# Application of multi-spectral CT imaging in Crohn's Disease:

# a systematic review

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## Abstract

*Purpose:* The objective of this systematic review was to assess the available literature on the application of multi-spectral CT imaging in Crohn's Disease; in particular on the use of IC as a quantitative parameter to distinguish normal from affected bowel, assess CD bowel activity and heterogeneity of activity along involved segments.

*Materials and methods:* A literature search was conducted to identify original research studies published up to February 2022. The inclusion criteria were: English language, focus on DECT of CD, in particular including IQ as an outcome measure. The exclusion criteria were: animal-only studies, language other than English, review articles, case reports, editor's letters and study population <10 patients. After screening 179 articles, 9 studies were included in this review.

*Results:* All the included studies proved a strong correlation between IC measurements and Crohn's disease activity markers such as: CDAI, endoscopy findings and score (SES-CD), routine CTE signs and histopathologic score. Statistically significant differences in IC were reported between affected bowel segments and normal ones, normal and segments with active inflammation as well as between active and remission groups.

*Conclusion:* DECT iodine density measurement could be a useful tool in assisting radiologists in the diagnosis, classification and grading of CD activity.



**Keywords**: Computed tomography; Dual-energy computed tomography; iodine quantification; iodine concentration; Crohn's disease.

## Introduction

Crohn's disease (CD) is a chronic granulomatous disease characterized by transmural inflammation and skip lesions that affects any segment of the digestive tract, particularly the terminal ileum and adjacent colon (50% of patients presenting with ileo-colitis) [1].

The current CD diagnosis reference standard is the endoscopic visualization and histologic evidence of the GI tract mucosal inflammatory changes.

The endoscopic scores are considered the gold standard tool to measure the activity degree of CD and may be used to monitor response to therapy. The Simple Endoscopic Score for Crohn's Disease (SES-CD) [2], evaluates 5 intestinal segments for 4 parameters (ulcer size, surface area of ulceration, surface area of disease, and stenosis), each on a 0 to 3 scale (score range=0 – 60).

The main clinical scoring system is CDAI (Crohn's disease activity index) [3], that can differentiate active disease (CDAI>150) from remission (CDAI<150) [4].

CDAI limitation is that it does not perfectly correlate with actual disease activity endoscopic, radiographic and histopathologic findings [39].

As we said, the small bowel is one of the most common areas affected by inflammation in CD, so much of it is beyond the reach of standard ileo-colonoscopic evaluation, making the assessment of disease activity, from endoscopic evaluation alone, incomplete [5].

Consequently, cross-sectional imaging is essential in the evaluation of CD; CTE (computed tomography enterography) and MRE (magnetic resonance enterography) of the small bowel have become alternative choices in the diagnosis and management of CD in order to detect both intestinal pattern of involvement and complications (abscesses, fistulas, or bowel obstruction due to strictures) [6]; they have comparable accuracies for assessing active inflammatory CD (sensitivity and specificity in the region of 85–95%) [7–9].

In CTE, visual assessment of mural stratification, hyperenhancement, wall thickening, lumen stenosis, haziness of the surrounding mesenteric fat and engorged vasa recta, have been well described and correlate with active inflammation [10,11].

The degree and pattern of bowel enhancement using Hounsfield Units (HU) has been shown to correlate with disease activity but are subject to technical (Kv, x-ray energy) and patient factors (cardiac status, patient weight, intravenous contrast iodine concentration rate, injection rate and timing) [12].

Severity indices using MRE have already been proposed and validated (e.g., Magnetic Resonance Index of Activity (MaRIA) score); however, no CT-based severity score has yet been developed [13].

**DECTE**

Dual-energy CT (DECT) is based on data acquisition at two different energy settings either through emission or through separation at the detector level; it combines morphological and multiple quantitative parameters evaluation [14].

DECTE scanners can obtain an imaging quality and diagnostic efficiency comparable to single-energy computed tomography (CT) reducing radiation and contrast media doses [15–19].

The acquisition of data with different spectra of photons in one single CT acquisition, allows material specific analysis: the material decomposition is the basis for spectral CT [14,20,21].

Materials with high atomic numbers, such as iodine, show large differences in attenuation at high and low kVp values so the decomposition algorithm can be used to calculate the relative contribution of iodine within a substance, enabling the identification and quantitative analysis of its properties [20,22].

DECT post-processing techniques can decompose contrast-enhanced images into iodine image that only show iodine (iodine maps) and virtual non-contrast (VNC) images (Iodine can be subtracted from one CT scan with contrast) [14].

The mono-energy application simulates a scan using a monochromatic x-ray beam and allows to choose the energy level, in keV, for the reconstruction, producing virtual monoenergetic images (VMI).

Conventional-equivalent mono-energetic images have been shown to have improved signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) in contrast-enhanced scans, particularly in obese patients [23,24].

The attenuation of structures increases as the mean energy of the photons decreases; energy in the range approaching the K-edge of iodine (which is 33 keV) causes markedly increased attenuation of iodine enhanced structures [25].

Low keV VM images accentuate iodine-enhanced structures without increasing the image noise, decreasing the amount of injected contrast media, improving the image contrast of normal blood supply vessels to clearly depict the boundary between an inflamed intestine and normal intestinal tissue [26,27].

Iodine maps give radiologists the confidence in quantitatively evaluating the contrast enhancement of a lesion with high accuracy regardless of acquisition parameters (as long as the radiation dose is within a clinical range) [28].

Iodine concentration (IC) or density (ID) is a feature of Iodine Quantification, most commonly defined by the units mg/mL; it can be applied in the different scan phases (e.g. arterial (IC-A), venous (IC-V) or delayed phase (IC-D).

The IC on iodine images may provide a more consistent, quantitative measurement about the iodine content of a tissue in the voxel than HU attenuation measurements in a conventional CT.

Normalized IC (NIC) is calculated based on the equation NIC = IC lesion/IC reference (the reference most commonly being the aorta). The main point of normalization is to reduce technical or physiological variabilities in iodine load within the tissue of interest due to varying cardiac output and phase times, making interscan comparisons more constant.

Iodine density has been shown to be a surrogate marker of perfusion [29]; as we know, active inflammation means more blood perfusion and consequently increasing in IC, and thus the iodine map can clearly indicate the activity of CD.

The main aim of this systematic review is to compare the newest studies about the applications of multispectral CT in CD. We focused on the use of IC as a quantitative parameter to distinguish normal from affected bowel, assess CD bowel activity and heterogeneity of activity along involved segments, in view of its future application in the clinical practice as a reliable biomarker, guiding disease management and follow-up.

## Materials and Methods

This systematic review of the literature was conducted according to the Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA) guidelines [30] and registered on the PROSPERO database (CRD42022330062).

### Search Strategy

The literature search was conducted in February 2022 using two different computerized databases: PubMed and Embase. The search was restricted to peer-reviewed publications of original research using the population, intervention, comparison, and outcome approach (PICO) model [31]*:* the patient group suffers from CD; the intervention consisted of DECT examination from which IQ was

measured; the comparison was to other verified methods of CD evaluation: clinical findings and scores, biochemistry, endoscopy scores, conventional CT signs and histopathologic score.

The main outcome was to establish whether DECT examination and IQ measurements correlate with verified measures of CD evaluation to distinguish pathological segments from normal ones and assess disease activity.

The search thread in PubMed contained two aspects. The first focused on DECT, including the terms: "DECT" or "DECTE" or "Dual-energy CT" or "Spectral CT" or "Multispectral" or "Dual-energy Computed Tomography". The second aspect focused on IBD and included the terms: "IBD" or "Crohn". The EMBASE search was conducted in a similar fashion using the same terms in combination with identical text words.

**Study Selection**

After duplicates and not pertaining studies removal, the initial selection was based on the presence of search terms in abstract and title, and the full text was retrieved for studies that were eligible or possibly eligible. Eligibility for this systematic review regarded two inclusion criteria: DECT of CD and DECT including or focusing on IQ as an outcome measure. Exclusion criteria were: animal-only studies, language other than English, review articles, case reports, editor's letters and study population <10 patients.

**Quality Assessment**

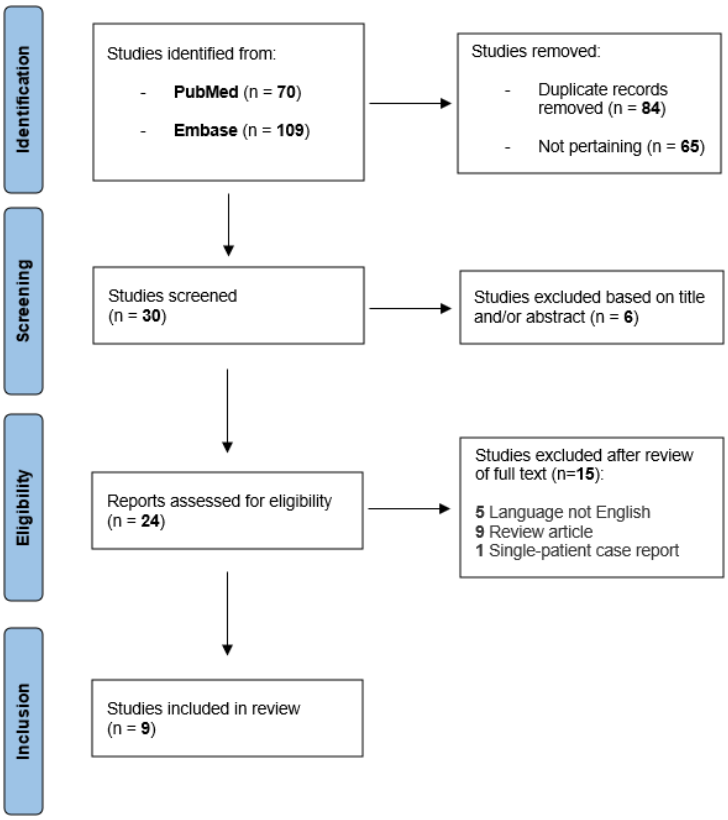
The presence of relevant biases in the included studies was evaluated by two readers according to QUADAS-2 criteria [32]. The performed quality assessment included 4 domains: 1 - patient selection, 2 - index test, 3 – reference standard, 4 - flow and timing. We used the proposed signalling questions

to determine the risk of bias and concerns regarding the applicability, grading them as low, high or unclear in case of insufficient data (figure 2).

## Results

The primary search thread identified 179 studies for inclusion in the methodological review. After duplicates and not pertaining studies removal, 30 studies were screened based on set inclusion and exclusion criteria, resulting in the inclusion of 9 studies (Figure 1).

**Figure 1.** PRISMA flowchart of the literature search and study selection.




### Quadas

The results of QUADAS-2 [32] assessment of the included studies are summarized in Figure 2.

The risk of bias for patient selection was low in the majority of studies (n = 5) due to a detailed description of patients' enrolment; 4 studies had a high risk of bias due to a case-control design. Overall, a low risk of applicability concerns was observed for all the included studies (n = 9). Two thirds of the studies (n = 6) demonstrated a low risk of bias for the index test (DECTE IQ) according

to their way of conduct and interpretation; 2 studies had a high risk of bias because the index test results were interpreted knowing the results of the reference standard; one study had an unclear risk due to incomplete information about the interpretation of index test results. All studies were deemed to have a low risk of applicability concerns for the index test.

3 of the included studies used Crohn's disease activity index (CDAI) as main reference (Kim et al. [35]; Dane et al., 2020 [37]; Xiao et al. [40]), 2 studies used endoscopy, biochemistry and clinical symptoms as reference (Peng et al. [33]; De Kock et al. [36]), other 2 studies used routine CTE findings (Villanueva Campos et al. [34]; Chen et al. [41]), one used the histopathologic score (Dane et al., 2021 [39]) and the last one used previous iodine density data (Dane et al., 2020 [38]) (table 2).

The risk of bias for the reference standard was low in two thirds of the included studies (n = 6); however, 3 studies had an unclear risk of bias since the interpretation of reference standard was conducted knowing the index test results. Finally, the applicability concerns about the reference standards and the estimated risk of bias about the flow and timing, was low for all the analysed studies (n = 9).

**Figure 2.**

| Study | RISK OF BIAS | | | | APPLICABILITY CONCERNS | | |
|---|---|---|---|---|---|---|---|
| | PATIENT SELECTION | INDEX TEST | REFERENCE STANDARD | FLOW AND TIMING | PATIENT SELECTION | INDEX TEST | REFERENCE STANDARD |
| Peng(2016) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Villanueva(2018) | ☺ | ☹ | ? | ? | ☺ | ☺ | ☺ |
| Kim(2018) | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| De Kock(2019) | ☹ | ? | ☺ | ☹ | ☺ | ☺ | ☺ |
| Dane(2020) | ☺ | ☺ | ? | ☹ | ☺ | ☺ | ☺ |
| Dane(2020) | ☹ | ☹ | ? | ? | ☺ | ☺ | ☺ |
| Dane(2021) | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Xiao(2021) | ☹ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |
| Chen(2021) | ☹ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |

☺Low Risk ☹High Risk ? Unclear Risk

**DECTE studies**

The 9 included studies involved 317 patients with a mean population size of 35 patients (range: 16–68) who underwent DECTE (table 1). All studies included focused on the role of DECT in the diagnosis of CD. The main aim of all the studies reported, was to find a quantitative imaging biomarker, using the post-processing tools of DECT (e.g., material decomposition, virtual monoenergetic images), to make diagnosis and assessment of CD activity easier, in daily clinical practice.

In order to distinguish normal from pathologic segments and assess CD segments activity, they compared DECTE quantitative parameters to clinical scores, evidence-based radiologic signs, endoscopic and histologic scores.

Quantitative image features are particularly important for CD in which patients undergo imaging over many years to monitor the effects of treatments.

Two studies (Peng et al. and Villanueva et al.) focused on the general distinction between normal bowel segments and pathological ones without specifying the status of the lesions (active or in remission); four studies (De Kock et al., Dane et al. [37,38,39]) investigated the differences between normal segments and segments with active inflammation; three studies (Kim et al., Xiao et al., Chen et al.) focused particularly on the distinction of active versus remissive disease.

Furthermore, two studies (Peng et al. and Dane et al. [39]) focused on the stratification of lesions' grading; two studies (Dane et al. [37,39]) proposed an IC threshold for the diagnosis of CD and one study (Dane et al. [38]) presented the heterogeneity of IC within the involved small bowel segments.

The outcome measure included NIC-V for all studies except studies by: Kim et al. [35] and Villanueva Campos et al. [34], which only included IC-V; Xiao et al. [40], which included IC-V and IC-A. The main acquisition technique was dual source acquisition except Kim et. al study which used detector-based spectral separation.

ROI placements were set manually on either iodine maps or conventional images, except in studies by Dane et al., 2020[38] and Dane et al., 2021[39] in which a new semiautomated technique was used.

All studies found a strong correlation between IC measurements and CDAI, endoscopy findings and score (SES-CD), routine CTE signs and histopathologic score.

**Normal vs pathological**

Firstly, Peng et al. [33] and then Villanueva Campos et al. [34] confirmed that the CTE measurements were closely related to the endoscopic results and the quantitative DECT parameters were significantly different between normal and pathologic segments (referred respectively to SES-CD and CTE radiologic signs of CD).

Villanueva Campos et al. considered, not only absolute iodine density (mg/dL), but also fat fraction (%) in bowel segments with radiological signs of active inflammation as well as in normal appearing ones of the same CD patients.

Absolute iodine density resulted higher in affected bowel loops than in normal appearing one ($p < 0.05$).

Although they reported a significantly higher fat fraction in normal appearing small bowel, De Kock et al. [36] proved that this parameter was not able to distinguish normal from active inflammatory CD.

A possible explanation for these contradictory results could be that Villanueva Campos et al., did not compare CD patients with a healthy control group, as De Kock study, but obtained control measurements from normal appearing bowel loops within the study group. More than one subtype of CD may be present in the same patient, especially in longstanding disease. So, the bowel

segments that Villanueva Campos et al. considered normal, presumably contained a certain degree of chronic inflammatory changes (e.g., submucosal fat deposition known as the “fat halo sign”). [42]

**Normal vs active inflammation**

De Kock et al. remarked the difference in IC of the intestinal wall, between normal and segments with active disease: absolute and relative iodine density measurements were significantly higher in patients with active CD (P<0.001).

The level of agreement between readers was good for wall thickness and attenuation, and excellent for absolute and relative iodine density measurements, suggesting that disease activity can reproducibly be measured using these quantitative parameters.

Dane et al. [37,38] confirmed this evidence proving respectively that the ICmax and ICmin of affected bowel differed significantly from normal bowel (p<0,0001) and the average IC-V of involved segments ranged 1,0-3,3 mg/ml and differed significantly from normal ileum (p<0,0001) and normal jejunum in CD patients (p=0,0009).

Dane et al. [39] retrospectively examined 16 patients with CD who underwent DECTE as well as either ileocolonic resection or biopsy of the terminal ileum.

Inflammation was quantified at DECTE by measuring ID in the bowel wall after normalization by the iodine density measured in the abdominal aorta to correct for effects, such as contrast bolus timing. Clinical markers (CDAI, HBI) of active inflammation, showed no difference between patients with versus without active inflammation and between patients with moderate-to-severe versus no-to-mild chronic inflammation, at histologic examination.

These evidences remarked the superiority of IC as a biomarker of CD activity.

In fact, relative iodine density (with aorta as reference) was significantly higher in the wall of the bowel segments that had active inflammation, of any amount at histologic examination, compared with segments without inflammation.

**Active vs remission**

Kim et al. [35] stressed the concept that ID could be used as a marker of CD activity, measuring it against CDAI, and comparing its value between remission and active groups of patients.

This study found that the IC, measured on the iodine map of spectral detector-based DECTE, was the sole independent variable associated with CDAI. This result was expected, because IC provides indirect information regarding blood flow by quantifying the estimated contrast material distribution across the diseased bowel wall, at a single point in time.

Inter-reader agreement for the measurement of quantitative CT parameters was very good (correlation coefficient = 0.838), which suggests that iodine quantification is a reproducible method to predict CD activity.

Many other DECTE features were also significantly different between remission and active groups; for example, comb sign and subjective degree of enhancement, two blood flow-related CT feature ($p < 0.001$, due to the fact that angiogenesis is closely related to CD activity).

In conclusion this study evidenced differences in IC between patients with active CD (3.39 ± 1.05 mg/mL, n = 12) compared with those in remission (2.00 ± 0.70 mg/mL, n = 27), with CDAI chosen as reference standard.

According to Xiao et al. [40], the reason could be found in the increased vascular permeability, congestion and oedema of the intestinal wall that is more obvious in the active stage of CD.

The degree of fibrosis, however, is more obvious in the remission stage in which the intestinal wall is mainly infiltrated by chronic inflammatory cells.

This could result in the different intestinal wall's absorption, attenuation to X-rays and characteristics of the energy spectrum. The disproportion in blood supply also led to differences in the iodine content of the examined tissues.

However, also Xiao et al. found statistically significant differences in iodine content of the intestinal wall: higher in the active group (IC-A=2.7±0.9; IC-V=3.0±0.5) than in the remission group (IC-A= 1.5±0.5; IC-V= 2.4±0.4), ($p<0,05$); and so did Chen et al. (active NIC= 6.31 ± 1.85 vs remission NIC= 4.78 ± 1.48).

**Stratification of lesions**

Firstly, Peng et al [33] suggested that the mucosal injury, intestinal wall congestion, oedema, and fibrotic changes of intestinal segments in different active stages of CD differed; consequently there were differences in the quantitative parameters of DECT.

They classified bowel segments into three categories: normal segment, mild lesions and severe lesions according to endoscopic examinations. This study proved that quantitative parameters (NIC, λHU) of spectral CT were superior to qualitative parameters (bowel wall hyperenhancement, ulcers, comb sign) of conventional CT and correlated well with endoscopic score (SES-CD) in assessing CD severity.

NIC increased with endoscopic severity; it was significantly higher in severe lesions than in mild ones. There was, also, a significant difference between mild lesions and endoscopically normal segments.

In predicting intestinal activity, sensitivity and specificity in spectral CT mode versus conventional CT, was reported to be increased from 94.7% to 99.6%, 93.4% to 99.1% and 94.4% to 99.9%, respectively.

In predicting intestinal severity spectral CT showed greater accuracy (96.5% versus 91.9%), sensitivity (96.5% versus 92.1%) and specificity (95.8% versus 89.8%) than those in conventional CT mode, as well. So, Peng et al. proposed NIC as alternative parameter to assess endoscopic severity. Few years later, the work of Dane et al. [39] compared a quantitative image measurement directly to a histopathologic standard of reference.

Although relative iodine density was able to establish the presence of inflammation, it did not distinguish different histologic grades: mild, moderate or severe (maybe because of the small sample size).

**IC threshold**

As we said before, also Dane et al. [37] proved that ID correlates with active CD when compared with the clinical assessment of disease activity and CDAI.

They proposed Imin (minimal iodine concentration, ROI on least bright involved bowel wall segment) as a possible threshold to use in daily clinical practice.

Iodine density of 2 mg/mL appeared to be a threshold between normal bowel segments and those with active Crohn's disease.

One year later, the group of Dane [39] found that a 20% mean normalized iodine density threshold (referred to aorta) was 100% sensitive and 75% specific in identifying segments with any active inflammation.

Dane et al. [38] stressed the fact that the average iodine density of involved segment ranged widely, in this particular study was reported varying from 1.0 to 3.3mg/mL, making difficult the definition of a precise IC threshold value but depicting the concept of heterogeneity of CD activity along pathological segments.

**Technical innovations**

An important technical innovation was the use of a semiautomated technique instead of manual region-of-interest measurements, to extract bowel wall iodine measurements from an entire segment (firstly introduced in the study by Dane [38]).

This approach potentially captures more fully the heterogeneity that may exist in a single segment and make the measurements less operator-dependent.

Another innovation in image post-processing, proposed by Dane et al., was a three-dimensional iodine density map for visualization of Crohn disease activity and heterogeneity within CD involved bowel segments.

3D-maps depict the quantitative iodine density distribution of CD activity within affected bowel, potentially undermining clinical disease severity assessment and aiding clinical decision making.

Because the iodine density values were normalized to the aorta, they can be compared between patients or in the same patient after therapy to assess response. The 3D depiction within a segment of affected bowel also allows the radiologist to create a histogram that can help separate the "bowel profile" even when maximal HU are similar.

Another technical step forward, was proposed by Chen et al. [41], with the combined use of VMI at 60 keV and conventional CTE at 120 kVp to improve the efficiency of CD diagnosis.

They innovatively compared patients with and without CD through DECTE, then utilized a VMI in CTE to subjectively evaluate the images at the best energy level, which was appropriate for displaying the intestinal walls and vessels simultaneously.

Chen et al. found no significant differences in CNR and SNR between 60 and 40 keV levels, and the overall imaging quality at 60 keV were higher than in the other energy level groups. Therefore, after a comprehensive consideration, they considered 60 keV to be the best energy level. This study

ulteriorly proved DECTE and NIC to be valuable for the diagnosis and evaluation of activity in CD patients, respectively.

**Table 1.** Keypoints of studies investigating applications of multispectral CT in CD.

| Author, year | Focus | N° pts | Reference standard | Outcome measure | Findings |
|---|---|---|---|---|---|
| **Peng et al., 2016** [33] | Activity and severity in ileocolonic CD | 50 | Simple Endoscopic Score for Crohn's Disease (SES-CD) | NIC-V | Significant differences in NIC-V between endoscopic normal and mild (p=0,002), mild and severe lesions (p<0,001) |
| **Villanueva Campos et al., 2018** [34] | Quantitative parameters differences between normal bowel segments and segments affected by CD | 33 | Radiologic signs of CD | IC-V (average) | Significant differences in IC-V between radiologically normal segments and pathological ones (p<0,05) |
| **Kim et al., 2018** [35] | Correlation CT parameters with CDAI | 39 | Crohn's disease activity index (CDAI) | IC-V | IC-V significant correlation with CDAI (r=0,744; p<0,001) |
| **De Kock et al., 2019** [36] | Distinguish normal small bowel from active inflammatory CD | 40 | Endoscopy, biochemistry and clinical symptoms | NIC-V, IC-V | Significant differences in NIC-V and IC-V between disease and control group (p<0,001) |
| **Dane et al., 2020** [37] | Quantification of CD activity using Iodine density as a biomarker | 22 | CDAI , overall clinical assessment | NIC-V (min,max and weighted average) | The ICmax and ICmin of affected bowel differed significantly from normal bowel (p<0,0001) |
| **Dane et al., 2020** [38] | Heterogeneity of CD activity along involved segments | 20 | Previous Iodine density maps from DECTE data | NIC-V | Average IC-V of involved segments ranged 1,0-3,3 mg/ml and differed significantly from normal ileum (p<0,0001) and normal jejunum in CD patients (p=0,0009) |
| **Dane et al., 2021** [39] | CD active inflammation assessment | 16 | Histopathologic score | NIC-V | Significant difference between mean NIC-V in segments with vs without active inflammation (p<0,001). |
| **Xiao et al., 2021** [40] | Role of quantitative parameters in assessment of intestinal CD activity | 29 | CDAI | IC-V IC-A | Significant differences in IC between remission and active group (p<0,05) |
| **Chen et al., 2021** [41] | Usefulness of optimized Kev for VMI combined with iodine map in diagnosis CD | 68 | Routine CTE findings | NIC | The combined routine CTE and optimized VMI improved the diagnostic efficacy (P < 0.001). |

**Table 2.** Technical keypoints of studies investigating applications of multispectral CT in CD.

| Author, Year | DECT scanner | Kvp range | Contrast | Flow rate | Total iodine | Phase | ROI placement | Normalization |
|---|---|---|---|---|---|---|---|---|
| **Peng et al., 2016**[33] | Discovery CT750 HD, GE | 80/140 | Iopamidol 370 mg I/mL | 4 ml/s | 1,5 ml/kg | 45 s | On iodine concentration maps, high enhancing areas | Artery (not specified) |
| **Villanueva Campos et al., 2018**[34] | SOMATOM definition flash, Siemens | 80/140 | Ultravist, 300 mgI/ml | 3 ml/s | n/a | 75 s | On iodine concentration maps, highest enhancement mucosa | n/a |
| **Kim et al.,2018**[35] | IQon Spectral CT, Philips | 120 | Iohexol, 350 mgI/ml | 3-5 ml/s | 1,6 ml/kg | 35 s | On iodine concentration maps, strongest enhancement area | n/a |
| **De Kock et al., 2019**[36] | SOMATOM definition flash, Siemens | 80/140 | Visipaque | 3,5 ml/s | 100 ml | 70 s | Normal bowel=ROI over entire wall; CD=ROI on high enhancing area | Aorta (infrarenal) |
| **Dane et al.,2020**[37] | SOMATOM FORCE, Siemens | 80/150 | Ultravist 300 mgI/ml | 3-4 ml/s | 1.5 ml/kg | 60 s | Imax=ROI on brightest involved bowel wall segment Imin=ROI on least bright | Aorta |
| **Dane et al., 2020**[38] | SOMATOM FORCE, Siemens | 80/150 | Isovue, 300 mg/ml | 3-4 ml/s | 1,5 ml/kg | 60 s | Semiautomated: 8 tracks on curved MPR sampling the mucosa of affected bowel segment | Aorta |
| **Dane et al., 2021**[39] | SOMATOM FORCE, Siemens | 80/150 | Ultravist 300 mgI/ml | 3-4 ml/s | 1,5 ml/kg | 60 s | Semiautomated: 8 tracks on curved MPR sampling the mucosa of affected bowel segment | Aorta |
| **Xiao et al., 2021**[40] | SOMATOM FORCE, Siemens | 80/150 | Ioversol 320 mg/ml | n/a | 1,2 ml/kg | AP VP | 70–80% of the overall intestinal wall | n/a |
| **Chen et al., 2021**[41] | SOMATOM FORCE, Siemens | 90/150 | Iopramine 350mg/ml | n/a | n/a | 40 s 75 s | Thickest level of diseased intestinal wall, covering 60-90% of the wall | Aorta (carrefour) |

Studies listed chronologically according to the publication year.

## Discussion

This review reveals the potential of DECT in the diagnosis of CD.

The mean normalized iodine density at DECTE could be an accessible non-invasive cost-effective examination for the diagnosis and assessment of CD activity, less dependent on scan parameters (manufacturer, energy, contrast material timing) than conventional Hounsfield unit-based measurements. In particular, it seemed useful in the differentiation between not only normal and pathological, but also, potentially, between active and remission lesions of CD, depicting the level of activity within the pathological bowel segments. All of this with a quality and diagnostic efficiency comparable to single-energy computed tomography (CT) but with the advantage of reduced radiation and contrast media doses.

Naturally this review presents also some limitations. The limited number of studies available about the topic and included, with an extreme heterogeneity between them, prevented us from performing a meta-analysis: use of different DECT brands and different protocols (IC normalization, IQ scan phase, ROI placement, reference standards).

Common limitations, in all studies, were the small number of patients and the retrospective nature. Actually, there is not enough knowledge, not enough literature, precluding our ability to reach clinically robust threshold for the use of IC in daily clinical practice, because different hardware and algorithms are used by the different vendors and users. There is the need of larger multicentre prospective clinical trials to determine how generalizable and reproducible these measurements are across vendors, across patients and how benefits patients when this technology is applied prospectively. Another significative problem is the poor accessibility, in some countries, of the DECT scanners that also require qualified staff.

Manually applied ROIs for involved bowels, are vulnerable to inter-reader or intra-reader variabilities; this limitation has partially been overcome by Dane et al.'s introduction of a semi-automatic method.

CD is characterized by transmural inflammation and radiologic-pathologic analysis correlation was mainly targeted at the mucosa and inner hyperdense portion of bowel wall, this could result in underestimation of disease presence and severity.

Furthermore, histological confirmation was not performed in all patients, but when performed, surgically resected bowel specimens showed predominantly severe inflammation whereas the endoscopic specimens showed more mild inflammation. The retrospective approach lends itself to selection bias: only patients with severe enough disease to get resection or endoscopy were included.

Other limitations were the variable time between imaging and histopathologic analysis, and lack of differentiation between treatment nor disease duration among patients in the study group.

## Conclusion and future developments

However, further studies with multicenter large-scales external validation and homogeneous research design are needed to assess reproducibility and generalizability of the IC as a validated biomarker of activity. The target is to develop a quantitative scoring system for grading CD activity using DECT iodine density measurement, as a marker of disease severity, to improve diagnostic accuracy and evaluate the effectiveness of therapy (IC changes within the bowel wall during treatment).

Future directions include automation of 3D iodine density map creation, more sophisticated renderings that can sample the full thickness of the bowel wall, further refining the status of the disease: a percentage of most severely and less severely affected portions within bowel loops. These

renderings should be able to provide a more targeted guide for management decisions, facilitate scan-to-scan comparison of success or failure of therapy, refine the choice between multiple treatment options and identify patients in whom medical management is likely to fail, potentially facilitating earlier surgical intervention.

**Abbreviations**

AP=Arterial Phase
CD=Crohn's disease
CDAI=Crohn's disease activity index
CNR=Contrast-to-noise ratio
CT=Computed tomography
CTE=Computed tomography enterography
DECT=Dual-energy Computed Tomography
DECTE=Dual-energy Computed Tomography Enterography
HBI= Harvey-Bradshaw index
HU=Hounsfield unit
IBD= inflammatory bowel disease
IC=Iodine concentration
IC-A=Iodine concentration in arterial phase
IC-V=Iodine concentration in venous phase
ID=Iodine density
IQ=Iodine quantification
KeV=Kiloelectron volt
kVp=Peak kilovoltage
MaRIA=Magnetic Resonance Index of Activity
MDCT=Multi-detector computed tomography
MRE=Magnetic resonance enterography
NIC=Normalized iodine concentration
NIC-A=Normalized iodine concentration in arterial phase
NIC-V=Normalized iodine concentration in venous phase
PRISMA=Preferred reporting items for systematic reviews and meta-analyses
PTS=Patients
ROI=Region of interest
SES-CD=Simple Endoscopic Score for Crohn's Disease
SNR= Signal-to-noise ratio
VMI=Virtual monoenergetic images
VNC=Virtual non-contrast
VP=Venous phase

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