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Dual-energy spectral CT in renal cell carcinoma: dawn of a brand-new era?

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1. Introduction

Renal cell carcinoma (RCC) is one of the most common cancers worldwide [1], and clear cell histological subtype represents approximately 75-80% of all cases, followed by papillary RCC (10-15%) and chromophobe RCC (5%) [2]. Over the past three decades, mortality rate has constantly declined in view of the advent of several novel therapeutic strategy, such as tyrosine kinase inhibitors (TKIs), immunotherapy and the combination of both (immune combinations) [2]. Conversely, an increased incidence due to the large use of computed tomography (CT) and ultrasound has been reported [2].

CT with contrast represents the cornerstone for diagnosis and treatment monitoring, but standard CT may only provide data about dimension, morphology, and contrast uptake of RCC lesions [3]. Response to therapy is routinely assessed on CT scans with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. These criteria only take into account size, without considering biologic modifications of disease sites. However, immunotherapy and antiangiogenic TKIs may cause necrosis and colliquation without a reduction in size, suggesting that their role in monitoring the response to these modern therapies should be reconsidered [3,4]. According to that, an emerging field of research, involving radiomic, wants to validate new diagnostic imaging able to overcome these limitations.

2. The promise of dual-energy spectral CT in RCC diagnosis

Recently, a new CT technology, called ”dual-energy”, represents a significant advancement in radiological imaging. Three main techniques allow for dual-energy imaging: "dual-source," "rapid kilovolt peak switching," and "spectral dual-layer" [5, 6]. This technology guarantees a rapid acquisition of images at two different X-ray energies, facilitating the identification of features specific to tissues or materials, the measurement of contrast uptake and the computation of virtual unenhanced images. As a result, tumors can be described and tracked for any alterations throughout the course of oncological therapies [6].

In particular, dual-energy spectral CT (DECT) may be a useful diagnostic tool in RCC, in view of its ability to detect and analyze the vascularization, which is a prominent feature of this kind of cancer (Figure 1.) The potential role as surrogates of vascularization of two spectral-derived parameters, iodine concentration (IC, expressed as mg/ml) and the effective atomic number (Zeffective, expressed as pure number), has already emerged in previous analysis [7,8,9]. In the last years, the utility of DECT has been demonstrated in several setting.

First, DECT proved its diagnostic ability of discriminating between low-grade and high-grade clear cell RCC, as reported in two retrospective Chinese studies [10,11]. Thus, spectral CT may help the pathologists to improve the accuracy in differentiating the WHO/ISUP pathological grading. Another retrospective analysis, in addition to confirming the ability of DECT to differentiate RCC grading, revealed that iodine quantification with dual-energy CT can be exploited to distinguish between clear cell and papillary RCC in a noninvasively way. The tumor IC of 0.9 mg/mL was found to be the optimal cut-off, with a sensitivity of 98.2% (95% CI: 97.7%-98.7%) and a specificity of 86.3% (95% CI: 85.0%-87.7%) [12].

Interestingly, the use of low MonoEnergetic images with DECT, by enhancing the attenuation of iodine, permits to reduce the amount of contrast administered, maintaining a good image quality and decreasing the radiation dose, if compared to conventional multiphasic CT that could require multiple contrast medium administrations [13].

These advantages could be meaningful in patients with compromised renal function, a common condition in subjects underwent nephrectomy for RCC.

Another plus of MonoEnergetic images with DECT consists of reducing metal artifacts, especially during CT-guided interventions, allowing an easier and more correct execution of the procedures [14]. In fact, the high MonoEnergetic (160 keV) images in post-processing analysis may limit these artifacts, also improving probe visualization during radiological interventions. Moreover, DECT could be used to evaluate the iodine concentration of cancer lesions before and after locoregional approach, as ablation, to assess the success of the ~~intervention~~ procedure [14].

A valuable insight on the potential utility of DECT emerged from a retrospective study that suggest the ability of this CT in discriminating the origin of pulmonary metastases based on IC, thus presenting the latter as a promising imaging biomarker [15].

All these features of DECT make it a superior method for the evaluation and management of RCC compared to conventional CT, suggesting that its adoption worldwide should be promoted.

3. The prognostic and predictive role of DECT in metastatic RCC: a light in the dark

Recently, several studies have begun to highlight the role of IC and Zeffective as predictive biomarkers of response and as prognostic indicators of improved outcomes in patients with metastatic RCC [4,7]. Specifically, a study published in 2022 demonstrated that, in unselected mRCC patients with respect to previous treatments received, the early reduction in IC and Zeffective one month after the initiation of treatment with immune checkpoint inhibitors or TKIs are independent prognostic factors of better overall survival and predictive biomarkers of better objective response [7]. The same analysis further indicated that clear cell RCC patients present higher baseline IC and Zeffective compared to non-clear cell subtypes, but their variation between baseline and reassessment at one month resulted to be independent of histology [7]. Another prospective study by the same group confirmed the potential role of spectral-derived parameters at baseline as independent prognostic factors in advanced-stage RCC [4]. Specifically, patients with metastatic RCC treated with TKIs or immune checkpoint inhibitors were included and underwent dual-energy spectral CT within 2 days of starting systemic therapy and subsequently during treatment. The results showed that patients characterized at baseline scans by higher IC and a greater Zeffective exhibited a better objective response to treatment received (OR 4.35, $p = 0.001$), improved progression-free survival (HR 0.51, $p = 0.004$), and increased overall survival (HR 0.37, $p < 0.001$), compared to those patients with lower baseline values [4]. This association between high IC and Zeffective and greater benefits in survival and response to therapies also appears to be independent of the treatment received and the baseline characteristics of the patients, such as the IMDC risk score [4]. Of note, an Italian prospective study financed by the Ministry of Health is currently investigating the predictive and prognostic role of spectral-derived parameters in RCC patients treated with first-line immune combinations, the actual standard of care in first-line setting. New data could also emerge from the correlation of these parameters with patient's molecular profile (RC-2024-2790617).

4. Expert Opinion:

In RCC evaluation, new radiological techniques are a clinical necessity that remains unresolved. As stated above, conventional contrast CT could have some limitations, while other instrumental technique, as Positron Emission Tomography (PET), do not have sufficient sensitivity and specificity. In this scenario, DECT could definitively represent a successful option in view of the several

advantages that have been previously demonstrated. However, several limitations could be pointed out.

One of the primary concerns is the increased complexity of data interpretation and the need for trained radiologists. Additionally, the cost and availability of DECT technology may pose a barrier, particularly in resource-limited settings and in developing countries. These aspects may impair its widespread adoption. This advanced imaging modality hold great promise but considerations regarding cost-effectiveness and accessibility must also be addressed.

Moreover, the ongoing development of artificial intelligence (AI) and machine learning algorithms may further enhance the efficacy and accuracy of DECT. The implementation of AI in imaging analysis may expedite diagnosis, standardize interpretation, and reduce variability among radiologists.

DECT with its ability to enhance lesion characterization, improve staging accuracy, evaluate treatment response, and aid in the differentiation of tumor subtypes, presents the potential to revolutionize our approach to renal cancer care, also paving the way towards personalized medicine and optimized treatment strategies. Nevertheless, to fully realize this potential, ongoing research, education, and investment in DECT technology are essential. As we continue to explore the capabilities of DECT, it is imperative to foster collaboration between radiologists, oncologists, and researchers to ensure that advancements in imaging translate into improved patient outcomes.

Surely, prospective trials are needed to better investigate the efficacy and to validate DECT as the preferred imaging analysis for evaluating RCC patients. However, its potentialities have already been unveiled.

Disclosure statement

The authors have no conflicts of interest to disclose.

Declaration on AI use

I hereby declare that the article submitted is my original work and has been written without the assistance of artificial intelligence (AI) tools or software. All ideas, research, and content are my own, and I take full responsibility for the authenticity and integrity of this work.

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Figure legend

Figure 1. Conventional (A, B) and spectral-based (C, D, E) CT images on arterial and portal phase of a left clear-cell RCC.

A) Portal phase, B) Arterial phase, C) Virtual MonoEnergetic 40 KeV, D) Iodine density, E) Zeffective.

Abbreviation: RCC, Renal Cell Carcinoma.