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Scientific article

The method of extracorporeal resection of the kidney in conditions of pharmaco-cold ischemia in kidney cancer with orthotopic renal replantation

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BACKGROUND: Increasing the effectiveness of the treatment of patients with kidney cancer is one of the main problems of oncourology. That is why much importance is attached to the development of new surgical technologies.

AIM: The aim of the study was to evaluate the results of extracorporeal kidney resection in conditions of pharmaco-cold ischemia with orthotopic renal replantation in kidney cancer patients. Our study is aimed at assessing the results of extracorporeal resection of the kidney under pharmaco-cold ischemia with orthotopic replantation of renal vessels in patients with kidney cancer.

MATERIALS AND METHODS: 44 patients [70.5% (*n* = 31) – men and 29.5% (*n* = 13) – women] with kidney cancer were recruited in this study. All patients were treated between 2012 and 2021. The mean age of patients was 55.92 ± 12.6 years. The stage was determined using the TNM system: pT1a-3bN0M0-1 G1-3. 75% (*n* = 33) of patients had stage pT1a–1b; 11.4% (*n* = 5) – pT2a–2b, one patient was present with multiple lesions; 13.6% (*n* = 6) – pT3a–3b, one patient had up to 15 lesions in a single kidney. Two previously operated patients had cancer of a single kidney with intraluminal invasion. The mean R.E.N.A.L nephrometric score was 10.32 ± 1.34.

RESULTS: The duration of the surgery was 402.07 ± 83.21 minutes. The duration of cold ischemia was 149.9 ± 53.1 minutes. Blood loss – 751.1 ± 633.6 ml. Renal vascular replacement was performed in 13 patients. Postoperative complications >II degree according to Clavien – Dindo were detected in 36.6% (16) patients. There was only one lethal outcome due to mesenteric thrombosis at day 4. Disease progressed in 6.8% (*n* = 3) of cases. The GFR level before surgery was on average 72.3 ± 16.8 ml / (min · 1.73 m^2), in the early postoperative period – 58.7 ± 28.3 ml / (min · 1.73 m^2), 1 year after surgery – 69.4 ± 26.2 ml / (min · 1.73 m^2). The follow-up period ranged from 8 to 86 months (on average 58.7 ± 19.1 months). Five-year overall survival in these patients is 91%, and cancer-specific survival is 93%.

CONCLUSIONS: This technique is effective in patients with multiple foci, centrally located and large tumors, for hard-to-reach localizations, as well as in patients with the impossibility of intracorporeal pharmaco-cold ischemia, peculiarities of organ blood supply.

Keywords: renal cell carcinoma; cold ischemia; kidney resection; nephrectomy.

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Научная статья

Метод экстракорпоральной резекции с ортотопической реплантацией почки в условиях фармакохолодовой ишемии при раке почки

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Актуальность. Повышение эффективности лечения больных раком почки — одна из основных проблем онкоурологии. В ее решении большое значение придается разработке новых хирургических технологий.

Цель исследования — оценка результатов экстракорпоральной резекции почки в условиях фармакохолодовой ишемии с ортотопической реплантацией у больных раком почки.

Материалы и методы. В исследование включены 44 пациента с раком почки, среди них 31 мужчина (70,5 %), 13 женщин (29,5 %). Все пациенты проходили лечение в период с 2012 по 2021 г. Средний возраст пациентов составил 55,92 ± 12,6 года. Стадирование по системе TNM: pT1a — 3bN0M0-1 G1-3. Стадия pT1a–1b диагностирована у 75 % (33) больных; pT2a–2b — у 11,4 % (5), у одного пациента обнаружены множественные образования; pT3a–3b — у 13,6 % (6), у одной пациентки выявлено до 15 образований в единственной почке; двое оперированных больных имели рак единственной почки с интралюминальной инвазией. Средний балл нефрометрического индекса R.E.N.A.L. — 10,32 + 1,34.

Результаты. Длительность оперативного вмешательства составила 402,07 ± 83,21 мин. Продолжительность холодовой ишемии — 149,9 ± 53,1 мин. Кровопотеря — 751,1 ± 633,6 мл. Протезирование почечных сосудов выполнено у 13 больных. Послеоперационные осложнения выше II степени по классификации Clavien – Dindo выявлены у 16 (36,6 %) пациентов. Летальный исход был один, обусловленный мезентериальным тромбозом на 4-е сутки после операции. Прогрессирование заболевания имело место в 3 (6,8 %) случаях. Уровень скорости клубочковой фильтрации до операции составлял в среднем 72,3 ± 16,8 мл/(мин · 1,73 м^2), в раннем послеоперационном периоде — 58,7 ± 28,3 мл/(мин · 1,73 м^2), через 1 год после операции — 69,4 ± 26,2 мл/(мин · 1,73 м^2). Сроки наблюдения составили от 8 до 86 мес. (в среднем 58,7 ± 19,1 мес.). Пятилетняя общая выживаемость у этих пациентов — 91 %, а канцерспецифическая — 93 %.

Выводы. Данная методика выполняется при множественных очагах, центрально расположенных, и опухолях больших размеров, для труднодоступных локализаций, а также у больных с невозможностью проведения интракорпоральной фармакохолодовой ишемии и особенностями кровоснабжения органа.

Ключевые слова: почечно-клеточный рак; холодовая ишемия; резекция почки; нефрэктомия.

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ЭКО•ВЕКТОР

INTRODUCTION

The incidence of kidney tumors has been increasing over the past decades [1]. Approximately 610,000 malignant tumors are newly diagnosed annually in Russia. These include renal cell carcinoma, which ranks tenth, which is 4.0% of all malignant neoplasms in the Russian Federation [2].

Surgical treatment methods always bear certain risks and adverse effects. With kidney resection (KR), the overall incidence of adverse outcomes can reach 25% [3, 4]. The most common complications after KR are hemorrhage (1.2%–4.5%), urinary fistulas (17%), and acute renal failure (25%) [5].

Currently, despite the widespread introduction of new chemotherapy drugs and the development of targeted and immune therapies, surgery remains the only effective method of treating patients with malignant neoplasms of the kidney [6–8].

Radical nephrectomy (NE) has been the gold standard of treatment for renal cell carcinoma for many years. KR was used as the method of choice in bilateral tumor lesions, with a solitary kidney or one functional kidney. The improvement of modern diagnostic methods has increased the number of cases detected of the disease at an early stage of the tumor process. In some cases, when *in situ* kidney resection is not possible (such as multiple tumors and centrally located tumors), extracorporeal KR (ECKR) is performed with orthotopic or heterotopic autografting of the resected kidney [9–11].

In this regard, there is a need to study actively the possibilities of using contemporary technologies in renal cell carcinoma surgery. To preserve renal function in patients with obligate indications for organ-sparing treatment, with multiple foci, large tumors, and localizations difficult to resect, a technique for ECKR under cold pharmacological ischemia with its subsequent autografting has been developed [12–14].

MATERIALS AND METHODS

From 2012 to 2021 in the Department of Oncourology of the A.V. Vishnevsky National Medical Research Center of the Ministry of Health of Russia, 44 patients with morphologically confirmed renal cell carcinoma (stages pT1a-T 3vN0M0-1G1-3) with intraparenchymal and central localizations of the tumor were treated. Patients underwent ECKR using pharmaco-cold ischemia with Custodiol solution without transection of the ureter, followed by orthotopic autografting.

Among the patients, 70.5% (31) were men and 29.5% (13) were women, and their average age was 55.9 ± 12.6 years. The ratio of damage to the left and right kidneys was comparable, with 22 cases each.

The stage of the tumor process was determined based on the TNM classification [15]. Stage pT1a was diagnosed in 22 (50%) patients; pT1b was detected in 11 (25%) patients, in which two patients had multiple lesions; pT2a was registered in 4 (9%) patients, in which one patient had multiple lesions; pT2b was identified in 1 (2.4%) patient; pT3a was diagnosed in 4 (9.1%) patients, in which one patient had up to 15 lesions in a solitary kidney; and T3b was registered in 2 (4.5%) patients; both patients had renal cell carcinoma of a solitary kidney with intraluminal invasion. Table 1 presents the distribution of patients depending on the disease stage.

The tumor size and localization were assessed preoperatively based on the data from magnetic resonance imaging, computed tomography, and ultrasound examination of the abdominal organs. The average tumor size was 48.83 ± 21.7 mm in the axial plane, 42.15 ± 18.6 mm in the sagittal plane, and 41.9 ± 27.21 mm in the coronary plane.

To assess the functional state of the kidneys, serum creatinine and urea levels were measured, and the glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16].

The RENAL nephrometric scale was used to assess the complexity of the upcoming surgical intervention and predict possible complications. On this scale, the average score of the nephrometric index was 10.32 ± 1.34. According to the RENAL scale, the average score was 2.1 ± 0.73 for the (R)adius of the tumor (maximum radius), 2.7 ± 0.5 for the (E)xophytic/endophytic location of the tumor, 2.7 ± 0.5 for the (N)earness of the tumor to the kidney-collecting system or hilum (proximity to the pelvicalyceal system, in millimeters), and 2.6 ± 0.6 for the (L)ocation of the tumor (position of the tumor relative to the polar lines). Given the above, most of the surgical interventions performed are high complexity surgeries.

Simultaneously, thrombectomy was performed with the resection of the inferior vena cava (renocaval tumor thrombus) and ECKR of a solitary kidney with orthotopic replantation of vessels in 2 (4.5%) patients.

Table 1. Distribution of patients by stages of the tumor process (*n* = 44)

Таблица 1. Распределение больных по стадиям опухолевого процесса (*n* = 44)

Indicator	Stage I	Stage II	Stage III	Stage IV
n	33	4	4	3
%	79.5	9.1	9.1	6.8

Methodology of the ECKR

Depending on the lesion side, patients underwent J- or L-shaped laparotomy. Access to the retroperitoneal space was achieved along the Toldt line. The kidney was mobilized along with the pararenal fat body within the Gerota fascia, with the separation of the adrenal tissue

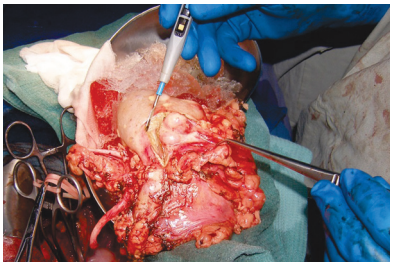

Fig. 1. The mobilized kidney on the crossed vessels in a tray with ice crumbs
Рис. 1. Мобилизованная почка на пересеченных сосудах в лотке с ледовой крошкой

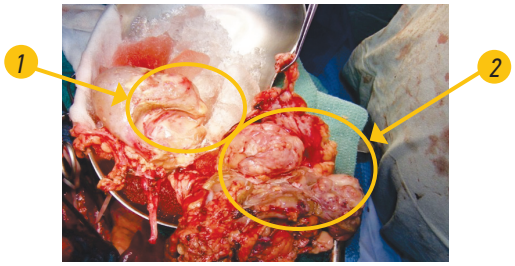

Fig. 2. Resection of a tumor within healthy tissues. *1* – wound surface of the kidney; *2* – conglomerate multiple tumor
Рис. 2. Резекция опухоли в пределах здоровых тканей. *1* — раневая поверхность почки; *2* — конгломератная множественная опухоль

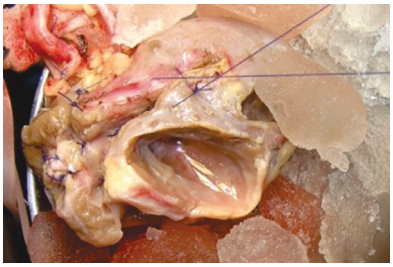

Fig. 3. Reconstruction of the collecting system of the kidney
Рис. 3. Реконструкция собирательной системы почки

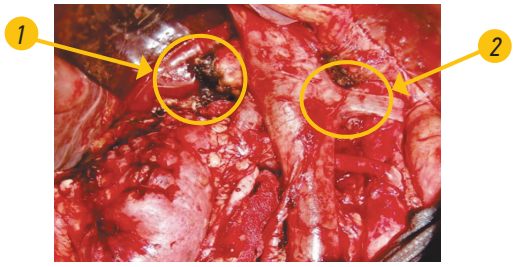

Fig. 4. Reimplanted kidney. *1* – venovenous anastomosis between the renal vein stump and the inferior vena cava; *2* – vascular anastomosis between the renal artery stump and the aorta
Рис. 4. Реимплантированная почка. *1* — вено-венозный анастомоз между культей почечной вены и нижней полой веной; *2* — сосудистый анастомоз между культей почечной артерии и аортой

(in situations justified from the oncological standpoint). The vascular pedicle and ureter were mobilized to the level of its intersection with the iliac vessels. In all cases, regional lymphadenectomy was performed.

The preparatory stage from the skin incision to the total mobilization of the kidney with lymphadenectomy took 45–72 (64.92 ± 4.25 min). The aorta was mobilized in the supra-, intra- and infrarenal sections, and the left (right) renal artery and veins were then isolated. An additional Doppler study of the kidney lesions, renal vessels, inferior vena cava, and aorta was performed intraoperatively.

Before the main resection stage, systemic heparinization of 5000–7500 IU was performed. Renal vessels were selectively clamped. On vascular clamps, the renal artery was transected at the entry, while the proximal stump was tied and sutured. The renal vein was transected directly at the entry with vascular clamps. The clamp at the renal vein entry remained until venous reimplantation. Thermal ischemia of the kidney was initiated at the time from clamping of the vessels to the placement of the kidney in ice crumbs and the start of injection of conservation agents.

The mobilized kidney on a non-transected ureter was placed in a special tray with ice crumbs (Fig. 1). Simultaneously, transarterial perfusion of the kidney was established with the plegic solution Custodiol. The Custodiol solution cooled to 5°C–8°C was supplied under hydrostatic pressure at the rate of 1.5 mL/(min · g) of the kidney mass.

The perfusate flowing from the lumen of the renal vein was aspirated. The mean perfusion time was 9.62 ± 1.55 min. The temperature in the thickness of the kidney parenchyma was recorded using a thermometric sensor. The mean temperature upon completion of perfusion was 10.3 °C ± 0.7 °C (Table 2).

With the full observance of the rules for cooling the kidney, the duration of organ protection can reach 48 h. After intraoperative echographic examination, tumor sharp dissection was performed within healthy tissues (Fig. 2). In one case, multiple lesions (up to 15) were found in the patient's solitary kidney, which were resected within healthy tissues.

The segmental arteries transected during the resection stage were restored by forming an end-to-end oblique anastomosis with a 8/0 polypropylene thread or sutured tightly with the same thread. In all cases, the pyelocaliceal system of the kidney was resected, and its integrity was restored with absorbable polyglactin thread 3/0 (Fig. 3).

The integrity of the kidney parenchyma was restored with 2- to 3-story single sutures with absorbable polyglactin thread 1/0 to 2/0. Upon completion of the final hemostatic suture on the kidney parenchyma, vessel reimplantation and kidney revascularization were started (Fig. 4). After an additional 100–300 mL of Custodiol

Table 2. Physical parameters of kidney cooling during extracorporeal kidney resection

Таблица 2. Физические параметры охлаждения почки во время экстракорпоральной резекции почки

Parameters	Indicators
Solution temperature	5–8°C
Perfusion rate	90–110 mmHg
Height of the container with the solution above the kidney level	120–140 cm
Perfusion time	Not less than 8–10 min

solution was injected into the renal artery, the kidney was placed in an ortho-optic position, and blood flow was induced.

RESULTS

All patients were on endotracheal anesthesia on an average of 485.73 ± 96.41 min. The duration of the surgical intervention varied from 190 to 560 min (average, 402.07 ± 83.21 min). The mean warm ischemic time was 8.65 ± 5.53 min. In 11 (25%) cases, the integrity of the resected segmental arteries was restored. The number of renal arteries varied from 1 to 3 (1.23 ± 0.56), and the number of veins varied from 1 to 2 (1.09 ± 0.29). Intraoperative antegrade stenting of the ureter was performed in 27 (61.3%) cases. In 13 (29.5%) cases, given the insufficient length of the artery stump, it was necessary to replace the renal artery with polytetrafluoroethylene prosthesis. The mean cold ischemic time of the kidney was 147.8 ± 53.1 min. In 11 (25%) cases, ipsilateral adrenalectomy was performed for oncological indications. The intraoperative blood loss volume was 751.1 ± 633.6 mL. Two patients underwent simultaneous surgery; one patient underwent resection of the infrarenal aorta with prosthesis for aneurysm, and the other underwent extirpation of the esophagus with simultaneous plastic surgery for esophageal cancer. The main intraoperative characteristics are presented in Table 3.

The preoperative mean creatinine level was within the normal range (96.4 ± 16.3 μmol/L), while on postoperative day 10, the value increased to 141.9 ± 126.6 μmol/L. The mean postoperative urea value remained within the upper normal limits (7.1 ± 5.9 mmol/L), but it was not significantly different from the preoperative value ($p \geqslant 0.05$). The average preoperative GFR calculated using the CKD-EPI equation was 72.3 ± 16.8 mL/(min · 1.73 m^2), which corresponds to the initial decrease in GFR. On postoperative day 10, the GFR level decreased significantly [58.7 ± 28.3 mL/(min · 1.73 m^2)], which in this case corresponded to a moderate decrease in GFR and was a stage III chronic kidney disease (CKD). With further follow-up after 1 year, the GFR increased on average to 69.4 ± 26.2 mL/(min · 1.73 m^2).

Twenty complications were identified above grade II of the Clavien–Dindo classification, which accounted for 40% of the total number of surgeries. However, on detailed examination, grade II complications accounted for 30% of the total number of complications. This complication was mainly represented by a hematoma in the resection area, which did not require surgical intervention. Clavien–Dindo IIIa and IIIb complications occurred in 4 (20%) and 6 (30%) patients, respectively, which were represented by single cases of acute pyelonephritis, eventration, acute renal failure, intra-abdominal bleeding, and destructive pancreatitis. Moreover, 3 (15%) patients with a solitary kidney developed acute renal failure, requiring

Table 3. The main characteristics of the operation

Таблица 3. Основные характеристики операции

Criteria	Patients (*n* = 44)
Number of excised lymph nodes, *n*	6.24 ± 4.67
Multifocal tumors, *n* (%)	2 (4.5)
Ureteral stenting, *n* (%)	31 (70.5)
Resection and microvascular grafting of segmental arteries, *n* (%)	11 (25)
Adrenalectomy, *n* (%)	11 (25)
Mean temperature of cold ischemia, °C	10.3 ± 0.7
Renal artery replacement, *n* (%)	13 (29.5)
Simultaneous surgery, *n* (%)	2 (4.5)
Number of renal arteries, mean	1.23 ± 0.56
Number of renal veins, mean	1.09 ± 0.29

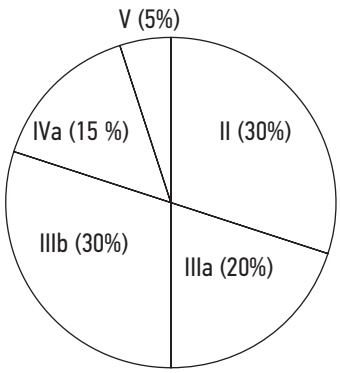

Fig. 5. Distribution of postoperative complications according to the severity according to the Clavien–Dindo classification
Рис. 5. Распределение послеоперационных осложнений в соответствии со степенью тяжести по классификации Clavien – Dindo

1–3 hemodialysis sessions. One (5%) lethal outcome was caused by mesenteric thrombosis on postoperative day 4, which induced multiple-organ failure.

The ratio of postoperative complications in accordance with the Clavien–Dindo classification is presented in Fig. 5.

The presence of a kidney tumor was confirmed by histological examination in all patients who underwent surgery. Clear-cell carcinoma was diagnosed in 35 (79.5%) patients, urothelial cancer in 2 (4.5%), chromophobic cancer in 1 (2.3%), and papillary cancer in 6 (13.6%). The distribution of patients according to the histopathological gradation of the neoplasm is presented in Table 4.

The follow-up period for patients who underwent surgery ranged from 8 to 86 (average, 58.7 ± 19.1) months. The tumor progressed in 3 (6.8%) patients. In our patients, the 5-year and cancer-specific overall survival rates were 91% and 93%, respectively.

DISCUSSION

Surgery is the only treatment option for most patients with localized renal cell carcinoma. Radical NE is a standard procedure with good oncological outcomes. Given the above, new surgical approaches will provide survival rates similar to NE. However, surgeons must make efforts to minimize the consequences of cancer treatment. Improved surgical approaches will probably lead to a reduction in the rates of new comorbidities, with CKD as the most serious and directly associated with NE. With KR, a part of the kidney that is not affected by the tumor at the time of surgical treatment is preserved, which reduces significantly the CKD risk [17, 18].

The results of reviews of nonrandomized trials should be interpreted with caution because of the risk of selection bias. A cohort study using the Surveillance, Epidemiology, and End Results dataset demonstrated that KR improved the overall survival rate compared with a control group of patients without cancer. The authors concluded that the apparent survival benefit provided by KR is probably interpreted as the result of selection bias associated with unmeasured confounding factors [19]. The same conclusion was made by Tobert et al. [20]. Evidence from non-randomized trials revealed that KR was used more frequently in younger patients and patients with fewer comorbidities, smaller tumor size, less aggressive pathology, lower American Society of Anesthesiologists scores, better renal function, and better indicators of the quality of life compared with NE [21–24].

In these studies, the follow-up period was 6–7 years, and kidney function [estimated GFR (eGFR) <60] was reduced with KR compared with NE. Although the preservation of renal function is desirable in all patients, its importance is unclear in patients with a normally functioning contralateral kidney and normal renal function at baseline. For example, NE may be the preferred approach in older patients, given that any improvements in kidney function are registered only over a long period [25].

In 2017, Kunath et al. [26] published data from a randomized controlled trial that compared the results of KR and NE in patients with renal cell carcinoma. This study included 541 patients. The mean follow-up period

Table 4. Histopathological gradation of kidney tumors in operated patients (*n* = 44)
Таблица 4. Гистопатологическая градация опухолей почки у оперированных больных (*n* = 44)

Histopathological gradation of cancer	Patients	
	n	%
Clear-cell G1	16	36.4
Clear-cell G2	15	34.1
Clear-cell G3	4	9
Urothelial G1	1	2.3
Urothelial G3	1	2.3
Chromophobic	1	2.3
Papillary G2	3	6.8
Papillary G3	3	6.8

was 9.3 years. The time to death from any cause was reduced with KR [odds ratio (OR) 1.50, 95% confidence interval (CI) 1.03–2.18]. No significant difference was found in time to disease recurrence (OR1.37, 95% CI 0.58–3.24). The authors concluded that KR improves the overall survival rate. As regards postoperative mortality, scientists did not reveal a significant difference in the timing of disease recurrence; however, patients who underwent KR had significantly improved quality of life [26].

In the USA, Streja et al. [27] performed a randomized trial comparing KR with NE, as well as CKD progression and mortality, in patients who received surgical treatment. The study included 7073 patients who underwent KR or NE from 2004 to 2013. GFR was assessed before hospitalization, immediately after surgery, and 180 days after surgery. The study assessed the type of surgery (KR or NE) and GFR at different treatment periods, with estimated mortality in adjusted survival models. In patients with a history of NE (compared with KR), GFR decreased by two times [–21.8 ± 17.7 versus –10.3 ± ± 17.4 mL/(min · 1.73 m^2)] immediately after the surgery. Patients who underwent NE (compared with KR) also had a 2.2 times higher mortality rate (95% CI 1.91–2.55). Decreased renal function and high mortality rate after NE have been reported [27].

Van Poppel et al. [28] noted that a decrease in the number of nephrons as a result of surgical interventions (KR or NE) did not affect the GFR over the long-term follow-up. Moreover, a typical progressively decreasing trajectory of GFR was noted in patients with CKD for other medical reasons, was not found in most patients who underwent NE, and was not registered after KR, despite the critically reduced GFR in the early postoperative period of patients who underwent KR.

Several interpretations are possible for the lack of association between GFR and mortality in KR and NE. First, patients who underwent NE may have a higher mortality rate from cancer. However, numerous studies have shown that the difference in mortality rate is caused by the difference in the overall rather than in the cancer-specific survival rate [29–32].

Only a few studies have investigated the risk of non-fatal and fatal cardiovascular diseases after kidney surgery. In two studies, mortality from cardiovascular diseases after NE was more than two times higher than after KR [31, 33]. In another study, Huang et al. [34] revealed several cardiovascular diseases after NE; however, the time to the development of the first disease or the risk of death from them did not increase.

CONCLUSION

ECKR is performed in multiple foci, centrally located foci, and large tumors with localizations difficult to access for resection, cases where intracorporeal pharmacological ischemia is impossible, and cases with peculiarities of the blood supply to the organ. ECKR under pharmacological cold ischemia without transection of the ureter, with orthotopic reimplantation of renal vessels, is a safe technique for the organ-sparing treatment of renal cell carcinoma, which reduces the duration and injury rate of the surgery.

Tumor eradication, adequate control of the resection margin, and removal of the pararenal fat body ensure compliance with all oncological principles during this intervention. ECKR is technically feasible with controlled complications and is justified in patients with large, centrally located, and multifocal tumors with the preservation of natural renal function. Surgery can be performed in multidisciplinary specialized institutions by specialists with the necessary qualifications (oncourologist and vascular surgeon) and experience in performing such surgical interventions.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with ICMJE. All authors have made a significant contribution to the development of the concept, research, and preparation of the article and have read and approved the final version before its publication.

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