

SURGERY

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APPLICATION OF THE DIFFUSION-WEIGHTED MRI FOR PREDICTION OF THE INTRAOPERATIVE BLOOD LOSS DURING THE NEPHRECTOMY IN PATIENTS WITH RENAL CELL CARCINOMA AFTER EMBOLIZATION OF RENAL ARTERY

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Abstract: During the last decade renal artery embolization (RAE) is used for preparation of patients with renal cell carcinoma (RCC) of large size or significant vascularization to surgical treatment. Currently there is no accurate method of prediction of intraoperative blood loss in patients with RCC after RAE, that may give possibility for more adequate pre- and postoperative patient management and to define the indications for re-embolization. Goal. The goal of the study was to evaluate the possibility of application of diffusion-weighted imaging (DWI) of MRI and of apparent diffusion coefficient (ADC) for the prediction of the estimated intraoperative blood loss (EIBL) during the open radical nephrectomy in patients with RCC and after RAE. **Materials and methods.** The study enrolled 33 patients (main group, 18 males and 15 females) with solid RCC according to clinical and radiologic data and with the indications to selective RAE with subsequent radical nephrectomy. Mean size of the tumor was 8.6 ± 3.8 cm in greatest dimension. In all patients with RCC in the same day or day before RAE and 7 days after the RAE MRI with additional DWI sequence with $b\text{-value} = 0.800$ was performed. Subsequent measuring of the ADC over the tumor region was done in all cases. ADC values of the normal renal parenchyma for control were achieved during the examination of 15 healthy volunteers. In all patients with RCC 7-8 days after the RAE open radical nephrectomy with simultaneous EIBL measurement was executed. **Results.** In patients with EIBL less than 500 ml and with no episodes of the hemotransfusions mean ADC value decreased by 18.4-31.9% in comparison with initial ADC value. As opposed to that in patients with EIBL more than 500 ml and in selected cases with hemotransfusions mean ADC value increased by 4.91-65.64% compared to baseline value. Analysis of the acquired data showed significant ($p < 0.05$) difference in main group of patients in whom no hemotransfusions were required in post-op period ($n = 27$, 81.82%) in mean ADC values before and after RAE (decrease by 20.25%): $1.63 \pm 0.31 \times 10^{-3}$ mm²/s vs $1.30 \pm 0.19 \times 10^{-3}$ mm²/s. In main group patients with hemotransfusions in post-op period this value increased by 28.83%: $1.63 \pm 0.31 \times 10^{-3}$ mm²/s vs $2.10 \pm 0.47 \times 10^{-3}$ mm²/s ($p < 0.05$). Conclusions. In the result of our study strong direct relationship (correlation coefficient $r = 0.96$) between the volume of EIBL during open radical nephrectomy and ADC values in patients with RCC after RAE was detected. Application of MRI and its imaging biomarkers may be valuable clinical instrument for the prediction of the EIBL volume during the open radical nephrectomy in patients with RCC after RAE and need of the hemotransfusion in post-op period.

KeyWords: renal cell carcinoma, embolization, biomarker, nephrectomy, blood loss, MRI.



INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3.7% of all adult malignancies and more than 90% of neoplasm arising from kidney. According to National Cancer Registry of Ukraine during last years the indices of morbidity and mortality continued at a stable high level with a tendency to growth.

In 2014 in Ukraine the indices of morbidity and mortality after RCC accounts for 11.3 (14 men and 9 women) and 5.3 (7.5 men and 3.4 women) and in 2015 11.7 (15.0 men and 8.8 women) та 5.1 (7.3 men and 3.2 women) per 100 thousand of population accordingly [1].

The «gold standard» for localized and locally advanced RCC treatment is nephrectomy in despite of new alternative methods. During the last decade renal artery embolization (RAE) is used as preparation of patients with big or/and hypervascularized RCC's for surgical treatment [2]. The main advantages of RAE before nephrectomy are: re-

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duction of tumor clots` size (that facilitate its removal), blood loss reduction during surgery, alleviation of dissection because of edema development. RAE is usually performed 7-10 days before surgery.

The adverse side of RAE is postinfarction syndrome, which appear as pain in the iliac region, nausea and fever, this syndrome occur in $\frac{3}{4}$ of patients. Some authors observe significant blood loss during nephrectomy after RAE, perhaps it is caused by the incomplete schematization of tumor tissues. Literature data about efficiency of RAE performed as preparation of patients with RCC to nephrectomy are often contradictory, especially concerning estimated intraoperative blood loss (EIBL) volume and amount of blood transfusion, operative time, complications and survival rates [7, 13]. Thus, according to Schwartz and co-authors EIBL volume during radical nephrectomy in patients with RCC after RAE with median tumor size of 11.2 cm was variable and ranged from 100 to 5000 ml [11]. In another new research conducted by Ramaswamy, was established, that blood transfusion volume after radical nephrectomy in patients with RCC after total RAE also was also significantly variable and ranged from 222 to 1050 ml [10]. At the same time, according to Suad and co-authors, medium volumes of EIBL and intraoperative blood transfusion amounted 300 ml and 250 ml accordingly [5].

Currently there is no accurate method of prediction of EIBL volume during nephrectomy in patients with RCC after RAE, that may give possibility for more adequate treatment planning and postoperative patient management and to define the indications for re-embolization. In the last years the attention of researchers was focused on investigation of MRI and its modalities as diffusion weighted imaging (DWI) to estimate the efficiency of arterial embolization in treatment of benign and malignant tumors, as uterine fibroid and leiomyoma, hepatocellular cancer and breast cancer [3, 6, 9, 12]. DWI is the MRI sequence, which uses strong bipolar gradients to enhance sensitivity to thermally induced Brownian motion of hydrogen molecules, that allows to measure molecular diffusion in tissues in vivo and it is important for profound characteristic of

neoplasm [4]. However, all conducted studies were directed toward estimating the efficiency of arterial embolization, which was performed as a disease palliation but not during preparation to surgery.

In our previous work we investigated the efficiency of DWI MRI and its quantitative parameter - apparent diffusion coefficient (ADC) as imaging biomarkers in differential diagnostic of solid and cystic RCCs, benign renal tumors, benign cysts and abscesses [8]. We achieved statistically significant difference in mean ADC values of RCC and of the healthy renal parenchyma. We observed significant restriction of diffusion of hydrogen molecules in regions of solid neoplasms and it's increase in renal cysts and in abscesses in comparison with normal kidney parenchyma. Taking into account that tissue density affects diffusion of hydrogen molecules in them and that ADC consists of 3 main components - intracellular (inside the cytoplasm), extracellular (in the interstitial liquid, in blood and lymph vessels) and diffusion between intra- and extracellular environments, we suggested that DWI and ADC may be used as imaging biomarkers for evaluation of changes, which occurs in RCC tissues after RAE and for prediction of intraoperative blood volume loss in patients in whom nephrectomy will be executed.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose The goal of the study was to evaluate the possibility of application of DWI of MRI and of ADC for prediction of the EIBL during the open radical nephrectomy in patients with RCC and after RAE.

2.2 Subjects & Methods

The study was allowed by Ethics Committee and conducted on the basis of the Departments of Urology and Radiology of Danylo Halytsky Lviv National Medical University, Department of Interventional Radiology of Lviv Emergency Hospital, Center of Endourology of Lviv Clinical Railway Hospital and at the Medical Center "Euroclinic", Lviv, during 2013-2017 years.

The main group enrolled 33 patients (18 males and 15 females) with solid RCC according to clinical and radiologi-

cal data and with the indications to selective RAE with subsequent radical nephrectomy. The age of the patients ranged from 52 to 70 years old, the mean age was 62 ± 6.3 years. Tumor size ranged from 7.3 to 11.4 cm, the mean size was 8.6 ± 3.8 cm in the greatest dimension. Before surgery males had the level of hematocrit of 38-49% and females of 33-43%.

In all patients with RCC in the same day or day before RAE abdominal MRI using 1.5 T scanner (Signa HDxt, General Electric, USA) and 8-channel coil was performed. In all cases was applied same standardized scanning protocol (General Electric), which additionally included DWI sequence with following parameters: repeat time (TR)=12000 ms, echo time (TE)=90 ms, field of view (FOV)=40x40 cm, matrix=200 x 192, number of excitations (NEX)=3, bandwidth= 250 kHz, diffusion direction= slice, slice thickness= 6,0 mm, interscan gap = 1,0 mm with b-value=0.800 mm^2/s , acquisition time=17 sec. DWI was conducted before contrast media administration, using single-shot echo-planar imaging sequence with parallel imaging technique and fat saturation during one breath-hold. The mean duration of MRI examination was 35 minutes.

Selective RAE was performed under fluoroscopic guidance using the following method: under local anesthesia (0.5 % Novocaine) radial artery was punctured by Seldinger and after that introducer (6 Fr) was inserted. Selective angiography of right renal artery was performed using MR-catheter and injection of 80 ml of contrast (Ultratwist-370). After that one COOK spiral and three Gianturco spirals were alternately introduced (all spirals MRI-compatible), achieving total RAE. After RAE puncture area was bandaged with compression for 6 hours. The mean duration of the procedure was 120 minutes. Re-RAE wasn't performed in any case.

In all patients with RCC 7-8 days after selective RAE open radical nephrectomy with further pathologic verification of diagnosis was executed: in 100% of cases RCC diagnosis was confirmed. Measurement of EIBL was performed in all patients according to the following method: it was accepted, that 1 ml of blood weigh is 1 g; swabs saturated with blood were weighted and then the mass of blank

swabs from the same lot were subtracted; during weighing capacities for blood the mass of blank capacities were subtracted; blood volume, which got on surgical sheet, under body of the patient was assessed; the volume of the solution for irrigation was taken into account and it was subtracted from the general volume of EIBL.

Control MRI was performed in all patients 7 days after nephrectomy, which on purpose to reduce financial and temporal expense, included only 2 sequences: coronal T2-weighted single shot fast spin echo (SSFSE) and DWI with identical to above mentioned parameters. The mean duration of the examination was 10 minutes.

ADC was measured using ADC-maps, which were generated automatically on the workstation based on DWI and which were used for assessment of diffusion in RCC tissues before and after RAE. Region of interest (ROI) was placed over the tumor region to measure the ADC value where-upon it was measured (image 1).

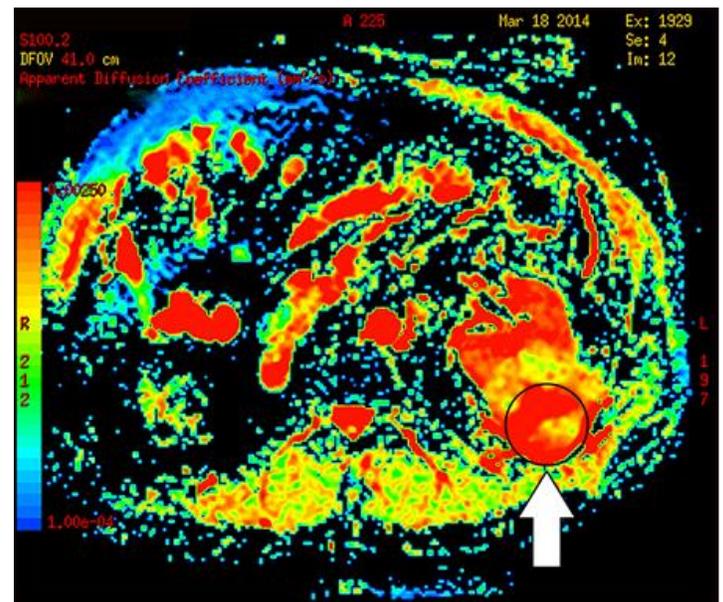


Fig. 1. ADC-map of the patient with RCC of the left kidney before RAE (pointer), ROI is placed over the tumor region, obtained ADC value - $1,62 \times 10^{-3} \text{ mm}^2/\text{s}$.

We obtained ADC values of the healthy renal parenchyma in 15 healthy volunteers without renal pathology (control group) according to data of clinical and imaging research (9 males and 6 females), aged from 38 to 50 years old (with median age $48,2 \pm 1,8$ years). For assessment of morpho-functional status of kidneys all volunteers passed

through appropriate examination before been included into research: general analysis of blood and urine, biochemical analysis of blood (creatinine, urea, ALT, AST), renal US. MRI was done to all volunteers using 2 sequences: coronal T2-weighted SSFSE and DWI with analogical to the main group parameters. For measurement of ADC values, ROI with median diameter of 3,5 cm was located over renal parenchyma and then registration was performed according to technique described earlier [8].

Antitumor therapy wasn't performed before MRI, RAE and surgery. People with metallic details inside the body weren't included in the study.

Statistics. Microsoft Exel 2016 was used for statistical analysis of obtained data, by Student-Fisher's method and for calculation of Pearson correlation coefficient. Value $p < 0.05$ considered as a statistically significant result.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

During the open nephrectomy in patients with RCC after RAE, EIBL varied from 158 to 1250 ml, the mean volume was $457,3 \pm 260,52$ ml. Depending on the EIBL all patients of the main group were separated into 4 different categories: I category- EIBL - 0-250 ml (n=9, 27,27%), II category - EIBL 250-500 ml (n=14, 42,42%), III category - EIBL 500-1000 ml (n=8, 24,24%) and IV category - EIBL more than 1000 ml (n=2, 6,06%). Medium values of EIBL for each category were: I - $216,55 \pm 34,45$ ml, II - $387,29 \pm 64,19$ ml, III - $669,36 \pm 118,23$ ml, IV - $1182,5 \pm 95,46$ ml.

We established, that medium ADC value of the healthy renal parenchyma of volunteers was $2,47 \pm 0,12 \times 10^{-3}$ mm²/s. In a result of analysis of the obtained ADC data we obtained statistically significant ($p < 0.05$) difference between the mean ADC values in the main group before and after RAE and in control group: $1,63 \pm 0,31 \times 10^{-3}$ mm²/s vs $1,44 \pm 0,40 \times 10^{-3}$ vs $2,47 \pm 0,12 \times 10^{-3}$ mm²/s accordingly. We observed direct correlation between the values of EIBL volume and ADC in patients after RAE, Pearson correlation

coefficient was $r=0,96$. In patients of I and II categories with EIBL volume less than 500 ml and with no episodes of hemotransfusions mean ADC value decreased by 18.4-31.9% compared to baseline value, because of bigger infarct areas of the tumor tissues, decrease of microcirculation and as a result the restriction of hydrogen molecules diffusion. As opposed to that in patients of III and IV categories with EIBL volume more than 500 ml and in some cases with hemotransfusions mean ADC value increased by 4.91-65.64% compared to baseline value. The interconnection between the increase of this ADC value and EIBL volume in the IV category of the patients can be explained with expressed oedema of the renal tissue near infarct area, necrotic process and deficient decrease of microcirculation in tumor area. All of this together conducted the increase of molecular diffusion in tumor tissues and possibly as a result of it the increase of bleeding during surgery. The detailed description of EIBL and ADC values of the patients with RCC before and after RAE presented in table 1.

Table 1.

Mean ADC values of the main group of patients before and after RAE and EIBL volume.

Category of patients/subgroup	Mean ADC before RAE, $\times 10^{-3}$ mm ² /s	Mean ADC after RAE, $\times 10^{-3}$ mm ² /s	Mean EIBL, (range), ml
Category I, EIBL 0-250 ml (n=9)	1.63±0.31	1.11±0.10	216.55±34.45 (158-250)
Category II, EIBL 250-500 ml (n=14)		1.33±0.08	387.29±64.19 (275-487)
Category III, EIBL 500-1000 ml (n=8)		1.71±0.12	669.36±118.23 (510-823)
Category IV, EIBL >1000 ml (n=2)		2.70±0.06	1182.5±95.46 (1115-1250)
Patients, in whom no hemotransfusions were required (n=27)		1.30±0.19*	351.33±119.75 (158-570)
Patients, who had hemotransfusion (n=6)		2.10±0.47*	899.0±226.45 (720-1250)

*comparison of groups between each other ($p < 0.05$)

Analysis of the acquired data showed significant ($p < 0.05$) difference in mean ADC values in subgroup of patients in whom no hemotransfusions were required in post-op period ($n=27$, 81.82%) in comparison with baseline mean ADC value: $1.30 \pm 0.19 \times 10^{-3}$ mm²/s vs $1.63 \pm 0.31 \times 10^{-3}$ mm²/s accordingly (decrease by 20.25%). In subgroup of patients with hemotransfusions in post-op period ($n=6$, 18.18%), the mean ADC value increased by 28.83% compared to baseline value: $1.63 \pm 0.31 \times 10^{-3}$ mm²/s vs $2.10 \pm 0.47 \times 10^{-3}$ mm²/s, such difference was statistically significant ($p < 0.05$).

CONCLUSIONS

1. In the result of our study strong direct correlation ($r=0.96$) was observed between the volume of EIBL during open radical nephrectomy and ADC values in patients with RCC after RAE;

2. In patients of the main group that required hemotransfusions in post-op period the mean ADC value increased by 28.83% compared to baseline, in patients in whom hemotransfusion wasn't performed mean ADC value increased by 20.25%: $2.10 \pm 0.47 \times 10^{-3}$ mm²/s vs $1.30 \pm 0.19 \times 10^{-3}$ mm²/s ($p < 0.05$);

3. The application of MRI and its imaging biomarkers DWI and ADC may be valuable clinical instrument for prediction of the EIBL volume during the open radical nephrectomy in patients with RCC after RAE and need of the hemotransfusion in postoperative period.

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