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POINT OF VIEW

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PREDICTING CHANGES IN GLOMERULAR FILTRATION RATE IN PATIENTS WITH KIDNEY CANCER USING A MATHEMATICAL MODEL

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Chronic renal failure is one of the most challenging complications after the completed surgical treatment for renal cell cancer. In 2016, a grading system of tumorous renal involvement was developed, referred to as NCIU nephrometry. However, the systematic parameter to reflect the functional status of the functional renal parenchyma is defined by tumor volume only, with no regard for spatial disposition of the segment(s) where the tumor is located. Our research team decided to improve the NCIU nephrometry system by developing and testing a modified formula for calculation of creatinine clearance, which makes allowance for spatial disposition of tumor within the kidney. We performed numerical computations and analysis of changes in functional status of renal parenchyma depending on coordinate-based spatial location of the tumor in order to augment the existing NCIU nephrometry scale; Matlab, a specialized software package was used as a principal instrument to calculate the number of nephrons and functional renal parenchyma depending on the coordinate-based position of the mass center of the tumor and tumor volume. This model was shown to create a feasible opportunity to increase the percentage of organ-sparing procedures for renal cell cancer and to reduce the incidence/progression of chronic renal failure in these patients.

Key Words: **chronic renal failure, nephrometry, organ-sparing surgery.**

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Renal cell cancer (RCC) is one of the most frequent solid neoplasms in renal parenchyma, accounting for up to 90% of all renal malignancies [1, 2]. The principal instrument-based diagnostic modalities used to detect and characterize renal tumors include ultrasound, computer tomography and magnetic resonance imaging [3–5]. Patients with signs of decreased renal function are recommended to undergo radioisotope renography and a full range of renal function assessments for better planning of the subsequent treatment [6, 7]. To date, organ-sparing treatment of malignant lesions remains the fundamental concept of clinical oncology [8–10]. Chronic renal failure (CRF) is one of the most challenging complications after the completed surgical treatment for RCC, reported in 1–12% of cases [11–14]. Some authors believe that better preservation of renal function in organ-sparing treatment actually improves overall survival rates, as opposed to radical surgical interventions. For instance, ischemia time is greater in laparoscopic resection of the kidney than in open kidney resection [5]. Postoperative kidney function long-term largely depends on the duration of intraoperative renal ischemia [6–8].

The incidence of nephrological complications resulting from treatment and/or cancer progression ranges from 5–20% to 40–60% and sometimes achieves 80% [9]. An empirically established non-linear relationship between reduced glomerular filtration and increased serum creatinine levels allowed simplifying the standard renal function assessments in oncology practice just to monitoring of serum creatinine levels. The routine nephro-urological control in management of cancer patients is based on the established clinical, biological and imaging assessments of urogenital system. However, it does not allow obtaining a timely picture of reduction in functional reserves of the kidneys and prognostication of renal failure in patients with kidney cancer. The emergence of radionuclide methods in urology has greatly improved the options for functional assessment of renal parenchyma and contributed to the emergence of new informative modalities for prognostication of development and progression of renal failure. The sensitivity and specificity of radionuclide tests has vastly improved with the advent of modern radiopharmaceuticals, gamma-ray chambers and combination (superimposition) of radionuclide imaging with/on computed tomography images. Such assessments currently include tissue-specific radiopharmaceuticals, which allow for a targeted assessment of renal structure and function [12, 14]. Computer-based data processing allows selecting test area and using various formats for data representation, i.e. plots (renographic curves), tabulated data or scintigraphic images [12].

In 2016, a grading system of tumorous renal involvement was developed referred to as NCIU nephrometry. This system allowed for a more precise definition expanding the indications for kidney resections [1]. However, the systematic parameter to reflect the functional status of the kidney, the functional renal

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Abbreviation used: CRF – chronic renal failure; FRP – functional renal parenchyma; GFR – glomerular filtration rate; RCC – renal cell cancer.

parenchyma (FRP), is defined by tumor volume only, with no regard for spatial disposition of the segment(s) where the tumor is located [2]. The existing NCIU nephrometry scale can be improved by the use of numerical computations and analysis of how changes of the above parameter affects the functional status of renal parenchyma depending on coordinate-based location of the tumor. This, in turn, will allow for a better selection of patients with RCC as candidates for a particular surgical procedure [1, 2].

Glomerular filtration rate (GFR) is a time-dependent renal variable; therefore, it is a more sensitive parameter of kidney disease than static parameters (i.e. those obtained over a given time interval), such as the levels of urea, creatinine, ammonia, etc. [13]. This is why a matter of current interest in modern medicine is to develop new and to improve the various existing methods of RCC management and to pinpoint the indications for their use; this includes expanding the indications to organ-sparing surgical procedures and kidney resection in RCC with due consideration for the functional status of the kidney. We attempted to perform numerical computation and analysis of changes in functional status of renal parenchyma depending on coordinate-based spatial location of the tumor in order to augment the existing NCIU nephrometry scale.

The computation was performed based on the data of 10 patients with RCC of stages T_1 to T_2 treated at the Department of Urology, Faculty for Post-Graduate Education, Danylo Halytsky National Medical University of Lviv (Lviv, Ukraine) and at the Clinic of Plastic and Reconstructive Oncourology of National Cancer Institute (Kyiv, Ukraine). The nephrometry using the NCIU scale was performed with additional adjustments made for the functional status of the kidney and the spatial position of the tumor. All patients gave their consent for impersonalized use of their examination data for scientific purposes. The functional status of the kidneys was assessed using the Cockcroft-Gault formula. Table 1 presents the key parameters of medical data.

Table 1. Basic datasets for GFR calculations

Index	
Age (years)	56–75
Gender (M)	6
Gender (F)	4
Weight (kg)	56–96
Creatinine(mmol/l)	0.081–0.117
Longitudinal size (tumor) (mm)	24–96
Transverse size (tumor) (mm)	24–84
Type of growth (exophytic)	2
Type of growth (endophytic)	8
Tumor volume (mm^3)	7.5–57.8
Kidney volume (mm^3)	177–370.1

The existing formula for calculation of GFR (Cockcroft-Gault formula) with $k = 1.23$ for males and 1.05 for females does not accommodate the impact of the number of nephrons (N), FRP and a coordinate-based relationship with the mass center of the renal tumor, that is, which respective portions of the tumor are located in the renal segments U, N, C and I. The coordinates of the mass center of the tumor define not only in which specific segments (U, N, C and I) the tumor is located, but also the spatial position of the tumor and the percentage of tumor bulk in each of the segments.

In order to accommodate the above parameters, we will need to calculate the number of nephrons and renal functional parenchyma *FRP* (x_0, y_0, z_0; V_p, V_n) depending on the coordinate-based position of the mass center of the tumor $O_1 (x_0, y_0, z_0)$ and tumor volume V_t. To this end, we will modify the known and existing GFR equation with the methods of mathematical modeling, using Matlab, a specialized software package.

Fig. 1 presents a developed structural and functional algorithm to identify the probability of reduced nephrons in the kidney per unit volume, dV.

Let us assume a kidney of a volume V_k without a tumor. This kidney contains N_0 nephrons. As a tumor with a volume of V_t is developing in a kidney, the initial nephron count (N_0) will reduce to N. Then N is the number of nephrons present in the kidney in a tumor with a volume of V_t, and dN is the reduction in the number of nephrons in the kidney as tumor volume increases from V_t to $V_t + dV$, where $\lambda (x, y, z)$ stands for a constant of nephron reduction when tumor volume increases by dV. The coordinates of the mass center of the tumor $O_1 (x_0, y_0, z_0)$ within the kidney are obtained relative to the renal mass center, which is determined by the $O (0, 0, 0)$ point. As reported in [2], the kidney is conventionally divided into the following three segments: interpolar (middle) segment and two polar segments (upper and inferior) by the lines drawn transversely to the vertical axis of the kidney along the edges of the medial lip, where renal parenchyma continues into the kidney fat of sinuses, blood vessels or the renal cavitary system. Then let us draw an imaginary perpendicular line, which is consistent with the vertical axis of the kidney and passes

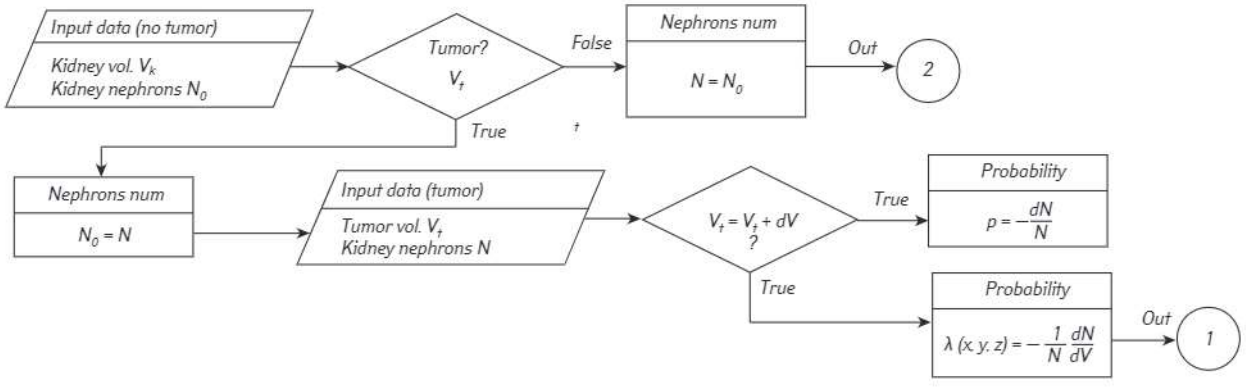

Fig. 1. Schematic diagram for kidney tumor identification

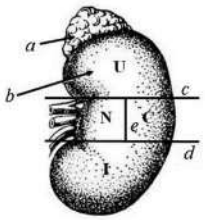

Fig. 2. Division of the kidney into the segments: N =Nearness (the segment adjacent to the vascular pedicle of the kidney or medial segment), C = Collateral (also known as lateral segment), I =Inferior segment and U =Upper segment, where: *a* — adrenal gland, b — kidney, c — upper interpolar line, d — lower interpolar line, e — axial line of the kidney

between the upper interpolar line and the lower interpolar line. In this manner, the middle segment is divided into two more segments, that is, N (for "nearness" — the segment adjacent to the vascular pedicle of the kidney, also referred to as medial segment) and C (for collateral, also referred to as lateral segment) (Fig. 2).

The degree of localization in the segments is suggested to be determined by the coordinates of the mass center of the tumor, $O_1 (x_0, y_0, z_0)$. The k coefficient is within the range of $0 < k < 1$. The value of k within this interval is determined by half the length of the (e) line in Fig. 3.

The derivative parameters, such as $\lambda_x^{\cdot}(0)$, $\lambda_y^{\cdot}(0)$ and $\lambda_z^{\cdot}(0)$ can be determined in an experiment using spiral computed tomography or a technique of nephrometry. After the computations are complete, the problem is reduced to an analytical representation of the kidney and the tumor in the shape of ellipsoids, with definition of their relative volumes, V_k and V_t, respectively, according to [15] and definition for the cases of tumor growth by introducing an additional parameter, V_z.

The resulting parameter of $FRP (x_0, y_0, z_0, V_t, V_t)$ that describes renal functional parenchyma is determined by tumor volume (V_t), the coordinate-based position of the tumor $O_1 (x_0, y_0, z_0)$ (Fig. 3) (that is, the segment where the tumor is located) and the semiaxes of the tumor ellipsoid (a_p, b_p, c_p). If the tumor is absent ($V_t = 0$), then the parameter that describes renal functional parenchyma is $RFP (x_0, y_0, z_0, 0, V_k) = 1$, and when the tumor is occupying the volume equal to the total volume of the kidney (that is, $V_t = V_k$), then it is $RFP = 0$ or the kidney is non-functional. In a utility model (patent No. 86311) [1, 2], the *RFP* parameter is defined by tumor volume only and does not take into account the coordinate-based relationship with the renal segment where the tumor is located.

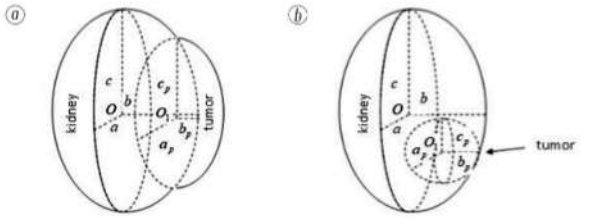

Fig. 3. The model of tumor involvement of the kidney in (*a*) exophytic and (*b*) endophytic growth of the tumor, where a, b, c are the semiaxes of a model ellipsoid of the kidney and a_p, b_p, c_p are the semiaxes of a model ellipsoid of the tumor.

Since GFR is directly proportional to the number of nephrons or to *FRP,* the GFR equation (i. e. the Cockcroft-Gault formula) will acquire the following multiplicand: $FRP(x_0, y_0, z_0, V_t, V_k)$. Depending on the type of tumor growth (endophytic or exophytic), we will have the following formulas for GFR calculation using a conventional (GFR_{con}) formula without coefficient p that determines the volume and modified (GFR_{mod}) formula with coefficient p that determines the volume of the tumor and type of tumor growth (endophytic — FRP_{end} or exophytic — FRP_{ekz}), which accommodate the relationship with the number of nephrons (N), the relationship with RFP and the coordinate-based relationship of the mass center of kidney tumor, that is, the fractions of the tumor in respective renal segments (U, N, C and I).

$$GFR_{con}\ (ml/m) = k \times ((140\text{-age (years)}) \times \text{body weight (kg)/blood creatinine (mmol/l)} \times \log(FRP_{end}, FRP_{ekz})) \times ((1 - V_p / V_n) / \exp(-1 / V_n^2 \times V_p (|x_0 b_p c_p| + |y_0 a_0 c_0| + |z_0 a_0 b_0|))) \quad (1)$$

$$GFR_{mod}\ (ml/m) = k \times ((140\text{-age (years)}) \times \text{body weight (kg)/blood creatinine (mmol/l)} \times \log(FRP_{end}, FRP_{ekz})) \times ((1 - (1\text{-}p) V_p / V_n) / \exp(-1 / V_n^2 (1\text{-}p) \times V_p (|x_0 b_p c_p| + |y_0 a_0 c_0| + |z_0 a_0 b_0|))) \quad (2)$$

where p is the coefficient that determines the volume of the tumor.

Analysis of formulas (1) and (2) demonstrates that in a given identical tumor volume (V_t) the GFR will be higher when the tumor is located in segment U or in segment I as opposed to tumors located in either segment N or segment C. This fact shows that GFR value may change depending on where the mass center of the tumor is located $O_1 (x_0, y_0, z_0)$ within a given segment [15].

In order to obtain results based on the model presented, we developed a simplified model using the above-mentioned software. In order to solve integral dependences, including the numeric Taylor series, we have used identification of geometric positions of the tumor in a three-dimensional coordinate sys-

Table 2. The outcomes of calculations and comparative assessments of GFR using a conventional (GFR_{con}) and modified (GFR_{mod}) formula for GFR calculation

№	Age	Gender	Weight (kg)	K_p (mmol/l)	A_p (mm)	B_p (mm)	C_p (mm)	V_t (mm^3)	V_k (mm^3)	GFR_{con} (ml/m)	GFR_{mod} (ml/m)
1	71	1.23	96	0.089	24	25	24	7.5	370.1	91.54	50.55
2	66	1.23	74	0.087	90	84	83	32.8	221.1	77.41	17.03
3	75	1.23	56	0.186	48	46	50	57.8	191.7	57.07	16.65
4	63	1.05	72	0.092	25	32	30	17.1	177.4	63.27	22.77
5	58	1.05	57	0.094	48	50	65	9.5	290.3	82.21	49.76
6	57	1.05	95	0.087	14	12	14	1.2	161.7	95.16	177.53
7	60	1.05	71	0.081	30	24	22	8.3	267.1	73.62	37.39
8	41	1.23	84	0.117	27	26	25	9	178.1	87.42	40.95
9	60	1.23	87	0.098	40	20	32	30.1	203.8	87.35	27.35
10	56	1.23	94	0.117	96	68	67	34.2	263. 9	83.01	14.33

tem as well as parallelization tools. As a result of our computations, we have obtained absolute and relative parameters of tumor location, which directly impact the outcomes of calculations using the modified formula (1). The calculation findings are presented in Table 2.

The above results suggest that using a model for calculation of creatinine clearance, which makes allowance for spatial location of tumor within the kidney, allows for a more precise stratification of RCC patients to a specific treatment modality. Pursuant to the analysis of the results obtained with the model for calculation of creatinine clearance with consideration for the spatial location of tumor within the kidney, the user may predict the impact of surgical treatment on postoperative renal function and recommend the best available treatment method on a case-by-case basis, as supported by the mathematical calculations performed and tested in actual patients taking part in our study.

In our opinion, the use of our modified formula for calculation of creatinine clearance, which makes allowance for spatial disposition of tumor within the kidney, would be useful for a more precise stratification of RCC patients to a specific treatment modality.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

STATEMENT

The Editorial Board of the Journal and the authors of this work admit that the version of mathematical modeling proposed needs further experimental and/or clinical verification.

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PREDICTING CHANGES IN GLOMERULAR FILTRATION RATE IN PATIENTS WITH KIDNEY CANCER USING A MATHEMATICAL MODEL

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Хронічна ниркова недостатність є одним з ускладнень хірургічного лікування нирково-клітинного раку, яке потребує найбільшої уваги. В 2016 р. було розроблено нефрометричну систему NCIU для оцінювання пухлинного ураження нирки. Однак за цією системою систематичний параметр, який віддзеркалює функціональний статус ниркової паренхіми визначається лише за об'ємом пухлини без урахування просторового положення сегментів, де локалізується пухлина. Наш дослідницький колектив спробував удосконалити нефрометричну систему NCIU. З цією метою ми розробили видозмінену формулу для обрахування кліренсу креатиніну, яка враховує просторове положення пухлини в нирці. Були проведені обчислення та аналіз змін функціонального статусу ниркової паренхіми в залежності від просторового положення пухлини в системі координат з метою посилення існуючої системи NCIU. Для розрахунку кількості нефронів та функціональної ниркової паренхіми в залежності від положення центру маси пухлини в системі координат та об'єму пухлини використовували спеціалізоване програмне забезпечення Matlab. Завдяки застосуванню цієї моделі можна сподіватись на збільшення відсотку органозберігаючих втручань у хворих на нирково-клітинний рак та зменшення ускладнень таких операцій у вигляді хронічної ниркової недостатності.

Ключові слова: хронічна ниркова недостатність, нефрометрія, органозберігаючі операції.