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ORIGINAL RESEARCH

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A comparative study of tumor markers and dynamic contrast-enhanced CT and their combined evaluation in the diagnosis of renal cancer patients

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Abstract

The objectives of this study were to investigate the diagnostic efficacy of dynamic contrast-enhanced Computed Tomography (CT) and tumor markers and their combined evaluation in renal cancer patients. A total of eighty male patients with solid renal lesions were selected from our hospital and categorized into two groups based on pathological examination findings: renal cancer group and benign lesion group. A comparison was made between the findings of dynamic contrast-enhanced CT and tumor markers and the diagnostic efficacy of either mono or combined evaluation were compared. Receiver operating characteristic curves were plotted to better analyze and compare different diagnostic techniques. The serum concentrations of carcinoembryonic antigen (CEA), Cytokeratin 19 fragment (CYFRA21-1), midkine (MK) and matrix metalloproteinase 9 (MMP-9) in renal cancer patients were significantly higher than those with benign lesions ($p < 0.05$). The Receiver Operating Characteristic (ROC) curve analysis demonstrated that the combination of dynamic contrast-enhanced CT and tumor markers had the highest area under the curve. This difference was statistically significant ($p < 0.05$). The analysis of the overall model quality results revealed that the model values for both single and combination indicators exceeded 0.5, with the combined indicators having the highest value of (0.84). The diagnostic efficacy of dynamic contrast-enhanced CT combined with tumor markers for renal cancer is significantly higher than either the dynamic contrast-enhanced CT or tumor markers alone. The combination of dynamic contrast-enhanced CT and tumor markers has a significant therapeutic benefit in diagnosing renal cancer. We envisage that, this approach can offer valuable guidance for the clinical diagnosis and treatment of renal cancer.

Keywords

Dynamic contrast-enhanced CT; Tumor markers; Combined examination; Renal cancer; Diagnostic efficacy

1. Introduction

Renal cancer is a malignant tumor that develops from the epithelial system of uriniferous tubule in renal parenchyma. Early symptoms include hematuria, low back pain, and abdominal mass, however, these symptoms are generally subtle and do not draw patients' attention. As the disease advances to the middle and late stages, there is aggravated hematuria, increased pain, mass enlargement and other symptoms. Before any measured could be taken, the patient's renal function may have already significantly compromised. Other organs will also be severely affected if cancer cell metastasis occurs [1–3]. The primary treatments for renal cancer at the present medical level are immunotherapy, targeted therapy and surgical treatment. Close attention, regular return visits, observation and follow-up are all that is necessary for patients with benign lesions. In order to guarantee the quality of life of patients with renal cancer, active intervention is necessary in the aforementioned treatment modalities. Consequently, the early detection of renal cancer lesions and the subsequent treatment are contingent upon timely and effective screening and diagnosis.

At present, renal cancer is typically diagnosed through pathological examination. Despite its status as the "gold standard" for the diagnosis of renal cancer, its invasive nature causes pain and bleeding in patients [4, 5]. Dynamic contrast-enhanced CT has become increasingly important in the diagnosis of renal cancer in recent years. It is easier for an attending physician to detect renal cancer lesions when the tumor size, shape, location and relationship with the surrounding tissues are clearly displayed [6]. Dynamic Contrast Enhanced Computed Tomography (DCE-CT) is an advanced CT imaging technique that assesses hemodynamic properties in tissues by performing multiple sequential scans

of the same anatomical region after the injection of a contrast agent. The main differences between DCE-CT and CE-CT (Contrast Enhanced Computed Tomography), are the scanning modality and the time of information gathering. DCE-CT provides dynamic flow information, while CE-CT delivers enhanced images at a single time point. Tumor marker detection in clinical biochemistry is a convenient and dynamic tool that can provide more accurate indications in the early stages of renal cancer. It can also be used in conjunction with other methods to enhance diagnostic accuracy [7].

Well-known clinical tumor markers including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), midkine (MK) and matrix metalloproteinase-9 (MMP-9) have varying levels of importance in diagnosing renal cancer due to their distinct roles and properties. CEA is a broad-spectrum tumor marker and may be elevated in a variety of malignant tumors. In renal cancer, CEA is not highly specific for the diagnosis of renal cancer, but if CEA is significantly elevated in patients with renal cancer, it may indicate tumor progression or metastasis. CYFRA21-1 is mainly used for the diagnosis of tumors such as lung cancer, and its level may be elevated in some cases of renal cancer. However, it is important to note that CYFRA21-1 does not possess adequate specificity. MK is a cytokine with pro-angiogenic effects. The expression level of MK is typically elevated in renal carcinoma, which can potentially provide further diagnostic value, particularly in early diagnosis.

MMP-9 possesses the ability to degrade extracellular matrix and promote tumor invasion and metastasis. Renal cancer tissues often exhibit elevated expression of MMP-9, and measuring its level can be useful in evaluating the malignancy and invasive potential of renal cancer. Nevertheless, the diagnostic accuracy of using only MMP-9 to detect renal cancer is limited. However, the existing clinical practice experience lacks a substantial number of reports and research regarding the identification of renal cancer using dynamic contrast-enhanced CT in conjunction with tumor marker detection [8–10]. Its diagnostic efficacy warrants further study and verification. This study aims to investigate the differences in the diagnostic efficacy of dynamic contrast-enhanced CT and tumor markers and their combined evaluation in renal cancer patients.

2. Materials and methods

2.1 Study subjects

A total of eighty male patients with solid renal lesions were retrospectively analysed at our hospital. Fifty-five patients diagnosed with renal cancer and twenty-five patients with benign renal dosease were analysed based on their pathological type.

2.1.1 Inclusion criteria

1. Patients who met the relevant diagnostic criteria for renal cancer via pathological (biopsy) examination;
2. Patients without contraindications for dynamic contrast-enhanced CT examination;
3. Patients age exceeded 18 years;
4. Completed clinical imaging data and signed informed consent;
5. All signed informed consent forms.

2.1.2 Exclusion criteria

1. Patients with heart, liver, kidney and other system dysfunction;
2. Patients who are pregnant or lactating;
3. Patients with psychological disorders;
4. Patients with allergy to contrast agents.

2.2 Methods

2.2.1 Dynamic contrast-enhanced CT examination

Prior to the examination, all patients were instructed to abstain from drinking and fasting for a period of 6 hours. Additionally, any metal objects were removed from the examination area, and patients were required to remain a supine position. SOMATOM Force (Dual Source CT Force, Siemens Medical Systems Co., Ltd., Beijing, China) was utilized to perform CT plain and enhanced scans of both kidneys of the patients.

Plain scan sequence were as follows: Axial fast spin echo-T2, weighted imaging-T2, weighted imaging (FSE-T2WI/T2WI) (interslice distance: 2 mm, slice thickness: 6 mm, echo time (TE): 1610 ms, inversion time (TI): 500 ms, field of view (FOV): 32 cm × 32 cm, matrix: 352 × 192); axial FSE-T2WI/T2WI (interslice distance: 2 mm, slice thickness: 6 mm, TE: 68 ms, repetition time (TR): 6000 ms, FOV: 24 cm × 24 cm, matrix: 320 × 256); transverse digital elevation model interpolation TR (DEI) (interslice distance: 1 mm, slice thickness: 4 mm, FOV: 42 cm × 130 cm, matrix: 96 × 130 cm, matrix: 1000 s/mm^2); The interslice distance and slice thickness of FSE-T2WI in sagittal view were 2 mm and 6 mm, respectively. TI: 72 ms, TR: 4500 ms, FOV: 28 cm × 28 cm, matrix: 320 × 320); three-phase dynamic enhancement (slice thickness: 4 mm, FOV: 38 cm × 37 cm, matrix: 320 × 224) in axial view; LAVA FLex enhancement (slice thickness: 4 mm, FOV: 28 cm × 28 cm, matrix: 320 × 224) in coronal and sagittal view.

Contrast-enhanced scanning was conducted, with the contrast agent administered intravenously via the patient's elbow. The medicine chosen was iohexol (manufactured by Yangtze River Pharmaceutical Group Co., Ltd., with state medical permit number H20065897, 300 mgI/mL, Taizhou, Jiangsu, China). The drug was administered at a rate of 2 to 3 mL/s and an injection volume of 70 to 100 mL. Contrast-enhanced scanning parameters were as follows: A continuous multi-phase non-interval scanning technique called Three-Dimensional Fast Low Angle Shot (3D-FLASH) was used. The specific parameters were: slice thickness: 2 mm, TE: 1~4 ms, TR: 4~8 ms, flip angle: 13°, matrix: 400 × 260, FOV: 40 cm × 40 cm, Number of Excitations (NEX): 1.

2.2.2 Tumor marker detection

Fasting venous blood was collected from patients at 3 to 5 mm. The collected blood was centrifuged using a centrifuge, and the upper serum was collected for tumor marker detection. The levels of CEA, CYFRA21-1, MK, MMP-9 and other

markers were detected by chemiluminescence and enzyme-linked immunosorbent assay, respectively.

2.3 Outcome measures

A comparison was made between the outcomes of dynamic contrast-enhanced CT scan and tumour marker detection, as well as a combined evaluation of the two. The pathological investigation results confirmed the accuracy of the diagnosis. In addition, dynamic contrast-enhanced CT test results were counted, and diagnostic efficacy was analyzed, which mainly included sensitivity, specificity, accuracy, positive predictive value, negative predictive value. To compare the detection levels of tumor markers in patients with renal cancer and benign lesions, changes in the levels CEA, CYFRA21-1, MK and MMP-9 levels were compared between the two groups. In order to analyze the diagnostic efficacy of tumor marker detection for renal cancer and analyze the diagnostic efficacy of dynamic contrast-enhanced CT combined with tumor markers for renal cancer, sensitivity, specificity, accuracy, positive predictive value and negative predictive value test was done. Receiver operating characteristic curve (ROC) was utilized to evaluate the diagnostic precision.

2.4 Data processing and statistical analysis

Data were analyzed and processed using SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA). Measured data were expressed as ($\bar{x} \pm$ s) and compared using *t*-test. Enumeration data were expressed as cases (%) and compared using χ^2 (chi-squared) test. $p < 0.05$ indicated statistically significant difference.

ROC (receiver operating characteristic curve) was plotted using SPSS to further compare the differences between the two diagnostic methods.

3. Results

3.1 Pathological examination

Out of the 55 patients with renal cancer, 9 had papillary renal cell carcinoma, 39 had renal clear cell carcinoma, and 7 had chromophobe renal cell carcinoma. Among the 25 patients with benign lesions, 8 had renal eosinophilic adenoma and 17 had angiomyolipoma with minimal fat (mfAML).

3.2 Comparison of tumor marker levels between patients with renal cancer and benign lesions

The serum levels of CEA, CYFRA21-1, MK and MMP-9 in patients with renal cancer were strikingly higher than that in patients with benign lesions ($p < 0.05$). The results are shown in Table 1.

3.3 Diagnostic value of combined diagnosis of tumor markers for renal cancer

The ROC curve showed that the area under the ROC curve for the combined diagnosis of the four indicators were 0.801 (95% CI: 0.680–0.923). The results are displayed in Table 2.

3.4 Comparison of the coincidence of the three diagnostic results with the pathological results and the diagnostic efficacy

The specificity, accuracy and positive predictive value of the combined examination were higher than that of the single examination, but the difference was not statistically significant ($p > 0.05$). The results are presented in Table 3.

TABLE 1. Comparison of serum tumor markers between renal cancer and benign lesions ($\bar{x} \pm$ s).

Group	Case	CEA (μg/L)	CYFRA21-1 (μg/L)	MK (ng/L)	MMP-9 (pg/mL)
Renal cancer	55	4.05 ± 0.76	3.83 ± 0.65	58.98 ± 7.65	388.35 ± 56.26
Benign lesions	25	2.80 ± 1.11	2.51 ± 1.31	47.87 ± 13.57	259.49 ± 121.25
t value	—	5.799	6.027	4.669	6.519
p value	—	*p*< 0.001	*p* < 0.001	*p* < 0.001	*p* < 0.001

CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19 fragment; MK: midkine; MMP-9: matrix metalloproteinase-9.

TABLE 2. Combined diagnosis of tumor markers in renal cancer.

Diagnostic indicators	AUC	Standard error	Asymptotic significance	Critical value	Asymptotic 95% confidence interval	
					Lower limit	Upper limit
CEA	0.824	0.060	0.000	3.485	0.706	0.942
CYFRA21-1	0.778	0.067	0.000	2.480	0.648	0.909
MK	0.745	0.071	0.001	43.510	0.606	0.885
MMP-9	0.773	0.064	0.000	203.455	0.648	0.898
Combined	0.801	0.062	0.000	0.361	0.680	0.923

CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19 fragment; MK: midkine; MMP-9: matrix metalloproteinase-9; AUC: Area Under Curve.

TABLE 3. Comparison of diagnostic efficacy indicators of the three test methods (%).

Method	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Dynamic contrast-enhanced CT	94.55	76.00	88.75	89.66	86.36
Tumor marker detection	100.00	60.00	87.50	84.62	100.00
Combined	94.55	88.00	92.50	94.55	88.00

CT: Computed Tomography.

3.5 ROC curve analysis results

It showed that the area under ROC curve of combined diagnosis of the two was the largest, and the difference was statistically significant ($p < 0.05$), suggesting that the combined diagnosis yielded the most favorable outcome. The results are shown in Table 4 and Fig. 1.

3.6 Overall model quality

The analysis of the overall model quality results indicated that both the single indicator and combined indicators had values greater than 0.5. This demonstrates that the three diagnostic approaches had a high diagnostic value for renal cancer. Out of all the indicators, the combined indicators have the highest model value, indicating their superior predictive value. The result is displayed in Fig. 2.

4. Discussion

Renal cancer is a malignancy that arises from renal cells, with renal cell carcinoma being the predominant form of renal cancer. The prevalence of renal cancer has significantly risen on a global scale. Global figures indicate an annual incidence of approximately 400,000 to 500,000 new cases, accounting for 2% to 3% of all malignant tumors [11–13]. The pathological manifestations of renal cancer are diverse, encompassing papillary renal cancer, collecting duct carcinoma and benign renal tumor. These can be distinguished and diagnosed through needle biopsy and surgical pathological biopsy. Nevertheless, these two techniques are intrusive, hence causing a discernible effect on the patient's physique [14]. Due to advancements in imaging technology and clinical biochemistry, CT scans and tumour marker detection have increasingly become viable alternatives [15, 16]. The former can comprehensively master the location, size, shape and other information of the tumor. This method is highly valuable in the process of diagnosing the tumour [17, 18]. The latter has convenience, dynamics and cooperativity and can make a more accurate prompt in the early stage of renal cancer. Additionally, it can serve as a supplementary tool to enhance the diagnostic efficacy and proficiency [19]. Currently, there is a lack of extensive research and practical knowledge on the identification and diagnosis of renal cancer patients utilizing dynamic contrast-enhanced CT conjunction with tumour marker detection. Furthermore, there is no established consensus or standardized protocol in this regard. Hence, this study scrutinizes and deliberates on this problem.

The results showed that the specificity, accuracy and positive predictive value of dynamic contrast-enhanced CT combined with tumor markers were higher than that of single examination, but the difference was not statistically significant ($p > 0.05$). The findings of this study are partially incongruent with existing literature and can be attributed to the limited sample size of this study. Upon conducting additional research, we discovered that dynamic contrast-enhanced CT possesses specific diagnostic significance in distinguishing renal cancer from benign lesions [20, 21]. The dynamic contrast-enhanced CT scan is effective in highlighting the abundant blood supply characteristics of renal cancer, which are less prominent in benign lesions Following the injection of contrast agent, renal cancer shows a higher degree of enhancement with obvious characteristics, whereas benign lesions exhibit a relatively lower degree of enhancement with no clear pattern [22]. In terms of the time-density curve performance, renal cancer demonstrates a rapid increase, followed by a stable and gradual decrease, which is distinct from the slow increase, lack of plateau, and faster decrease observed in benign lesions [23].

The results showed that the serum levels of CEA, CYFRA21-1, MK and MMP-9 in patients with renal cancer were significantly elevated in patients with renal cancer compared to patients with benign lesions ($p < 0.05$). This result suggests that tumor markers have diagnostic value in differentiating renal cancer from benign lesions. CEA is a type of glycoprotein that is generated during the growth of an embryo and is seen in extremely small quantities in the blood after birth. It is raised in certain individuals with cancer and is frequently employed for the detection and tracking of colorectal cancer. Additionally, it has the capability to

TABLE 4. ROC curve analysis results.

Indicators	AUC	Standard error	p value	95% confidence interval	
				Lower limit	Upper limit
Tumor marker detection	0.800	0.050	$p < 0.001$	0.702	0.898
Dynamic contrast-enhanced CT	0.853	0.046	$p < 0.001$	0.762	0.943
Combined	0.913	0.037	$p < 0.001$	0.841	0.984

CT: Computed Tomography; AUC: Area Under Curve.

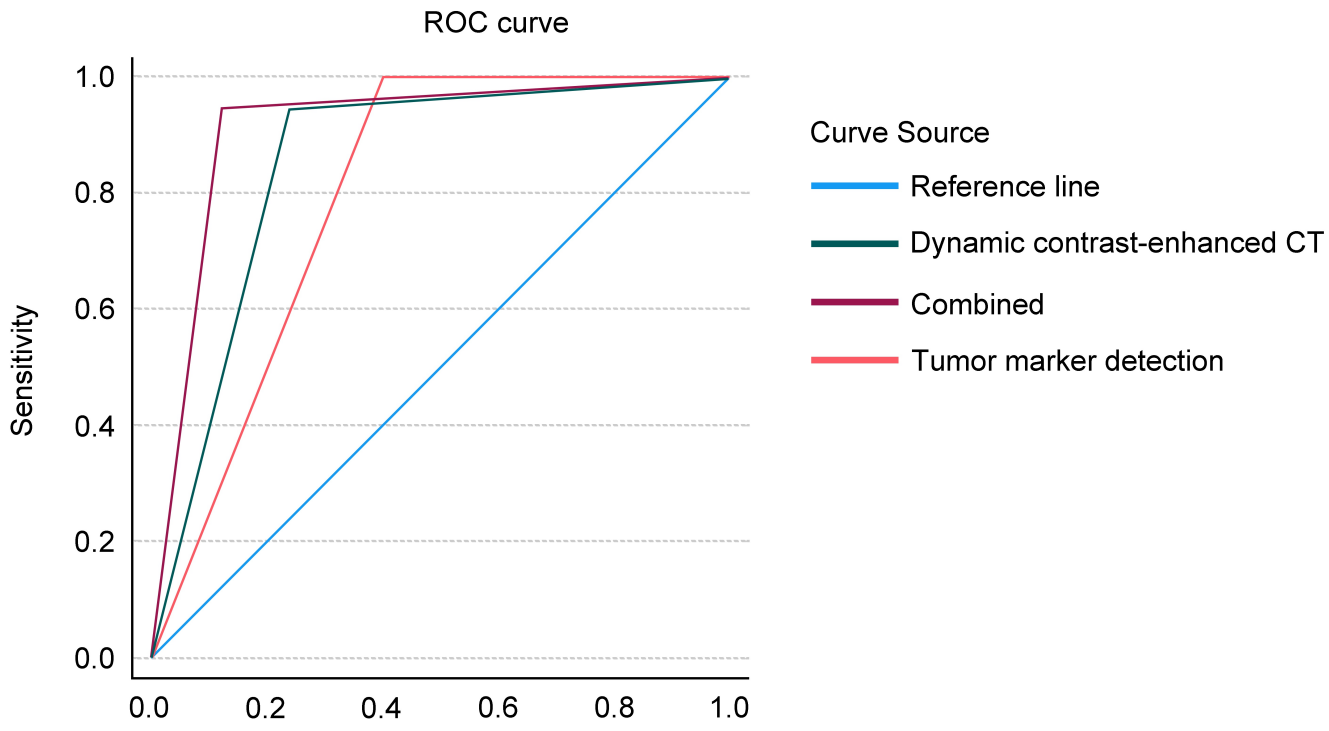

FIGURE 1. ROC curve analysis plot. ROC: Receiver operating characteristic curve; CT: Computed Tomography.

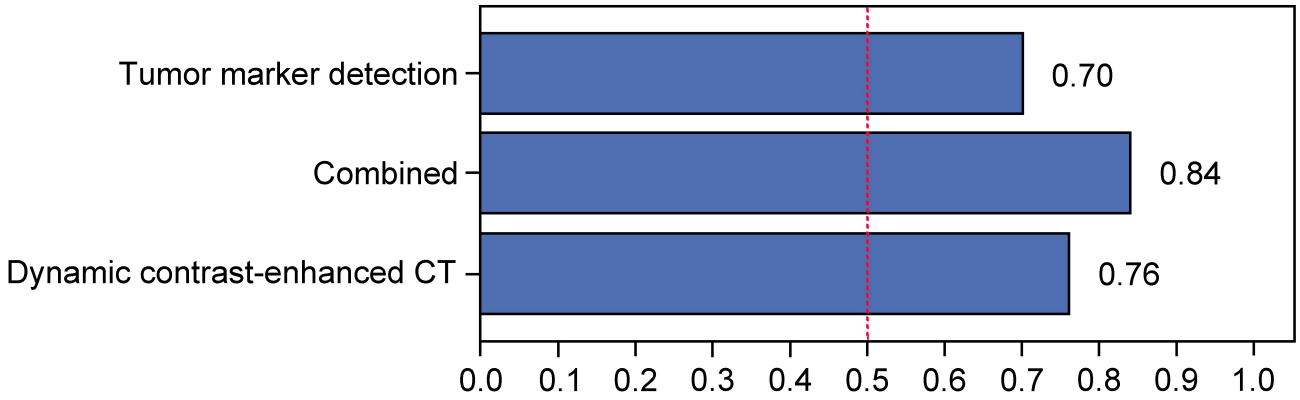

FIGURE 2. Overall model quality chart. CT: Computed Tomography.

identify various forms of cancer, including kidney, lung, stomach and breast cancer [24]; MK is a growth factor involved in cell proliferation, migration and survival of cells. It is up-regulated in a variety of tumors and correlates with tumor aggressiveness and metastatic ability. MK can serve as a poor indicator of cancer prognosis. As a midkine, it can regulate macrophage activity and express the degree of kidney-associated system dysfunction with high levels in the tumor state [25]. CYFRA21-1 on the other hand is a soluble fragment of cytokeratin 19 mainly used to detect non-small cell lung cancer (NSCLC). Elevated levels are often associated with disease progression and poor prognosis in lung cancer patients. When kidney cancer develops, degradation products of cytokeratin 19 increase, raising their levels in the blood [26, 27]. As an enzyme capable of degrading extracellular matrix components, MMP-9 can promote tumor cell invasion and metastasis. High levels of MMP-9 are associated with cancer aggressiveness and metastatic ability. MMP-9 is able to degrade the extracellular matrix and promote invasion and metastasis of tumor cells, and its increased level is indicative of deteriorating renal cancer [28].

The combined diagnosis of the two showed the highest area under the ROC curve and a statistically significant difference ($p < 0.05$) in terms of the overall model quality results. The combined indicators' model value was also the largest. This result indicates that the integration of the DCE-CT and tumor markers showed the best diagnostic effect and the highest predictive value. While tumour markers can represent the activity of tumour cells *in vivo*, dynamic contrast-enhanced CT scans can clearly display the shape, size, location and

other features of renal lesions, hence combination diagnosis is proposed to have some benefits over single diagnosis. When combined examination is conducted, the two can complement and validate each other. Tumour markers can further provide auxiliary information and enhance diagnostic accuracy when dynamic contrast-enhanced CT identifies worrisome lesions; at the same time, aberrant tumour markers can also prompt physicians to undergo additional imaging examination to prevent missed diagnosis. The results and conclusion we had is consistent with those reported in the relevant literature [24–28].

The advantages of dynamic contrast-enhanced CT combined with tumor markers are as follows: (1) Comprehensive evaluation: dynamic contrast-enhanced CT provides high-resolution images about tumor morphology, size, location and vascular supply, while tumor markers provide biological information of tumor cells, such as cell differentiation, proliferative activity and metabolic status. By combining these two types of information, physicians can perform a more comprehensive tumor assessment, thereby better understanding the nature and behavior of the tumor. (2) Improving specificity: the combination of dynamic contrast-enhanced CT and tumor markers can promote the specificity of tumor diagnosis. CT images provide direct tumor morphological information, while tumor markers provide tumor cell-specific biological markers. The integration of the two can reduce the incidence of false positive results and thus improve the specificity of diagnosis. (3) Early diagnosis and prognostic evaluation: tumor markers can be detected in the early stages of the tumor, even before the tumor is visible on imaging. Therefore, the combined use of these two can upgrade the diagnostic ability for early tumors and help physicians perform therapeutic interventions earlier. In addition, changes in tumor markers can also be used to monitor treatment outcomes and predict patient outcomes. (4) Individualized treatment strategy: the combined use of dynamic contrast-enhanced CT and tumor markers can also help physicians to develop individualized treatment strategies. According to the imaging characteristics and biological markers of the tumor, physicians can select the most appropriate treatment options for patients, such as surgery, radiotherapy, chemotherapy or targeted therapy, thereby maximizing the therapeutic effect and reducing treatment-related risks and side effects [29, 30].

The main limitations of this study are the small number of patients included, which hinders the ability to statistically analyze and generalize the results. The small sample size may lead to random outcomes, limiting the applicability of the findings to the overall population. The small sample size is primarily due to two factors. Firstly, the use of DCE-CT requires multiple scans in a short period, resulting in higher radiation exposure for patients. Secondly, DCE-CT necessitates a large amount of contrast agent, which may pose additional risks to certain patients, particularly those with renal insufficiency. Additionally, this study was conducted at a single center, limiting the representativeness of the results. In the future, larger, multicenter, prospectively designed studies will be conducted to validate and further confirm the findings presented in this study.

5. Conclusions

In summary, the diagnostic efficacy of dynamic contrast-enhanced CT combined with tumor markers for renal cancer is significantly higher than using dynamic contrast-enhanced CT or tumor markers alone. The clinical application value of dynamic contrast-enhanced CT combined with tumor markers is high, which can provide guidance for the clinical diagnosis and treatment of renal cancer.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

XFW, MHY—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. XFW, PPH, MHY—supervised the data collection; analyzed the data; XFW, PPH—interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Ningbo Yinzhou No.2 Hospital (Approval no. 2023024). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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