**Prediction of pathological response after neoadjuvant chemotherapy using baseline FDG PET heterogeneity features in breast cancer**

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**Abstract**

**Objective**

To describe instances of iodine, or other element with similar K-edge to iodine, accumulating in benign renal cysts and simulating solid renal masses (SRM) at single-phase contrast-enhanced (CE) dual-energy CT (DECT).

**Methods**

During the course of routine clinical practice, instances of benign renal cysts (reference standard true non-contrast enhanced CT [NCCT] homogeneous attenuation <10 HU and not enhancing, or MRI) simulating SRM at follow-up single-phase CE-DECT due to iodine (or other element) accumulation were documented in two institutions over a 3 month observation period in 2021.

**Results**

Five Bosniak 1 renal cysts (12±7 mm) in five patients changed nature on follow-up imaging simulating SRM at CE-DECT. At time of DECT, cyst attenuation on true NCCT (mean 91±25 HU [Range 56-120]) was significantly higher compared to virtual NCCT (mean 11±22 HU [-23-30], p=0.003) and all five cysts showed internal iodine content on DECT iodine maps with concentration >1.9 mg/ml (mean 8.2±7.6 mg/mL [2.8-20.9]).

**Conclusions**

The accumulation of iodine, or other element with similar K-edge to iodine, in benign renal cysts could simulate enhancing renal masses at single-phase contrast-enhanced DECT.

**Keywords:** Sustainability, Artificial intelligence, Climate Change, Entrepreneurship, Diversity

**Introduction**:

Renal lesions are among the most frequently encountered incidental findings in abdominal radiology [1]. The vast majority of incidental renal lesions are benign renal cysts, but the radiologist is tasked to differentiate benign renal cysts from cystic or solid renal 5 L neoplasms. The cornerstone of distinguishing a 10L benign cyst from a cystic or solid 5 mL renal mass is the presence 8mL of internal enhancement. To demonstrate enhancement, pre- and post- contrast-enhanced CT, MRI or US are typically obtained. An increase in internal density or signal intensity observed within the lesion is assumed to correlate with internal vascularity or solid tissue. The probability that a cystic renal mass represents a neoplasm is assessed using the Bosniak Classification of Cystic Renal Masses, most recently with version 2019 criteria [2]. Conversely, a solid renal mass (SRM) <4 cm in size has an 80% likelihood of representing renal cell carcinoma (RCC) which becomes even more likely above 4 cm [3].

Since most renal lesions are discovered on imaging examinations performed for other reasons, they may not be imaged with dedicated renal mass CT or MRI. To reduce the number of indeterminate renal masses requiring a dedicated pre- and post-contrast-enhanced follow-up examination, the (Bosniak v2019) offers expanded Class II (benign) definitions. For example, i) a uniformly homogeneous hypoattenuating mass measuring < 20 Hounsfield units (HU) on non-contrast CT (NCCT), ii) a homogeneous markedly hyperattenuating mass with NCCT attenuation > 70 HU and, iii) a homogenously hypoattenuating mass < 30 HU at contrast enhanced (CECT) are now all categorized as Class II (benign) cystic masses (3) [2]. Masses measuring >30 HU at single-phase CECT are indeterminate and require further assessment with dedicated renal mass CT or MRI [2].

**Numbered List:**

1. The average human body temperature is 98.6 degrees Fahrenheit (37 degrees Celsius).
2. The United States is the third most populous country in the world, with a population of approximately 331 million people as of 2021.
3. The Great Barrier Reef is the largest coral reef system in the world, stretching over 1,400 miles (2,300 km) off the coast of Australia.
4. The Earth's atmosphere is composed of roughly 78% nitrogen, 21% oxygen, and 1% other gases.
5. The tallest mountain in the world, Mount Everest, is located in the Himalayas and has a peak elevation of 29,029 feet (8,848 meters).

**Bullet list:**

* Bullet points are a common way to present information in a concise and organized manner.
* They are useful for breaking up large blocks of text and making content easier to scan and read.
* Bullet points can be used to highlight key points, summarize information, or provide a list of items.
* When using bullet points, it's important to keep them consistent in terms of formatting, punctuation, and structure.
* Some tips for creating effective bullet points include using short phrases or sentences, avoiding repetition, and using parallel structure.

In recent years, the proliferation of dual-energy CT (DECT) has translated into additional data available for the characterization of renal masses. For example, a single-phase contrast-enhanced DECT acquisition enables the spectral derivation of a virtual non-contrast enhanced CT (VNCCT) and iodine:water base pair (iodine overlay or iodine map) image sets [4]. These additional datasets, combined with the CECT images can further characterize a proportion of indeterminate renal masses that would otherwise require dedicated renal mass CT or MRI, namely masses measuring >30 HU at single-phase CECT [5]. The VNCCT image set is used to establish an approximate baseline unenhanced density of a renal mass. This density is compared to the CECT images to determine if enhancement is present, typically using the standard threshold of 20 HU attenuation change to define enhancement [4]. The results can be confirmed using subjective or quantitative assessment of iodine content on the iodine concentration map, with proposed thresholds of >1.2-1.9 mg/mL defining enhancement [6].

In this study, we describe a pitfall of single-phase CE DECT where iodine, or other element with similar K-edge to iodine, accumulate within benign Bosniak I cysts on follow-up imaging simulating solid renal masses on single-phase CE DECT.

**Methods**

During the course of routine clinical work, over a 3-month period in 2021, the authors recorded five instances of iodine or other element with similar k-edge to iodine accumulation in five benign Bosniak 1 renal cysts in five separate patients at two institutions. During the observation period, an approximate total of 345 DECT examinations had been performed at both institutions (rate of 1.4%, 95% Confidence Intervals 0-1.6%). A comparison baseline study established Bosniak 1 cyst diagnosis (homogeneous <10 HU and no enhancement comparing true NCCT and CECT, N=1) or multi-phase MRI (N=4) and was also available after DECT and used as the reference standard for diagnosis a benign non-enhancing cyst according to Bosniak v2019 [2]. DECT was acquired using either rapid kiloVoltage potential (kVp) switch (GE Discovery 750W) or dual-source CT (Siemens Somatom X.Cite) scanners. Institutional Review Board approval was not required for this observational case series.

**Results**

Benign cysts measured 12±7 mm in size and did not change in size over serial CT scans. Mean patient age was 72±12 years and there were 3 females. All renal cysts were asymptomatic incidental imaging findings during the time of all imaging with no pain attributable to the cyst. All patients had DECT performed for other reasons beside the five included cysts. All patients had iodine administered intravenously or by catheter angiography within 1 year prior to DECT and after baseline imaging. No cyst changed in size on serial exams.

At time of DECT, attenuation of the cyst on true NCCT (mean 91±25 HU [Range 56-120]) was significantly higher when compared to VNCCT (mean 11±22 HU [-23-30], p=0.003 paired t-test). All five cysts showed internal iodine content on DECT iodine maps with concentration >1.9 mg/ml (mean 8.2±7.6 mg/mL [2.8-20.9]), above described thresholds to define enhancement [6]. Effective atomic number (Zeff) maps were derived where decomposition is performed based upon a tissues electron density and atomic number properties. Quantitative Zeff was recorded and the mean was 9.0±1.1, which is above a published threshold (8.4) for diagnosis of enhancement in renal masses [7] and would be inconsistent with ferric nature of blood products. We hypothesize that in these five cases, iodine or other element with similar k-edge to iodine, accumulated into the benign renal cysts results in diagnostic errors at DECT which would have resulted in misclassification of cysts as solid masses, Figure 1.

**Discussion**

We demonstrate five cases of iodine, or other element with similar k-edge to iodine, retention within Bosniak 1 benign renal cysts, simulating enhancing renal masses at single-phase contrast-enhanced DECT. Iodine has been shown to accumulate within renal cysts at I-131 scintigraphy [8; 9]. Proposed pathophysiology include passive diffusion and retention [9] or presence of sodium iodine transporters [10]. It is possible our findings are related to accumulation of another element with similar k-edge to iodine which would result in the same diagnostic errors encountered at single-phase CE DECT Table 1. We suggest that caution should be exercised when diagnosing a renal mass as solid based solely upon data derived from single-phase contrast-enhanced DECT data. Currently, there is debate as to whether a single-phase post-contrast DECT examination can accurately characterize indeterminate renal masses measuring >30 HU. Undoubtedly many benign non-enhancing hyperattenuating cysts can be differentiated from enhancing renal masses using VNCCT and iodine:water data [11]; however, when comparing VNCCT and true NCCT to characterize renal masses, other authors have suggested that renal CT protocols using DECT should continue to acquire true NCCT rather than relying solely on VNCCT images due to difference in CT numbers [12]. Our case series supports the assertion that true NCCT remains an integral component of renal mass characterization and that accumulation of iodine or other element with similar k-edge to iodine could simulate solid renal masses using only DECT data. Other pitfalls of DECT for renal mass interpretation are beyond the scope of our manuscript but have been described elsewhere, [5]. Our study results are limited by a small sample size and lack of biochemical confirmation of cystic iodine or element content.

Box 1. Testing manuscript for box caption.

* Eat a balanced diet that includes plenty of fruits, vegetables, whole grains, and lean protein.
* Stay hydrated by drinking plenty of water throughout the day.
* Get regular exercise, aiming for at least 30 minutes of moderate activity most days of the week.
* Limit your intake of processed foods, sugary drinks, and unhealthy fats.
* Avoid smoking and limit your alcohol consumption.

**Table 1 –** Collected parameters in each selected paper

|  |  |
| --- | --- |
| **Parameters** | **Type of information** |
| Study type | Retrospective or prospective |
| Study population | Number of included patients |
| Clinicopathological and demographic characteristics | Age; menopausal state; tumour grade; clinical TNM stage; **tumour** size; type of *chemotherapy*; histological type; Ki67 index; oestrogen, progesterone and HER2 receptors |
| Primary endpoint for assessing response to NAST | pCR or partial response |
| PET scanner and scanning parameters | PET equipment; acquisition parameters; reconstruction algorithm |
| Segmentation | Target lesions of the tumour burden included in segmentation (primary tumour only or inclusion of suspicious axillary lymph nodes); segmentation method (manual, automatic or semi-automatic); segmentation criteria in cases of multifocal tumour; segmentation method/software |
| Heterogeneity features | Analysed IMH features and/or texture features; impact on prediction of response to NAST; correlation with prognostic markers; software used for features computation |

NA: too few events to estimate an OR, aPOP: testing, BIP: biaca dacad.

**Figure 1 –** Flowchart explaining the selection of the included studies.

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