**Spectral CT in Oncology**

**Onkologische Bildgebung mittels Spektral-CT**

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**ABSTRACT**

**Background** Spectral CT is gaining increasing clinical importance with multiple potential applications, including oncological imaging. Spectral CT-specific image data offers multiple advantages over conventional CT image data through various post-processing algorithms, which will be highlighted in the following review.

**Methodology** The purpose of this review article is to provide an overview of potential useful oncologic applications of spectral CT and to highlight specific spectral CT pitfalls. The technical background, clinical advantages of primary and follow-up spectral CT exams in oncology, and the application of appropriate spectral tools will be highlighted.

**Results/Conclusions** Spectral CT imaging offers multiple advantages over conventional CT imaging, particularly in the field of oncology. The combination of virtual native and low monoenergetic images leads to improved detection and characterization of oncologic lesions. Iodine-map images may provide a potential imaging biomarker for assessing treatment response.

**Key Points:**

- The most important spectral CT reconstructions for oncology imaging are virtual unenhanced, iodine map, and virtual monochromatic reconstructions.
- The combination of virtual unenhanced and low monoenergetic reconstructions leads to better detection and characterization of the vascularization of solid tumors.
- Iodine maps can be a surrogate parameter for tumor perfusion and potentially used as a therapy monitoring parameter.
- For radiotherapy planning, the relative electron density and the effective atomic number of a tissue can be calculated.

**ZUSAMMENFASSUNG**

**Hintergrund** Die Spektral-CT gewinnt mit vielfältigen Einsatzmöglichkeiten zunehmend an klinischer Bedeutung, so auch im Rahmen der onkologischen Bildgebung. Die Spektral-CT-spezifischen Bilddaten bieten durch verschiedene Nachbearbeitungsalgorithmen vielfältige Vorteile gegenüber konventionellen CT-Bildaten, was im folgenden Review genauer beleuchtet werden soll.


Introduction
Thanks to increasing availability, spectral CT systems are more frequently being used in daily clinical routine. Spectral CT, which allows specific material characterization, can be used for a number of different applications in oncological imaging [1]. In addition to improved detection and characterization of malignant lesions, spectral CT allows precise treatment planning and provides a novel imaging biomarker for tumor vitality [2–5]. This article discusses specific spectral CT systems and spectral reconstructions with a focus on oncological applications. In addition, spectral CT-specific pitfalls that need to be known in order to avoid interpretation errors are discussed.

Basics of spectral CT imaging
While conventional CT imaging is based on differences in physical density between two neighboring structures, spectral CT imaging is based on differences in the basic composition of structures [6]. By examining two different energy spectra, structures with a similar density but a different basic composition can be differentiated from one another based on differences in photon absorption. This material-specific imaging allows, for example, selective visualization and quantification of intravenously applied iodine. However, only materials with a strong photoelectric effect, e.g., calcium, iodine, barium, and xenon, can be differentiated from other body tissues like fat with a weak photoelectric effect. The two typically used energy spectra have a peak of 70–100 kilovolts (kVp) (low energy spectrum) and 140–150 kVp (high energy spectrum) [1].

All currently available clinical CT systems that offer spectral imaging can be classified into two groups: emission-based and detector-based systems [7]. Emission-based systems use X-ray beams with different energy spectra. This can be achieved either by using two independent X-ray tubes with one tube generating a low energy and the other having a high energy or by using a single X-ray tube that quickly switches between low and high energies. A further possibility for creating different energy spectra using only one X-ray source is to use a split beam with two different filters, e.g. of tin and gold, during a 360° rotation, thus allowing filtration into a low and a high energy spectrum [8]. Detector-based systems are based on the detector’s ability to separate energies by separating the signals of the low-energy X-ray photons from the high-energy photons. This separation can be achieved using a dual-layer energy-integrating detector with different photon registration in every layer (e.g., using a yttrium-based scintillator) or a photon-counting detector. The most common and most widely available clinical spectral CT systems in Europe [2–4] are the dual-source CT system (e.g., SOMATOM Force or SOMATOM Definition Flash, Siemens Healthineers), which is an emission-based system with two independent X-ray tubes, the dual-layer CT system (e.g., IQon Spectral CT, Philips Healthcare), which is a detector-based system with a dual-layer detector, and the ultrafast switching CT system (e.g., Discovery HD, GE Healthcare), which is an emission-based system with a single fast-switching X-ray tube. The first clinical photon-counting detector CT system introduced last year (NAEOTOM Alpha; Siemens Healthineers), which allows improved spectral separation, is not discussed here due to the small number of clinical studies available.

Image reconstruction of spectral CT datasets
Selective quantification of elements such as iodine can be achieved by a two- or three-material decomposition algorithm in the projection domain (Ultrafast switching and dual-layer CT systems) or in the image domain (dual-source CT systems) [7]. The following section describes the most common spectral CT image reconstructions in oncological imaging.

Material density maps
Manufacturer-specific material decomposition algorithms can be used to create material density maps that selectively display or remove materials. The most clinically relevant application in oncology is the material density map that shows iodine and calcium and to a lesser degree also the relative electron density and the effective atomic number. These maps allow selective fading out of the soft-tissue background while highlighting specific materials, the relative electron density, and the effective atomic number. Among other things, these material density maps make it possible to characterize vascularized and non-vascularized lesions (in the case of iodine maps), an important criterion for the characterization of kidney or liver lesions [9].

On virtual non-contrast (VNC) CT images and virtual non-calcium (VNCa) CT images, certain materials like iodine and calcium are selectively suppressed [7]. VNC images with selective suppression of iodine are comparable to true unenhanced images, which are normally acquired prior to contrast administration in the case of certain clinical questions. In oncological imaging, these images are often needed for the characterization, for example, of incidental renal lesions during an initial staging examination [10, 11]. Other applications include the differentiation between therapy-induced tumor hemorrhages and calcifications [12]. Due to the possibility of eliminating a true non-contrast CT examination, the radiation dose can be reduced [13]. This is an important aspect of curative treatment approaches because the cumulative radiation dose of imaging follow-up examinations can be significant [14].

Selective imaging of bone marrow involvement using VNCa maps e.g., in patients with multiple myeloma, can facilitate the detection of focal lesions and the differentiation between osteoporotic changes and plasma cell infiltration [15, 16].

Virtual monochromatic images (VMI)
The term polychromatic X-ray beam relates to an X-ray beam with a full energy spectrum in which the kVP represents the upper limit of the energy spectrum. It should be noted that low-energy photons of this polychromatic X-ray beam are responsible for a disproportionately high proportion of background image noise and image artifacts (e.g. beam hardening artifacts). Spectral imaging can be used to create virtual monochromatic images (VMI) from material-specific images using a complex algorithm [7]. These are then comparable with image data that would be generated with a theoretical monochromatic beam. The X-ray energy is measured
in kiloelectron volt (keV) instead of kVp and the VMI spectrum is 40–200 keV with manufacturer-specific differences (see 
Table 1). VMI image data reconstructed between 75–77 keV are comparable with image data from a polychromatic X-ray beam with 120 kVp. Low-energy VMI images (40–60 keV) result in higher iodine absorption due to the closeness to the k-edge of iodine (33 keV), leading to enhanced iodine contrast on the image [17]. This has a number of advantages for oncological imaging. Among other things, low-energy VMI images make it possible to detect lesions, e.g., hypervascularized liver metastases, with greater sensitivity [18]. In the case of high-energy VMI images (170–200 keV), artifacts caused by foreign materials, e.g., dental prostheses or prosthetic joints, can be reduced, resulting in better assessment of the size of lesions in the immediate vicinity of such foreign objects [19].

### Oncological applications

#### Improved detection of oncological lesions

By using low-energy VMI images or iodine maps, hypervascularized as well as faint hypodense lesions can be better delimited from parenchymatous background tissue ( Fig. 1). VMI reconstructions between 50–55 keV provide the best contrast-to-noise ratio for the majority of parenchymatous organs. However, it should be noted that other keV reconstructions (e.g., 70 keV) are more suitable in highly vascularized tissue (e.g., renal parenchyma) [20–22]. A number of studies were able to show the advantage of these two spectral CT reconstructions for malignancies in the head-neck/neck region for primary and secondary hepatic masses and pancreatic malignancies in which the lesion-to-tissue contrast is intrinsically lower [23]. For example, in the case of hepatic steatosis, either medically (e.g., during chemotherapy) or metabolically induced, it is often challenging to detect faint hypovascularized lesions on conventional CT. By using low-energy VMI images or iodine maps, improved lesion-to-tissue contrast can be achieved because the lesion has a greater density while the fatty liver tissue appears hypodense. Thus, in particular, hepatocellular carcinomas, cholangiocellular carcinomas, and hepatic metastases can be better detected.

In patients with bone marrow involvement in a malignant disease, e.g., multiple myeloma, MRI has been the imaging method of choice. Using spectral VNCa image data, both focal bone marrow lesions (>1 cm) and the pattern of involvement can be detected with a similar accuracy to that of MRI with equally precise detection of osteolytic bone lesions [15, 16]. This is an advantage compared to conventional CT in which trabecular bone structures currently cannot be sufficiently extracted making detection as well as the differentiation between plasma cell infiltration and osteoporotic bone demineralization difficult ( Fig. 2). However, it
must be noted that the currently available clinical spectral CT sys-
tems allow the generation of VNCa image data only from non-
contrast spectral CT examinations. Therefore, clinical application is
currently limited. In the future, the use of the aforementioned
clinical photon-counting detector CT systems could be expanded
to include contrast-enhanced CT examinations [24].

Patients with a malignancy have an increased risk of pulmonary
eMBOLism [25]. Depending on the phase, pulmonary embolisms are
sometimes overlooked in staging examinations, which are pri-
marily performed in a portal venous phase [26]. Both low-energy
VMI images and iodine maps provide better detection of pulmo-
nary embolisms due to the improved thrombus-to-vessel contrast
or the evaluation of a filling defect within the vessel (Fig. 3)
[27].

Characterization of oncological lesions
Detection of vascularization of solid masses is an important clin-
ical objective of all imaging methods since it can help to character-
ize masses. In conventional staging CT examinations performed in
a single phase, incidentally detected lesions, particularly adrenal
and renal lesions often cannot be characterized in greater detail
(Fig. 4, 5). As a result, it is recommended to perform supplemen-
tary imaging, follow-up examination, or biopsy. Spectral CT im-
gaging can provide important additional information both in pri-
mary staging and in follow-up examinations with various image
reconstructions and allow early characterization [2–5]. This can
reduce the patient’s emotional burden, accelerate the introduc-
tion of an appropriate treatment regimen, and reduce treatment
costs.

VNC images or iodine maps reconstructed from a spectral CT
dataset allow differentiation between a vascularized and non-vas-
cularized lesion which is particularly helpful for the differentiation
between a hemorrhagic/protein-rich cyst and a solid hepatic or
renal mass [9, 28]. Based on the cutoff value of true non-contrast
image data, a vascular lesion is defined as an increase in the den-
sity (measured in Hounsfield units (HU)) between the VNC and
the contrast-enhanced image data of > 20 HU [29]. When using
iodine maps, there are manufacturer-specific differences regard-
ing the definition of a contrast-enhancing lesion with iodine con-
centration cutoff values ranging from 0.5 mg/mL to 2.0 mg/mL
[30–32]. For the dual-source CT systems most commonly avail-
able in Germany, a cutoff value of 0.5 mg/mL has been established
[4]. Iodine maps can also be helpful for the differentiation be-
tween thromboses without iodine uptake and a tumor thrombus
with iodine uptake, e.g. in hepatocellular carcinoma or renal cell
carcinoma with venous infiltration.

VNC images and specific material density maps can also pro-
vide additional information about the composition of a lesion,
particularly about fatty, hemorrhagic, or faint calcified areas [1].
For example, this is helpful in the characterization of adrenal mas-
ses, in which fat-isodense lesion portions (density values in the
VNC datasets < 10 HU) indicate an adenoma [33]. The differentia-
tion, for example, between a postoperative hematoma and a new
metastasis can be difficult in the case of conventional single-phase
CT. However, VNC images or iodine maps can be used for precise
colorization without supplementary imaging.

Treatment planning and treatment monitoring
Precise knowledge of tumor location, extent, and relationship to
surrounding tissue and vascular structures is important for treat-
ment planning. In particular, image-based therapeutic methods
like radiofrequency ablation, stereotactic radiotherapy, and in-
traarterial therapies (e.g. selective internal radiotherapy or trans-
arterial chemoembolization) require imaging that is as exact as
possible in order to facilitate planning.

VMI images in the low-energy range and iodine maps with a
higher lesion-to-noise ratio allow better differentiation of a tumor
lesion from surrounding structures like vessels and adjacent or-
gans and exact determination of the number and size of lesions.
Particularly in liver or head/neck tumors, the determination of le-
sion margins compared to surrounding tissue can be difficult on
conventional CT imaging [34–36]. VMI images in the high-energy
range can greatly reduce metal artifacts thus allowing better deli-
mination of the area to be scanned, which can be advantageous,
for example, in the case of head/neck tumors with artifacts from
dental fillings [37].

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Spectral CT imaging makes it possible to estimate the relative electrode density ($\rho_e$) and the effective atomic number ($Z_{\text{eff}}$). Determination of these tissue parameters is of particular interest for dose calculation in radiation therapy treatment planning. They can be used either directly (e.g., the relative electron density) or as a substitute for other parameters (e.g., the effective atomic number as replacement for the average excitation energy) to calculate the stopping power ratio [38].

The objective evaluation of treatment response to systemic or local treatment is important to monitor the effect of oncological treatments so that treatment changes can be implemented as early as possible. The established and currently used imaging criteria for evaluating response, e.g., the “Response Evaluation Criteria in Solid Tumors” (RECIST1.1) and the modified versions (iRECIST and irRECIST), are based on serial measurement of tumor size. However, purely size-based response criteria overestimate and underestimate the treatment success of modern therapies that are not necessarily cytotoxic but rather cytostatic and thus do not necessarily result in a change in size. The treatment effect can be better quantified by biomarkers that characterize tumor vitality (e.g., metabolic or diffusion-weighted imaging) [39]. Spectral CT imaging provides advantages here compared to conventional CT since it allows differentiation between iodine uptake in vital tumor tissue after i.v. contrast injection and, for example, treatment-induced tumor hemorrhage (Fig. 6) [40]. Additional advantages include the elimination of errors that can occur in connection with a spatial misregistration between non-contrast and contrast-enhanced datasets (e.g., due to a different breathing position between the examinations). In particular, vitality quantification based on iodine maps is a promising approach that could have an advantage over the above-mentioned purely size-based response criteria both in systemic therapies (e.g., gastrointestinal stromal tumor under systemic tyrosine kinase inhibitor therapy) [41] and in locally ablative methods (e.g., evaluation of the short-term and long-term treatment success after hepatic and renal radiofrequency/microwave ablation) [42].
Artifacts and pitfalls

Based on the special reconstructions algorithms, there are specific artifacts and pitfalls with regard to spectral CT. As in the case of conventional polychromatic image data, the density values of VMI image data depend on the energy. Therefore, for example, the liver parenchyma can be 110 HU at 50 keV, 80 HU at 70 keV, and 65 HU at 140 keV [43]. Thus, the above-mentioned determination of the cutoff value for contrast enhancement can only be applied to VMI images that are equivalent to a polychromatic image dataset at 120 kVp (75–77 keV).

Numerous studies were able to demonstrate an excellent correlation between the density values of VMI images and true non-contrast image data with density differences < 5 HU [11, 44–52]. However, it should be noted that the density values for VMI images are subject to various influencing factors, e.g., patient habitus or the contrast phase, with some differences between VMI and true non-contrast image data being significant, which can result in an incorrect classification of lesions [11, 52]. A common cause of these discrepancies is incomplete subtraction of iodine from VNC images, which can be observed, in particular, in image areas with a very high iodine concentration. For example, contrast pooling in the pelvicalyceal system can result in incomplete subtraction, resulting in incorrectly high density values in the VNC images, leading to a risk of misinterpretation of blood clots or calcifications within the pelvicalyceal system. It should be noted that the application of iodine-containing materials, e.g., lipiodol in transarterial chemoembolization, results in a subtraction from the VNC images, thus complicating post-interventional characterization of remaining vital portions.

Moreover, calcium is selectively characterized using a cutoff value on iodine maps as well as VNC images. This results in small (<2 mm) or faint calcifications (<380 HU) being incorrectly extracted from the VNC image [53, 54]. This effect is enhanced...
particularity in the case of images with high background noise, for example, in obese patients. In these cases, a true non-contrast examination can sometimes be indicated.

**Clinically accepted areas of application**

In spite of the numerous potential applications of spectral CT mentioned above, only VMI and VNC image data has achieved clinical acceptance so far. For lesion detection and determination of the local size of hypervascularized lesions (e.g., hepatocellular carcinoma, clear cell renal cell carcinoma metastases, and neuroendocrine tumors) and head-neck tumors, VMI image data in the low-energy range (50–55 keV) should be used as the primary image data due to the improved lesion-to-tissue contrast and resulting increased diagnostic accuracy [21, 34].

VNC image data have become clinically established particularly in the evaluation of the macroscopic fat components of incidentalomas and renal masses due to their high diagnostic accuracy [11, 33, 34]. Precisely characterizing these lesions in single-phase CT examinations avoids additional radiation exposure with multi-phase CT examinations, subsequent costs incurred by additional examinations, and patient uncertainty. In the case of explicit characterization of renal lesions or adrenal lesions, using VNC datasets and consequently dispensing with a true non-contrast examination reduces the radiation by one third (e.g., characterization of renal lesions: spectral nephrographic phase including VNC image data and washout phase instead of a non-contrast, nephrographic, and washout phase). In patients undergoing treatment with tyrosine kinase inhibitors (e.g., imatinib) or monoclonal antibo-

dies (e.g., bevacizumab or nivolumab) with single-phase CT staging examinations, VNC image data should always also be considered to differentiate rare pseudoprogression caused by a tumor hemorrhage from true progression [4, 11].

**Conclusion**

There are a number of possible applications for spectral CT in oncological imaging. In particular, VMI image data in the low-energy range (e.g., 50–55 keV), iodine maps, and VNC images provide advantages regarding the detection of, e.g., hypervascularized tumors and the differentiation between vascularized and non-vascularized liver or kidney lesions. Iodine quantification with respect to a tumor provides a potential biomarker for the assessment of treatment response.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


