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Baseline perfusion CT parameters as potential biomarkers in predicting long-term prognosis of localized clear cell renal cell carcinoma

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Abstract

Purpose We aimed to explore the relationship among baseline perfusion CT parameters, clinical, and pathological factors with post-nephrectomy long-term progression-free survival in localized clear cell renal cell carcinoma.

Materials and methods This study retrospectively collected 127 patients from March 2005 to May 2007 who undertook perfusion CT. 61 patients were confirmed of pT1N0M0 or pT2N0M0 ccRCC. The mean follow-up time is 118.8 months (± 13.1 m, range 72–135 m). We compared clinical, pathological factors (gender, T stage, age, Fuhrmann grade, VEGF level, and MVD), and perfusion parameters before treatment [blood flow (BF), blood volume, mean transition time, and permeability surface-area product] between groups with post-nephrectomy metastasis and without metastasis. Association between covariates and progression-free survival (PFS) were analyzed using Cox proportional regression.

Results Among 61 patients, 11 developed distant metastasis (10 in the lung, one in the bone). BF in metastatic group [429.1 (233.8, 570.1) ml/min/100 g] was significantly higher than non-metastatic group [214.3 (153.3, 376.5) ml/min/100 g] ($p = 0.011$). Metastatic group also had more patients with higher Fuhrmann grade. Multi-covariant Cox regression demonstrated T staging, Fuhrmann grade, and BF were significantly associated with PFS [hazard ratio (HR) 3.35, 3.08, and 1.006]. In another model, BF > 230 ml/min/100 g was associated with PFS (HR 12.90), along with T staging and Fuhrmann grade (HR 4.73, 3.69).

Conclusion Baseline tumor BF is a potential biomarker in prediction long-term metastasis of localized ccRCC and may help screening for higher risk localized ccRCC patients who need personalized surveillance strategy after nephrectomy.

Keywords Renal cell carcinoma · Computed tomography · Perfusion · Prognosis · Blood flow

Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer. The rate of RCC in the United States has increased by 1.6% per year from year 2002 to 2011 [1]. There were an estimated 62,000 new cases of RCC in the United States in 2016 and 300,000 worldwide [2]. For localized RCC, surgery can be curative. However, recurrence is still the main cause of treatment failure and death from cancer. Five-year survival of localized RCC has increased to 91.8%, still over 20% of patients develop recurrence after curative surgery during long-term follow-up [1]. National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) both recommend up to 5 years' follow-up after surgery using chest and abdominal imaging [3, 4]. Relative short duration of follow-up has been criticized for its doubted ability to successfully capture RCC

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recurrences. A retrospective study of 3651 patients reported that NCCN and AUA guidelines would miss approximately one third of RCC recurrences (including local relapse and distant metastasis) even if strictly followed [5]. Another retrospective study of 1454 patients reported that patients who were disease-free for 5 years after surgery, 16% eventually developed recurrences [6]. On the other hand, more active surveillance would bring more health care cost and increase patients' radiation expose. Therefore, surveillance protocol based on improved risk stratification is needed [7]. Previous risk stratification is mainly based on TNM staging and pathological features such as Fuhrmann grade, tumor necrosis, and vascular invasion [8–11]. For radiologists, we aimed to find imaging signs and factors related with long-term prognosis. Perfusion computed tomography (CT) can non-invasively assess the tissue perfusion, especially in tumor. Clear cell renal cell carcinoma (ccRCC) accounts for 90% of RCC and has abundant vascularity. Thus imaging modalities, which can quantitatively assess the tumor vascularity, may be a useful tool. In metastatic RCC patients, several articles reported association between perfusion CT parameters and prognosis [12, 13]. In this study, we aimed to explore if perfusion CT parameters were suitable as potential pre-treatment biomarkers in predicting long-term progression-free survival of localized clear cell RCC.

Materials and methods

Patients' inclusion and follow-up

This study was a single-center retrospective study and was approved by the Institutional Review Board of Cancer Hospital. We collected 127 patients consecutively from March 2005 to May 2007 who were suspected of solid renal tumor and undertook kidney dynamic contrast-enhanced CT in our department. Among them, 73 patients were confirmed by surgical pathology with RCC (65 clear cell RCC, 5 chromophobe RCC, and 3 papillary RCC). For each patient, a thorough medical history was recorded. Other laboratory tests, chest CT, and other imaging (bone scan or brain MRI if clinical indicated) were performed before surgery to help determine the TNM stage. Surgical pathology and clinicians determined final pTNM staging. Among 65 ccRCC, 4 of them were proved to be locally advanced (T3) or metastatic, the rest 61 of them were T1 and T2 ccRCC. All these 61 patients received radical nephrectomy. None of the early stage ccRCC patients received neoadjuvant treatment before CT examination or surgery.

Patients were followed either in our hospital or in local hospital. We recorded all the following symptoms, lab results, imaging findings, and treatment after discharge through reviewing our medical records or questionnaire through telephone. Date of the last clinical follow-up was regarded as the end date of the follow-up. The mean follow-up time is 118.8 months (±13.1 m, range 72–135 m). Among 61 patients, 11 patients had distant metastasis (10 in the lung and 1 bone), 1 patient died of cardiovascular disease with no progression of the RCC, and the other 49 patients survived with no disease progression. Progression-free survival (PFS) was measured from the date when surgery was performed to end date or the death date. The protocol of follow-up was based on NCCN recommendation and the clinical practice in our hospital. Detailed follow-up protocol of every patient with metastasis was listed in Table 1 with PFS and metastatic site.

Perfusion CT technique and imaging data analysis

We used an 8-detector or a 16-detector CT scanner (LightSpeed Ultra, LightSpeed Pro16; GE Healthcare Technologies) to examine all the patients. To minimize motion artifact, a compression band was placed across the abdomen. And patients were trained to control breath during the scanning. For each patient, 50 mL of non-ionic contrast medium (Optiray 320, Tyco Healthcare, Canada) was injected at a rate of 4 ml/s. We used a cine mode acquisition (120 kV, 51 mAs, 36-cm scanning field of view, 512 × 512 mm matrix) to obtain four contiguous sections, each collimated to 5 mm at 1 s interval. Total scanning time was 50 s.

All perfusion CT scanning data were read by an experienced radiologist (14-year experience in body CT and 4-year experience in perfusion CT) using software (Kidney Protocol, Perfusion 3.0; GE Healthcare Technologies). We first selected a circular region of interest (ROI) within the abdominal aorta to define an arterial input. Then the tumor ROI was carefully depicted with portion of tumor necrosis, cyst, hemorrhage, and calcification component all excluded. For selected ROIs, the software automatically drew a tissue time-enhancement curve and generated four perfusion parameters [blood flow (BF), blood volume (BV), mean transition time (MTT), and permeability surface-area product (PS)].

Immunohistochemical staining and quantification of histologic parameters

Pathological examinations were done within a week after surgery. Quantification of microvascular density (MVD) was performed after immunostaining with a CD34 monoclonal antibody, according to Weidner's revised technique [14]. The most intensive area of tumor angiogenesis was found at 100 × FOV under the microscope. Then under the 400 × FOV, a pathologist counted the number of tumor vessels in six random areas and recorded the average number as MVD count. Two experienced pathologists independently

Table 1 Follow-up protocol and metastasis

Patient	Follow-up protocols	T staging	PFS (m)	Metastatic site
1	Routine protocol[a] within 5 years; then chest X-ray every year. Suspected X-ray finding was confirmed by chest CT	T1a	120	Lung
2	Routine protocol	T1a	22	Lung
3	Routine protocol	T1b	53	Lung
4	Routine protocol	T1b	36	Lung
5	Routine protocol	T1b	8	Lung
6	Routine protocol within 5 years; then chest CT every year. Metastasis confirmed by chest CT	T1b	75	Lung
7	Routine protocol within 5 years; then chest CT every year. Metastasis confirmed by chest CT	T2a	80	Lung
8	Routine protocol; presented with backache, then confirmed with bone scan	T2a	14	Bone
9	Routine protocol	T1a	20	Lung
10	Routine protocol	T1b	10	Lung
11	Routine protocol	T1a	10	Lung

For Stage I RCC After nephrectomy, PE and lab examinations every 6 month within first 2 years, then yearly thereafter to 5 years. Chest CT every year within 3 years. First abdominal CT within 3–12 months after surgery. If negative, abdominal CT every 1–2 years or symptom presented thereafter to 5 years. *For Stage II RCC* After nephrectomy, PE and lab examinations every 6 month within first 3 years, then yearly thereafter to 5 years. Chest CT every 6 months within 3 years, then yearly thereafter to 5 years. First abdominal CT within 3–6 months after surgery, then every 6 months within 3 year, then yearly thereafter to 5 years

[a]Routine protocol (based on NCCN recommendation)

counted the MVD and the mean value was recorded as the final MVD count.

Semiquantification of VEGF (vascular endothelial growth factor) expression was performed and scored as 0–3 according to the percentage of positive carcinoma cells with cytoplasmic staining [negative (0) < 5%, weak positive (+1) 5–25%, moderate positive (+2) 26–50%, and intense positive (+3) > 51%]. Two pathologists decided the VEGF score through discussion.

Statistical analyses

We divided the patients into two groups, patients with metastasis and without metastasis. Clinical and pathological characteristics of the two groups were described including gender, T stage, age, Fuhrmann grade, VEGF level, and MVD. Ratio of the perfusion parameters between the tumor and the normal cortex (the same side) were calculated and presented as rBF, rBV, rMTT, and rPS. Parameters were described as median (25%, 75% percentile).

First Kolmogorov–Smirnov test was used to test whether the variables have normal distribution. For parameters that have normal distribution (age, MVD, and perfusion parameters except MTT_T), *T* test was used to compare the differences between two groups. For categorical variables (T stage, Fuhrmann grade, VEGF) and parameters, which don't have normal distribution (MTT_T), Mann–Whiteny *U* test was used to compare two groups' differences. Uni-covariant Cox proportional regression was used to screen for candidate predictors. We chose factors with p value < 0.10 and included them into multi-variant Cox proportional regression model and calculated hazard ratio (HR). We plotted ROC (receiver operating characteristic) curve of BF for predicting long-term metastasis and determined cut-off value according to the sensitivity and specificity. BF higher than cut-off value was assigned 1, while, BF lower than cut-off value was assigned 0. We then included this binary variable into multi-variant Cox regression model instead of BF and calculated HRs. All statistical analysis was performed by SPSS 20.0 for Mac.

Results

Clinical and pathological features of the RCC patients

We followed the 61 patients with early stage clear cell RCC (ccRCC). The mean follow-up time is 118.8 months (± 13.1 m, range 72–135 m). The metastatic group accounted for 18.0% of all the patients. The mean PFS of the metastatic group is 27.5 months. We described the clinical and pathological characteristics of these patients and listed in Table 2. TNM stage, gender, age, follow-up time, tumor VEGF expression level, and tumor MVD showed no significant difference between the metastasis group and non-metastasis group. Only the distribution of Fuhrmann grade had significant difference between these two groups. The metastasis group had more patients with more advanced Fuhrmann grade.

Table 2 Clinical and pathological characteristics of ccRCC patients

Variables	Metastasis		*p* value
	No	Yes	
No. of patients	50	11	0.052
pT1a	31	4	
pT1b	17	5	
pT2a	2	2	
Male/female	35/15	8/3	0.932
Age (year) median (25%, 75% percentile)	50.0 (43.0, 57.5)	53.0 (48.0, 61.0)	0.147
Follow-up time (m) mean (±SD)	119.5 (±12.7)	114.1 (±15.7)	0.813
Fuhrmann grade (no. of grade 1/2/3/4)	13/27/8/2	1/4/5/1	0.024
VEGF expression (no. of 0/1/2/3)	24/21/4/2	5/3/3/0	0.708
MVD median (25%, 75% percentile)	46.4 (35.2, 58.1)	35.0 (29.6, 74.2)	0.936

Table 3 Perfusion parameters of ccRCC patients before treatment

Perfusion CT parameters[a]	Metastasis		*p* value
	No	Yes	
BF (ml/min/100 g)	214.3 (153.3, 376.5)	429.1 (233.8, 570.1)	0.011
rBF	0.5 (0.4, 0.8)	0.8 (0.5, 1.5)	0.042
BV (ml/100 g)	17.0 (12.4, 22.6)	16.0 (14.5, 28.8)	0.445
rBV	0.7 (0.5, 1.0)	0.8 (0.6, 1.3)	0.478
MTT(s)	5.9 (4.5, 10.2)	4.3 (3.3, 9.3)	0.115
rMTT	1.5 (1.0, 2.1)	1.1 (0.7, 1.5)	0.106
PS (ml/min/100 g)	29.3 (15.2, 37.5)	24.5 (19.5, 36.4)	0.940
rPS	0.5 (0.2, 0.6)	0.4 (0.3, 0.7)	0.956

[a]Values of parameters are described as median (25%, 75% percentile)

Perfusion CT parameters of ccRCC patients before treatment

We calculated perfusion parameters of the tumor (BF, BV, MTT, and PS) and the ratio between tumor and normal renal cortex (rBF, rBV, rMTT, and rPS), and summarized them in Table 3. BF of the tumor in metastasis group [429.1 (233.8, 570.1) ml/min/100 g] was significantly higher than non-metastasis group [214.3 (153.3, 376.5) ml/min/100 g] ($p=0.011$). rBF in metastasis group 0.8 (0.5, 1.5) was significantly higher than in non-metastasis group 0.5 (0.4, 0.8) ($p=0.042$). Rests of the perfusion parameters had no significant differences between two groups (Table 4).

The association of clinical, pathological and perfusion CT factors with prognosis

After uni-covariant Cox regression, T staging, Fuhrmann grade, and BF were included in multi-covariate Cox regression. The results showed that T staging, Fuhrmann grade, and BF of the tumor were significantly associated with PFS of localized ccRCC patients with the hazard ratio (HR) of 3.35, 3.08, and 1.006 (Table 3) in model 1. As BF value is a continuous variable, we transformed it into a binary variable 0 and 1. Cut-off value was determined by ROC curve of BF predicting long-term metastasis (Fig. 1). AUC was 0.75(0.60, 0.91) with $p=0.09$. Cut-off value was determined as 230 ml/min/100 g. BF230 was assigned 0 or 1 (0: BF ≤ 230 ml/min/100 g); 1: BF > 230 ml/min/100 g). Logrank test showed that survival faction had significant

Table 4 Cox proportional hazard regression model to assess association between covariates and PFS

Predictors	*p* value	Hazard ratio	95% CI	
			Lower	Upper
Model 1				
T staging	0.013	3.35	1.30	8.67
Fuhrmann	0.015	3.08	1.25	7.60
BF	0.003	1.006	1.002	1.010
Model 2				
T staging	0.006	4.73	1.56	14.31
Fuhrmann	0.015	3.67	1.36	9.86
BF230[a]	0.006	12.90	2.06	80.91

95% CI confidence interval

[a]BF230 was binary variable. (0: BF ≤ 230 ml/min/100 g; 1: BF > 230 ml/min/100 g)

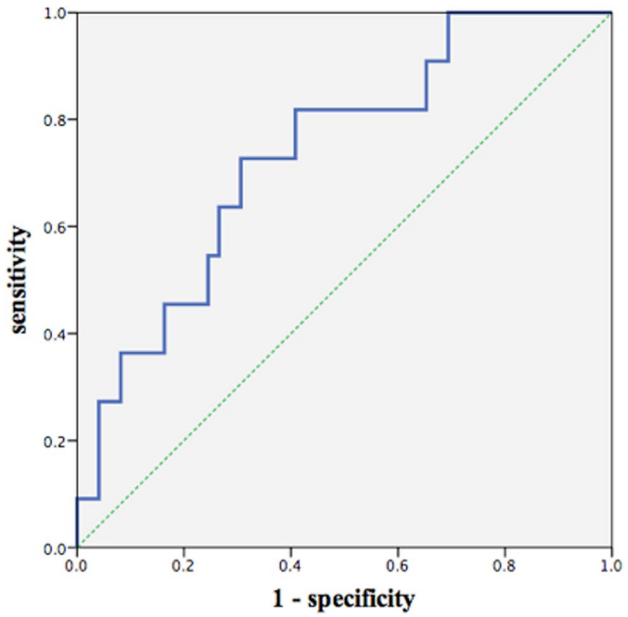

Fig. 1 ROC curve of BF for predicting long-term metastasis

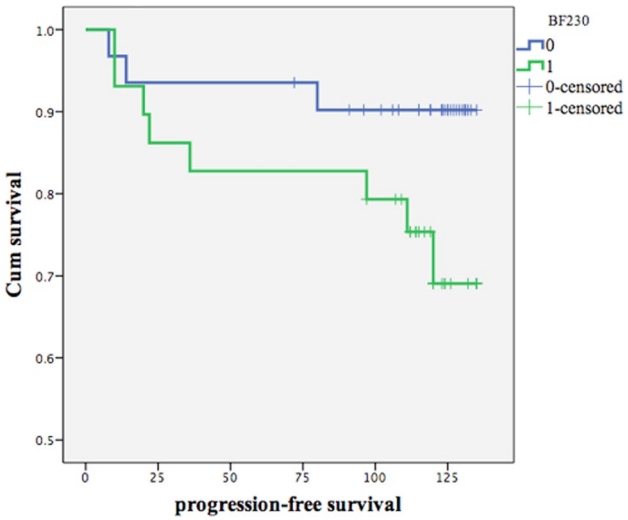

Fig. 2 Survival faction for different BF level

difference for BF value higher and lower than 230 ml/min/100 g ($p = 0.019$) (Fig. 2). Model 2 including T staging, Fuhrmann grade, and BF230 indicated three variables all strongly associated with PFS (HR 4.73, 3.69, and 12.90). Despite T staging and Fuhrmann grade, BF was associated with progression-free survival.

The hazard ratio calculated by Cox proportional regression was 1.006 for BF, which measured the risk when BF level increased by one unit (1 ml/min/100 g). For better understanding and clinical practical use, we transferred continuous BF level into binary variable according to ROC curve. BF higher than 230 ml/min/100 g showed strong association with progression-free survival, along with T staging and Fuhrmann grade. Previous study found that tumor BF were higher than normal renal cortex and significantly associated with pathological parameters of angiogenesis (MVD, VEGF) and Fuhrmann grade, indirectly showing the association of the perfusion parameters with the tumor biology [15, 16]. Our study first used long-term follow-up data of localized ccRCC to establish the relationship between perfusion CT parameters with metastasis after nephrectomy. The results provided direct evidence that BF derived from perfusion CT can be a potential biomarker in prediction of long-term prognosis and can be complementary to the current risk stratification of localized RCC surveillance after nephrectomy.

Majority of the RCC prognostic predictive models (such as Heng's, Motzer's, etc.) focused mainly on locally advanced or metastatic RCC (mRCC) [17, 18]. Few models concerning non-metastatic RCC only included clinical and pathologic factors like tumor size, TNM staging, and Fuhrmann grade [8–11, 19]. In previous studies concerning the predictive value of pre-treatment imaging, perfusion CT was associated with targeted therapy response and survival of metastatic RCC by non-invasively evaluating tumor's angiogenesis. Baseline tumor BF was reported to be inversely associated with progression-free survival in mRCC patients receiving targeted therapy [12, 13, 20, 21]. But there's no study concerning localized RCC. Other imaging modalities, such as dynamic contrast enhancing magnetic resonance (DCE-MRI) and DCE-Ultrasound (US), can also quantitatively assess tumor angiogenesis, and were reported to be valuable in predicting treatment response and tumor prognosis [22–24]. Comparing with other imaging techniques, abdominal perfusion CT is easier to operate and more standardized than DCE-MRI and DCE-US. For patients, the scanning time is short and it's easier to cooperate. The decrease of dose by recent technical progression would partially reduce the concerning in radiation exposure [25].

We also examined the association between tissue VEGF expression level and MVD with prognosis. Previously one of the most reliable methods for assessing vascularity and angiogenesis in a tumor is by measuring the mean vascular density. MVD and serum level of VEGF was reported to associate with tumor staging and Fuhrmann grade [26–29]. But the role of MVD and tissue VEGF expression in predicting localized RCC prognosis is still unclear. Our follow-up

Discussion

Our study indicated that baseline BF derived from perfusion CT of localized clear cell renal cell carcinoma was significantly higher in metastatic patients after nephrectomy.

data showed neither MVD nor VEGF has association with post-surgery metastasis in localized RCC. We speculated that tumor's high vascularity associating with prognosis might not show in the post-surgery pathology through the way of MVD or up-expression of VEGF.

Long-term follow-up is another characteristic in our study. The mean follow-up time reached nearly 10 years, which is rarely seen in kidney tumor studies. Our hospital monitored the patients based on NCCN guidelines and used chest CT to avoid missing lung metastasis. The duration of surveillance after nephrectomy is undetermined. It is not practical for clinicians to follow-up all the patients using chest CT yearly after 3 or 5 years of routine surveillance. Our study preliminarily indicated the value of baseline perfusion CT in risk stratification of localized RCC. More personalized surveillance protocols should be considered for this special group of patients.

Our study had several limitations. Because of the retrospective nature of the methodology, unknown selection bias may have affected the results. Similarly, the relative small sample size would cause selection bias and also affect the ratio of long-term metastasis. However, in the clinical situation, due to relatively good prognosis it is very difficult to gather a larger group of patients who undertook perfusion CT before surgery and followed strict follow-up procedure in 10 years. Thus the data from this group of patients were still very valuable. Thirdly, due to tumor biology, the ratio of the metastatic group is relatively low, causing bias in multivariant Cox proportional regression analysis. Fourthly, the selection of ROI and the analysis of perfusion parameters derived were influenced by the radiologists' experiences. Above all, from the cohort with relatively small sample size, our results were still preliminary, thus need further validation in larger cohort.

Conclusion

In conclusion, baseline tumor BF measured by perfusion CT, quantitatively evaluating tumor's angiogenesis, was associated with long-term metastasis of localized clear cell renal cell carcinoma along with T staging and Fuhrmann grade. Perfusion CT parameters may be a potential biomarker in prediction long-term prognosis of localized ccRCC and may help screening for higher risk localized ccRCC patients who need more intensive monitoring even after curative surgery.

Clinical practice points

During long-term follow-up, over 20% of renal cell carcinoma patients develop recurrence after curative surgery. Post-surgery surveillance strategy is controversial. Previous risk stratification is mainly based on TNM staging and pathological features such as Fuhrmann grade, tumor necrosis, and vascular invasion.

Our study in the first time used long-term follow-up data to demonstrate the relationship between baseline tumor perfusion and long-term metastasis. Blood flow of the tumor significantly correlated with metastasis. BF higher than 230 ml/min/100 g showed strong association with progression-free survival, along with T staging and Fuhrmann grade.

This finding preliminarily indicated that baseline tumor perfusion measured by perfusion CT may be of potential use in screening for patients with higher risk of recurrence. Baseline imaging parameters should be considered to make a more personalized and improved post-surgery follow-up protocol.

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