney was not impaired (Fig. 2, c, d).

The patient has been under our observation for eight years. Control ultrasound examination in September 2020 and Doppler ultrasonography of the kidneys showed that the right kidney was intact, the left kidney was located in the left iliac region, without impaired blood supply. The left kidney was 11.4 × 5.8 cm in size, the parenchyma was 1.5 cm thick, the pelvicalyceal system was not enlarged.

The patient leads an active lifestyle. He works (office worker), does sports (runs half marathons).

CLINICAL CASE 2

Female patient D, 51 years old, diagnosed with stage IIIB primary retroperitoneal tumor with T4N0M0 (according to histological examination of biopsy material – retroperitoneal multinodular liposarcoma (G1–G2) (Fig. 3, a) was admitted to our clinic.

The primary retroperitoneal tumor was removed (Fig. 3, b) with autotransplantation of the left kidney, corpuscular resection of the pancreas and splenectomy, resection of the left diaphragmatic dome, left-sided hemicolectomy, extirpation of the uterus with appendages, and formation of suspended jejunostomy.

Stages of kidney autotransplantation: 1, formation of vascular anastomosis between the renal artery and the left internal iliac artery (Fig. 3, c, d); 2, final view of autotransplanted kidney in heterotopic position after the formed intervascular anastomosis and interureteric anastomosis (Fig. 3, e).

The surgery lasted for 435 minutes; intraoperative blood loss was 2800 mL. The postoperative period was according to the extent of the surgical intervention performed.

According to morphological examination, retroperitoneal multinodular liposarcoma (G1–G2), predominantly well-differentiated lipoma-like (G1) with overgrowth to the diaphragm area, spleen capsule, pancreas, adrenal gland, fouling of these organs and myxoid liposarcoma

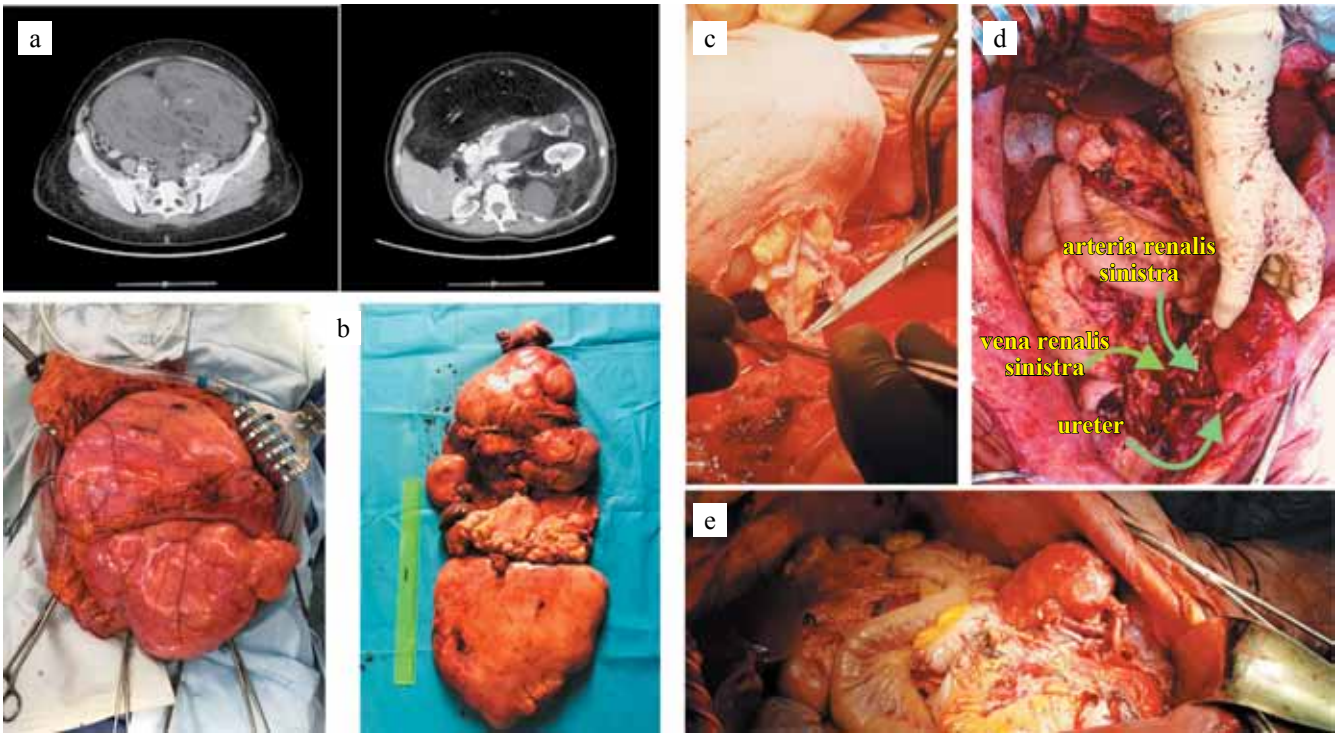

Fig. 3. a, MSCT of abdominal organs and retroperitoneal space with intravenous bolus contrast enhancement; b, intraoperative view of primary retroperitoneal tumor resection; c, d, e, kidney autotransplantation stages

node (G2) with ingrowth into the wall of one of the colon fragments were established.

Morphological examination of the removed specimen showed oncological radicality of the operation. The patient was discharged on day 18 after the surgery. She has been under our observation for 9 months with remission and intact function of the autotransplanted kidney.

CLINICAL CASE 3

Female patient V., 48 years old, diagnosed with stage IB primary retroperitoneal tumor pT4N0M0 (according to histological examination of biopsy material – low grade undifferentiated liposarcoma (G1)) (Fig. 4, a) was admitted to the clinic.

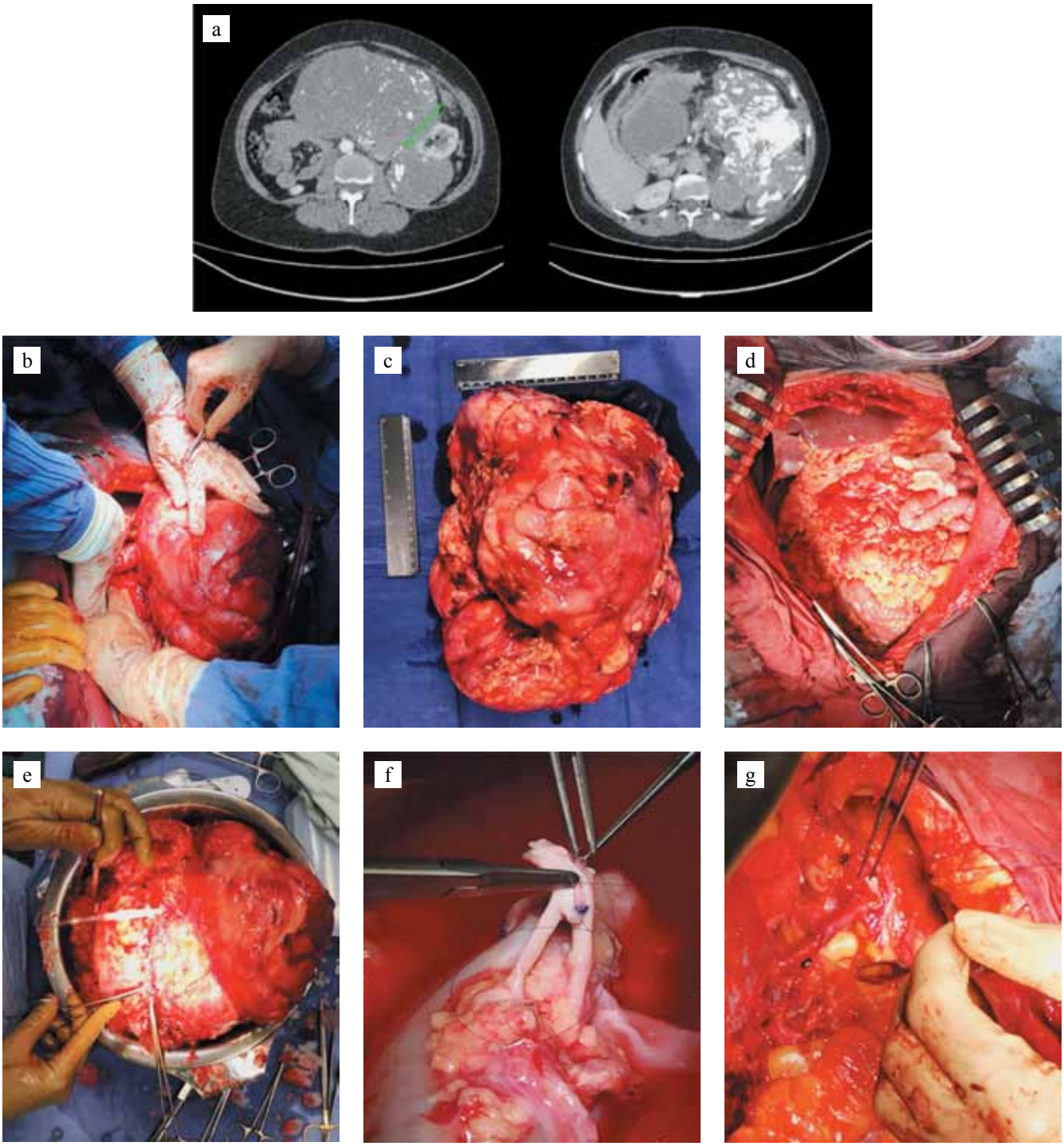

Fig. 4. a, MSCT of abdominal organs and retroperitoneal space with intravenous bolus contrast enhancement. b, intraoperative view of the tumor during resection; c, removed macro specimen; d, intraoperative view of the abdominal cavity after tumor resection; e, Ex vivo kidney isolation; f, kidney preparation for transplantation; g, completion of kidney autotransplantation stage

The primary retroperitoneal tumor was removed by left adrenalectomy, followed by extracorporeal resection of the upper pole of the left kidney and its autotransplantation to the iliac area; cholecystectomy, suspended jejunostomy were also performed (Fig. 4, b–g).

The surgery lasted for 370 minutes; intraoperative blood loss was 1200 mL. There were no complications during the postoperative period; it was according to the extent of the surgical intervention performed.

According to morphological study, undifferentiated low-grade liposarcoma (G1) of a spindle-cell structure, with small- and moderate-cell foci of necrosis, with 4 mitoses per 10 high power fields of view ×40 was established.

A morphological examination of the removed specimen showed oncological radicality of the operation. The patient was discharged on day 14 after surgery. Postoperative rehabilitation is ongoing (1.5 months after surgery).

DISCUSSION

Kidney autotransplantation is the method of choice for treatment aimed at preserving renal function. Its indications have varied since its introduction into clinical practice and up to the present time. New techniques, for example, endovascular surgery, has reduced the range of vascular indications for kidney autotransplantation.

Prolonged ureteric lesion remains one of the considered indications for kidney autotransplantation when there is a need for nephron-sparing treatment or social adaptation (sparing patients from lifelong use of nephrostomy tube or ureteric stent).

Recently, in the treatment of primary retroperitoneal tumors (PRT), there has been a tendency towards abandoning monobloc and cytoreductive surgery in favor of a balanced approach. A balanced approach in the treatment of primary retroperitoneal tumor includes: nephron-sparing interventions; removal of well-differentiated PRTs by separate "compartments" in order to maximize organ preservation; kidney autotransplantation. The importance of nephron-sparing interventions in PRT is due to minimization of the probability of acute kidney injury and chronic kidney disease, which increase the risk of mortality in cancer patients from non-cancer causes of stroke, and coronary heart disease [19, 20]. Preserved kidney function gives freedom in prescribing effective adjuvant therapy regimens. However, indications on the PRT side are extremely limited: well-differentiated (G1) liposarcomas; location of the kidney in the thickness of tumor nodules, involvement of renal vessels with preserved kidney function; extended involvement of the ureter; single kidney.

A multidisciplinary approach involving transplant specialists is necessary when extensive kidney involvement in the tumor process with kidney function intact is suspected. With proper planning of surgical intervention, it is possible to achieve good immediate and long-term treatment outcomes.

CONCLUSION

The literature and the clinical cases from urological and oncologic practice presented by us show that kidney autotransplantation can be safely used according to strictly chosen indications.

The authors declare no conflict of interest.

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