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APPROACHES TO KIDNEY ANTI-ISCHEMIC PROTECTION IN ORGAN-PRESERVING SURGICAL TREATMENT OF PATIENTS WITH RENAL CELL CANCER

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The advantages of organ-preserving kidney operations are the improvement of functional results, the reduction in the number of patients with end-stage chronic renal failure in long-term follow up and related cardiovascular complications along with overall patients' quality of life improvement. On the one hand, a dry surgical field is necessary for visualizing the resection margin and on the other hand, its creation starts the process of acute ischemic damage to the tissue of the operated kidney. Each minute of kidney ischemia proportionally increases the risk of developing renal failure in the long-term postoperative period. It is especially important to consider the duration of ischemia during operations on a single kidney, with bilateral tumor lesions of the kidneys, as well as in the presence of chronic renal failure. After resection of the kidney, its residual function depends on the preoperative level of glomerular filtration, the amount of parenchyma retained during surgery, and the duration of renal ischemia. The predicted functional insufficiency of the "healthy" contralateral kidney in the postoperative period is 18%. The possibility of the chronic renal failure onset or worsening of the existing one due to the progression of nephrosclerosis reaches almost 80%. The development of chronic renal failure stage III and above in the long term after renal resection is more than 30%. Thus, there is a need for the development of precision surgery, as well as the search for anti-ischemic kidney protection, aimed at maintaining the maximum volume of functioning renal parenchyma.

Keywords: renal cell cancer; kidney resection; anti-ischemic protection; impaired renal function.

СПОСОБЫ ПРОТИВОИШЕМИЧЕСКОЙ ЗАЩИТЫ ПОЧКИ ПРИ ОРГАНОСОХРАНЯЮЩЕМ ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ БОЛЬНЫХ ПОЧЕЧНО-КЛЕТОЧНЫМ РАКОМ

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Преимущества органосохраняющих операций на почках заключаются в улучшении функциональных результатов, уменьшении числа пациентов с терминальной хронической почечной недостаточностью в отдаленном послеоперационном периоде и связанных с ней сердечно-сосудистых осложнений и, как следствие, в повышении качества жизни больных. С одной стороны, сухое операционное поле необходимо для визуализации края резекции, а с другой — его создание запускает процесс острого ишемического повреждения ткани оперируемой почки. Каждая минута ишемии пропорционально повышает риск развития почечной недостаточности в отдаленном послеоперационном периоде. Особенно важно учитывать продолжительность ишемии при операциях на единственной почке, при двустороннем опухолевом поражении почек, а также при наличии хронической почечной недостаточности. После резекции почки ее остаточная функция зависит от предоперационного уровня клубочковой фильтрации, количества сохраненной в ходе операции паренхимы и длительности ишемии почки. Прогнозируемая функциональная недостаточность «здоровой» контралатеральной почки в послеоперационном периоде составляет 18 %. Возможность развития или усугубления уже имеющейся хронической почечной недостаточности вследствие прогрессирования нефросклероза достигает почти 80 %. Риск развития хронической почечной недостаточности III стадии и выше в отдаленные сроки после резекции почки составляет более 30 %.

Таким образом, развитие прецизионной хирургии, а также поиск средств противоишемической защиты почки представляют важную задачу, направленную на сохранение максимального объема функционирующей почечной паренхимы.

Ключевые слова: почечно-клеточный рак; резекция почки; противоишемическая защита; нарушение функции почек.

Organ-preserving surgeries for kidney disease are not without complications such as ischemic damage and can cause acute or chronic dysfunction of the organ. According to the literature, the incidence of postoperative urological complications (e.g., acute renal failure, urinary fistulas, pyoinflammatory processes, renal infarction) reaches 9% depending on the nosology and extent of surgery, even in patients with elective kidney resection [1, 2]. The predicted functional insufficiency of an intact contralateral kidney in the postoperative period is 18% [3], whereas the probability of chronic renal failure due to nephrosclerosis progression is approximately 80% [4]. The consequent incidence of chronic renal failure stage III and higher following kidney resection is more than 30% [5]. Renal function loss reduces life expectancy, increasing the risk of cardiovascular diseases and their life-threatening complications [6–9].

After resection, the residual renal function depends on the preoperative level of glomerular filtration, extent of parenchyma preserved during the surgery, and duration of renal ischemia during resection [10].

In organ-preserving surgery, warm renal ischemia (temporary clamping of the renal vessels) is the main factor that triggers acute ischemic damage to the kidney [11]. The duration of hemostasis is crucial in surgeries on a solitary kidney, in bilateral tumor lesions of the kidneys, and in chronic renal failure [10]. In 2007, Thompson et al. [12] analyzed the results of a large-scale multicenter study on the effect of warm ischemia on the function of a solitary kidney after open organ-preserving surgery for a tumor and concluded that warm ischemia lasting more than 20 minutes more likely leads to renal dysfunction. Moreover, a research by Mosoyana et al. (2014) showed that even with an average period of warm ischemia of 14.4 minutes, a decrease in renal function is noted after 24 hours, persisting for at least 1 year [13]. Porpiglia et al. (2012) detected a persistent decrease in the glomerular filtration rate 3 months following warm ischemia of the kidney without a tendency of further deterioration [14]. Additionally, Thompson et al. (2010) noted a significant increase in the probability of acute renal failure during kidney resection under conditions of warm ischemia than without it [15]. It has been observed that every minute of ischemia affects the long-term functional results of kidney resection [16, 17]. Choi et al. (2012) showed that warm ischemia for more than 28 minutes 3 months after surgery reduces the glomerular filtration rate by 22.4% and by 30.6% after 12 months, whereas when the duration of warm ischemia is less than 28 minutes, the glomerular filtration rate does not change significantly [17]. In the study by Petrov et al. (2009), warm ischemia of more than 15 minutes resulted in ultrastructural damage to the nephrons and a decrease in glomerular filtration by 20%–30% [18].

The reversibility of changes occurring during warm ischemia depends on the severity of circulatory disorders in the organ (hypoxia, incomplete or total ischemia). The decrease in function of the kidney after prolonged ischemic exposure following surgery is leveled out in the presence of the contralateral kidney function [19].

The factors influencing the duration of warm ischemia and the probability of complications were assessed in studies using the RENAL and PADUA scales, including renal tumor characteristics such as diameter, proximity to the cavity system, localization (anterior/posterior, medial/lateral), and involvement of the pelvicalyceal system. Using these scales in preparation for organ-preserving surgery, the time of warm ischemia can be predicted, as well as the intraoperative integrity damage of the renal pelvicalyceal system and amount of blood loss, and to plan the course of resection. The independent predictors of ischemia of more than 20 minutes and overall complication rate are the anatomical characteristics of the tumor as well as the experience of the surgeon [20, 21].

APPLICATION OF THE COLD ISCHEMIA METHOD

Cold ischemia of the kidney has been the most well-known and widely used method for the long-term protection of the kidney and preservation of its functions. The protective effect of the method involves reducing the intensity of energy processes by cooling the resected kidney. Anti-ischemic protection is implemented by perfusion with sterile cooled solutions through the renal artery or placing frozen components, such as ice, around the organ. Cold ischemia is a rather laborious process leading to general hypothermia of the body; as a result, it has not received sufficient recognition for the intracorporeal resection of the kidney. Hence, it is used for extracorporeal resection of the kidney followed by autotransplantation in patients with large, centrally located neoplasms, when organ-preserving surgery in situ involves prolonged ischemia and, therefore, often becomes technically impossible. Extracorporeal surgery is complex, laborious, and traumatic with a high risk of vascular complications, bleeding, and ureteral necrosis [22–25]. Komyakov et al. (2012) presented a method of intracorporeal conservation, namely, cold ischemia during in situ kidney resection under its complete intracorporeal disconnection from the blood flow and constant selective perfusion with cooled Custodiol solution [26]. In clinical practice, this method extends the ischemia time up to 95 minutes with acceptable postoperative results. Intracorporeal preservation promotes radical resection of any complexity with minimal risk of volemic, metabolic, and hypothermic complications (loss of renal function) and eliminates the need for organ autotransplantation, reducing trauma and the duration of surgery [26].

REDUCTION OF WARM ISCHEMIA DURATION

In several studies, the average time of warm ischemia during open resection of the kidney was found to be 14–21 minutes and 38 minutes for tumors in a solitary kidney or large tumors. With laparoscopic resection of the kidney, the ischemia time ranges from 27 to 35 minutes, whereas with robot-assisted surgery, it lasts for 19.7 to 32.1 minutes. Thus, the renal warm ischemia duration for various reasons does not always remain safe [27]. Several authors have investigated ways to reduce the period of organ ischemia.

The total warm ischemia time can be reduced through the use of techniques that shorten the time required to close the kidney defect. For example, the sliding clip technique can reduce warm ischemia to 7 minutes by eliminating additional sutures. Hem-o-lok clips placed on both ends of the suture are applied to the surgical defect and are shifted using manipulators, increasing the tension during suturing of the renal parenchyma to achieve reliable hemostasis and positioning of the parenchyma [28].

Dimitriadi et al. (2014) proposed a method for reducing the time of warm ischemia during laparoscopic resection of the kidney, which involved avoiding separate suturing of the opened cavity system when hemostatic sutures are applied using the "sliding clips" technique without the use of additional hemostatic materials. The authors noted that this method did not increase the risk of urinary fistula formation [29].

To reduce the period of renal warm ischemia, the clamp can be removed early, when the renal artery blood flow is restored after the first row of sutures is applied to the renal parenchyma with damaged vessels and elements of the renal collecting system. This method reduces the time of warm ischemia by 50% and can be applied in minimally invasive surgeries [30].

Additionally, reduction of warm ischemia duration can be achieved through the use of special suture materials, such as V-Loc suture, a monofilament absorbable suture with self-fixing notches to prevent eruption of renal parenchymal tissue during final hemostasis [31].

REDUCTION OF ISCHEMIA AREA

Renal parenchyma ischemization, depending on its prevalence, can be global in nature (involves the entire organ when the vascular pedicle is clamped) or regional (partial). Thus, in temporary hemostasis during organ-preserving kidney surgery, the extent of ischemic organ damage can be reduced through the following techniques:

- Simultaneous clamping of an artery and a vein (clamping en bloc);
- Clamping only an artery feeding a tumor or a segment of a kidney with a tumor (selective clamping of a segmental vessel);
- Applying vascular clamp on demand;
- Zero ischemia implies methods of an intervention that do not cause ischemic damage to even a part of an organ.

Clamping of the entire renal pedicle causes greater pathological abnormalities than clamping of the renal artery alone [32]. Due to the discrepancy between the real and the safe time, the concept of zero ischemia has been developed in recent years. This term refers to methods of performing an intervention that do not lead to ischemic damage even to a part of an organ.

These include the following:

- No-clamping technique;
- The method of selective microdissection of the tertiary and quaternary arteries of the kidney;
- Method of controlled hypotension.

The no-clamping technique involves resection of the tumor without clamping the renal pedicle at normal blood pressure. This procedure can be accompanied by a significant, often uncontrolled, volume of blood loss from the bed of the tumor removed; however, it maximizes the number of functioning nephrons. Due to the risk of bleeding, the no-clamping technique is used to a limited extent, only for resection of small tumors with predominantly extrarenal growth [13, 33].

In protecting the kidney from ischemic organ damage during resection, selective dissection and clipping of the third- or fourth-order arteries feeding the tumor is the most technically difficult method. The anatomical prerequisite is the radial blood supply to the kidney and, accordingly, the segmental structure. In the kidney, five segments are usually distinguished, each of which is supplied with blood by a separate branch of the renal artery: superior, inferior, antero-superior, antero-inferior, and posterior. This enables the removal of the pathologically abnormal part of the kidney without disrupting the organ function as a whole while preserving the remaining functioning parenchyma. Gill et al. (2012) described 15 cases of robotic-assisted and 43 cases of laparoscopic resection of the kidney under zero ischemia without clamping the renal pedicle by microdissecting the renal arteries of the third or higher order feeding the tumor and applying bulldog clamps on them with positive postoperative results [34].

Superselective embolization of the renal arteries feeding the tumor, performed prior to kidney resection, avoids intraoperative clamping of the renal vessels and increases the safety of laparoscopic intervention. Simone et al. (2011) described a 7-year experience of laparoscopic kidney resection under zero ischemia by transarterial tumor embolization with positive results and suggested using the technique for tumors with mean values of nephrometry [31]. According to Alyaev et al. (2016), this technique has a number of advantages; it prevents warm ischemia of the normal renal parenchyma, which could subsequently negatively affect its function; enables to perform resection in cases of complex vascular anatomy, when mobilization of the renal artery, moreover segmental vessels, is technically difficult or impossible; leads to a decrease in intraoperative blood loss, which has a positive effect on the general course of the postoperative period; and promotes the expansion of indications for the use of superselective embolization in laparoscopic surgeries. Moreover, the authors note that the disadvantage of the method was the decreased visual differentiation between tumor and intact tissue during resection along the demarcation line [32].

Controlled hypotension, a method when systemic blood pressure is reduced to 65 mmHg, enables kidney resection without clamping the renal vessels with the minimum possible hemorrhage. Gill et al. (2012) described good results in 12 cases of laparoscopic and 3 cases of robotic-assisted kidney resection for small tumors (1–4 cm in diameter) without clamping the vascular pedicle with pharmacological hypotension up to 60 mmHg within 1–5 minutes. However, with such low blood pressure values, especially in cases of pneumoperitoneum, filtration in the renal glomeruli is severely impaired and vital oxygen-dependent organs (i.e., heart, brain) may suffer. Therefore, several authors consider this method unsafe.

Martin et al. (2012) compared the total, selective, and non-arterial clamping techniques during laparoscopic and robotic-assisted kidney resection and obtained comparable medium-term results of selective clamping of the renal arteries and performing the procedure without ischemia [35].

Local compression of the renal parenchyma at the site of resection presents another possibility of a “dry” surgical field in organ-preserving kidney surgery without clamping the renal vessels. In open surgeries, this can be finger compression or the use of a clamp on the kidney parenchyma. The literature describes various modifications of clamps used for selective clamping of the renal parenchyma in open (Reniclamp, DeBakey) and laparoscopic (Simon, Aesculap) and robotic-assisted (Semenov – Mosoyan, Al-Shukri – Mosoyan, and Korosta – Mosoyan) surgeries [13, 36–39]. Indications for parenchymal compression during kidney resection are small (up to 3 cm) tumors of the upper or lower pole at stage T1 or larger extrarenal tumors and a high risk of postoperative acute renal failure. Studies have shown that resection of the kidney under conditions of selective ischemia with clamping the parenchyma is an alternative to clamping the renal pedicle and avoids intraoperative bleeding. The disadvantage of this method is it can only be applied for the resection of the renal poles.

In addition, flexible structures belong to mechanical instruments for intraoperative compression of the renal parenchyma. In 1995, Gill et al. proposed the use of a special tourniquet, a double loop put on the kidney parenchyma, which provided compression and exsanguination of the organ pole. Furthermore, Loran et al. (2013) proposed the use of preventive sutures around the tumor along its entire diameter, about 1 cm from its margin, which are then tied over the parenchyma [40]. After suturing, the kidney with the tumor is resected within the designated circumference. Once hemostasis is reached, the tumor bed is sutured, most often with the use of a kind of gasket. Previous provisional sutures are used for suturing the renal parenchyma in the area of the tumor bed. These sutures are captured into the suture, preventing eruption. The technique reduces the intensity of bleeding during resection, the risk of tissue eruption when suturing the tumor bed, the duration of the surgery during hemostasis, and the probability of clamping the renal artery [40]. Moreover, when tumors are polarized, the Endoloop can be used to compress the renal parenchyma [41].

Various techniques can be combined to improve long-term functional results during kidney resection. For example, some authors propose selective microdissection and clamping of the artery feeding the tumor, in combination with pharmacological hypotension [42]. Nosov et al. (2016) performed laparoscopic kidney resection under zero ischemia and without hemostatic suture in 70 patients with positive postoperative results; the volume of the functioning parenchyma of the resected kidney decreased only by the volume of the tumor removed [43]. The authors revealed that to prevent bleeding and seal the pyelocaliceal system, only electrohemostasis with local adhesive compositions is sufficient [43].

CONTROL OVER THE RESECTION MARGIN

Radical removal of the kidney tumor during organ-preserving surgery is determined by the absence of a positive margin in the resection area. On the one hand, control over the edge of the resection zone ensures a long-term relapse-free course of the disease; on the other hand, it allows the parenchyma and, accordingly, renal function to be maximally intact by the oncological process. For oncological control, an express biopsy of the resected area of the removed tumor bed is used. However, this assessment cannot be considered accurate owing to the times that it is not possible to visualize clearly the tumor tissue at the resection margin; that is, the specimen for biopsy from different parts of the resection area is taken not taken from a targeted part, but from a random area. Consequently, a false-negative result is possible. In addition, morphological examination takes a long time, which increases the period of ischemia and can lead to serious renal function impairment [44]. The use of intraoperative ultrasound, including the marking of the resection margin with sonocontrast needles, determines more accurately the tumor boundaries. Additionally, this enables the preservation of a healthy kidney parenchyma without affecting the number of early complications and specific and relapse-free survival rate. Owing to this variant of the control of the resection margin, the indications were expanded for organ-preserving treatment of patients with renal cell carcinoma with tumors larger than 7 cm and those with tumors of "inconvenient" localizations [45].

Fluorescence diagnostics (primary and secondary) of malignant neoplasms belongs to modern methods of controlling the resection margin. The method is based on the use of photosensitizers (e.g., various derivatives of porphyrin and related macrocycles), which, when exposed to light of a certain wavelength, become excited and initiate physicochemical processes accompanied by luminescence and tumor destruction. Autofluorescence diagnostics (primary) implies the determination of differences in intensity and spectral composition of intrinsic fluorescence of healthy and tumor tissue without the use of photosensitizers; since tissues with increased proliferative ability (neoplastic, embryonic, and regenerative) accumulate more porphyrins, the intensity of their luminescence will be higher. Secondary fluorescence diagnostics includes the use of photosensitizers that are tropic to cancer cells, with the possibility of detecting them by the characteristic fluorescence of exogenous or endogenous fluorochromes. The bright fluorescence of fluorochromes, accumulating selectively in the tissue of a malignant neoplasm, enables to distinguish objects reaching the size of a fraction of a millimeter. Fluorescence diagnostics is non-invasive and does not affect the dynamics of various biological processes in tissues. Due to the instant processing of optical analysis data, the resection volume can be immediately adjusted according to the information obtained, the surgical site after surgery can be evaluated, and, if a residual tumor is detected, an urgent biopsy from a specific area can be performed. Through the method, the biochemical changes in tissues can be detected during the transformation of normal cells into dysplastic and malignant ones (which occur before structural rearrangements), micro-foci of neoplasms and micrometastases (including multiple ones), invisible under normal light. Studies show that fluorescence diagnostics is a highly effective method in assessing the radicality of surgical intervention, the use of which reduces the risk of local recurrence of the disease and lengthens the relapse-free period [46, 47].

Preoperative virtual planning is a crucial stage in preparation for organ-preserving surgery, as it enables the prediction of the characteristics of the surgery and its difficult and dangerous stages and anticipated possible complications. Augmented reality technology for intraoperative navigation based on preoperative 3D modeling of the area of surgical interest by combining a computer model and an image of a real organ during video endoscopic surgery provides critical information about the spatial structure of the organ, localization of the pathological process, and select segmental vessel for warm ischemia [48].

CONCLUSION

Organ-preserving kidney surgery improves functional results and reduces the number of patients with end-stage chronic kidney disease and associated cardiovascular complications. This is especially beneficial in patients with an anatomically or functionally solitary kidney as it can significantly improve their quality of life. Currently, the development of a precision surgery is warranted, as well as the further improvement of anti-ischemic protection methods for the kidney, aimed at maintaining the maximum volume of the functioning renal parenchyma.

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