Applications of Dual Energy CT in the Neck

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Please note that these lecture notes are supplemented with 3 open access articles (Appendix) by the presenter. The articles have images that are referred to and meant to supplement the text.

Overview:

Dual energy computed tomography (DECT) is an advanced form of computed tomography (CT) in which simultaneous or near-simultaneous acquisitions are performed at two different peak energy levels, enabling material density and spectral attenuation characterization beyond what is possible with conventional single energy CT (SECT) scans. In this presentation, the main clinical platforms currently used and applications of the technology to head and neck imaging will be reviewed. First, there will be a brief overview of different approaches to DECT scanning, important practical issues pertaining to image quality, acquisition dose, and standard reconstructions similar to what is obtained using conventional SECT. Thereafter, different emerging applications of DECT will be reviewed, particularly for oncologic imaging. These include use of different image reconstructions for enhancing tumor visibility, evaluation of thyroid cartilage invasion, artifact reduction, as well as less well developed applications such as using DECT for the evaluation of lymphadenopathy, among other emerging applications. Non-oncologic applications of DECT such as use for the evaluation of sialolithiasis and parathyroid adenoma characterization will also be briefly reviewed. The presentation will conclude with a brief overview of challenges and barriers to widespread implementation, as well as potential future applications both in terms of quantitative analysis and future advances in spectral CT.
technology. By the end of the presentation, the attendees should be familiar with the current approaches to DECT scanning, basics of implementation and use of the technology, as well multiple potential applications for enhancing diagnostic interpretation in the neck.

**Principles of DECT acquisition and current widely used clinical platforms:**

The main requirements and objectives of DECT scanning are emission and detection of X-Ray quanta at different energies and the use of information at different energy spectra for tissue differentiation. These depend both on factors related to the scanner itself and the material or tissue that is being characterized. For SECT, a polychromatic beam at a single peak energy emitted by the tube passes through the patient’s body and is recorded by detectors. For DECT, emission or detection of X-ray quanta at two different energies is required. The data at the two energies are then combined to generate different types of reconstructions beyond what is possible with SECT. For robust results and in order to enable advanced analysis, the different energy quanta need to be emitted and recorded simultaneously or near-simultaneously. Approaches based on sequential scan acquisition that results in a significant time delay between the low and high energy acquisitions introduces confounders and precludes some important and interesting advanced analysis. Current clinically used DECT platforms acquire DECT scans by either using two different X-ray tubes or sources, or alternatively, one can take advantage of the polychromatic nature of emitted X-rays and achieve this using a single source. In some instances, this is combined with a special type of detector referred to as a layered detector that can be used to separate different energy quanta.
Currently, most of the published studies on applications of DECT for head and neck imaging in the peer reviewed literature used either a single-source DECT with rapid kVp switching, also known as Gemstone Spectral Imaging, or dual-source DECT. The former DECT platform consists of a single source and detector combination, as its name would imply (Appendix 1: Figure 1). With this approach, the tube voltage follows a pulsed curve, and projection data are collected twice for every projection (one at high and one at low tube voltage), during rapid kilovoltage switching at the X-ray source. Precise temporal registration and spectral separation with this system is achieved through the fast sampling capabilities of a proprietary, garnet-based scintillator detector with low afterglow, also known as Gemstone Spectral Imaging (GSI).

In the dual-source DECT system, on the other hand, there are two source X-ray tubes with corresponding detectors aligned at perpendicular or near-perpendicular angle (Appendix 1: Figure 1). This enables simultaneous acquisitions at high- and low-energies. Other DECT platforms are also available although so far there is little or no published applications specifically for head and neck imaging. These include TwinBeam DECT and dual-layer detector DECT, among others. In TwinBeam DECT, the X-ray beam emitted from a single source is pre-filtered and split into high- and low-energy spectra before reaching the patient. In dual-layer detector DECT, there is a single source and detector but the detector is composed of two different scintillation layers on top of each other (Appendix 1: Figure 1). In this system, separation of high and low-energy spectra is achieved at the level of the detector.

Once acquired, the success of DECT image reconstruction and analysis for tissue differentiation depends on the composition of the tissues being examined. In order to distinguish different tissues or materials using DECT, they must have different spectral properties. This means that there needs to be a difference in the way the different tissues of interest attenuate X-rays at
different photon energies. In general, attenuation on CT scanning results mainly from Compton scatter and the photoelectric effect (Rayleigh or coherent scatter also occurs but accounts for only a small percentage of photon interactions at energies typically used for diagnostic imaging). Whereas Compton scatter accounts for the largest component of attenuation in CT scanning, the photoelectric effect is key for DECT scanning. The photoelectric effect is strongly related to the atomic number (Z), and therefore, to the number of protons in the atomic core. Only elements with a considerable difference in atomic number values will be distinguishable based on their spectral properties, explaining the importance of the photoelectric effect for DECT scanning.

Understanding these basic physical principles is essential for proper understanding and successful application of DECT for tissue differentiation in the clinical setting. Common constituents of tissues in the human body such as hydrogen, carbon, and oxygen have low atomic numbers and relatively weak photoelectric effect and as such would be difficult to distinguish based on their spectral properties. On the other hand, certain elements, such as iodine with a high atomic number (Z = 53) have a strong photoelectric effect. Because of this, a strong spectral contrast can be achieved between the heavy atoms of iodinated contrast agents and the light atoms of the tissues in the body. Because of this, many DECT applications are possible and of interest in the clinical setting such as accentuation of iodine content, creation of iodine overlay maps, or creation of virtual unenhanced images.

It is also important to understand the conditions affecting photoelectric interactions. For the photoelectric effect to occur, the X-rays must have energy equal to or greater than the binding energy of the innermost, or K-shell, electrons. This is represented by the K-edge. Photoelectric interactions sharply increase just above the K-edge of an element, but thereafter the probability of the photoelectric interactions and absorption also decreases rapidly with further increases in
photon energy above the K-edge. Therefore, the photoelectric effect is most pronounced just above the K-edge of a given element. For example, iodine has a K-edge of 33.2 keV and therefore, the photoelectric interactions with iodine containing substances or tissues are greatest just above this energy. This is the basis for the use of low energy reconstructions for increasing attenuation of iodine containing tissues such as tumor. However, one has to be aware that there is always a trade-off and this comes at the expense of increased image noise on lower energy reconstructions.

**Basic considerations, implementation, and routine reconstructions using DECT:**

Truly deleterious effects of radiation from occasionally performed basic diagnostic imaging studies are debatable, particularly in adults and in head and neck cancer patients who may receive radiation therapy as part of their treatment regimen. Nonetheless, one must always consider radiation dose in CT and minimize radiation exposure to as low as reasonably achievable. When evaluating and comparing radiation dose, it is important to keep in mind current variations that exist between different protocols, scanners within the same institution, and different institutions. It is also important to keep in mind that radiation dose will affect image quality and therefore, any meaningful comparison of dose needs to take into account image quality. With early generation DECT scanners, the radiation doses reported were at times much higher than that achieved with SECT. However, with current generation DECT scanners, the protocols can be optimized to achieve a similar dose to SECT for a given or in some instances better image quality. When making the transition to DECT scanning, it is advisable for the radiologists to have an idea of typical radiation doses for each protocol using SECT as a benchmark and to be able to evaluate and compare it to the radiation exposure after switching to a DECT protocol/acquisition mode. Once the DECT has been optimized with a
similar/acceptable radiation dose, any additional reconstructions compared to SECT essentially represent an advantage since these are generated through post-processing and without the need for additional patient scanning or radiation exposure.

When starting or transitioning to DECT mode acquisitions, the first essential step is to be familiar with the basic reconstructions that are possible and those similar to that obtained with a SECT acquisition. Using sophisticated image reconstruction algorithms, the information on the high- and low-energy DECT data acquired for a DECT scan can be used to create virtual monochromatic images (VMIs). VMIs represent image reconstructions at different predicted energy levels. This means that for a given keV, the image is depicted as if it were obtained with a monochromatic beam at that energy. Current clinical DECT platforms have post-processing capabilities that enable the reconstruction of VMIs at a wide range of energies, typically between 40 and 140 keV or even higher from some manufacturers. Based on current data in body imaging or head and neck imaging, the VMI reconstruction that is similar to a standard 120 kVp single-energy CT acquisition is at 65 or 70 keV for the neck. In one study using a fast kVp switching technique, the signal-to-noise ratios in normal muscles, normal thyroid and major salivary glands, as well as head and neck squamous cell carcinoma (HNSCC) was consistently highest at 65 keV, supporting the use of VMIs at 65 keV as the standard default reconstruction for the evaluation of the neck (Appendix 2: Figures 3 and 4). However, VMIs reconstructed at other energy levels may be used to increase tumor conspicuity or reduce artifact, as will be discussed below in the section on applications to head and neck imaging.

Another type of reconstruction that one needs to be familiar with if using a dual-source DECT system is the weighted-average (WA) image. These images are created by blending the high- and low-energy acquisition data with dual source CT scanners. The standard reconstruction used is
based on linear blending and merging of 30% of the low (commonly 80 kVp) and 70% of the high (commonly 140 kVp) data. This blended image is typically used to replace the standard 120 kVp single-energy acquisition. However, similar to what is discussed for VMIs, different methods of blending may be used for specialized applications such as improving tumor visualization.

Other than VMIs and WA images that can resemble images from a conventional SECT acquisition depending on the reconstruction energy (VMIs) or weighting factor used (WA), DECT acquisitions also enable creation of another type of reconstruction based on material decomposition. The energy-dependent attenuation of two basis materials of interest at the two different spectral energies can be used to generate images reflecting the composition or content of certain materials. One of these is iodine, because of its strong spectral contrast. This includes generation of iodine overlay maps reflecting the iodine content of tissues, that can of interest for tumor evaluation in the head and neck (Appendix 1: Figure 3). Another type of reconstructions that are widely reported, particularly outside the head and neck, are the virtual unenhanced (VUE) images (VUE). In neuroimaging, these have been used to distinguish hemorrhage from iodine and in body imaging, they have been used for the evaluation of renal stones, among other applications. What has been described so far are some of the most common reconstructions possible with DECT. Many additional and quantitative applications are also possible, including other types of material decomposition, quantitative ROI analysis for creation of spectral Hounsfield attenuation curves, and evaluation of effective Z of tissues, among others that could potentially be used to supplement the above reconstructions for the evaluation of head and neck pathology in the future.

**Applications of DECT for the evaluation of head and neck pathology:**
There are multiple studies suggesting potential utility of additional DECT post-processing and manipulations for the evaluation of head and neck cancer. As discussed earlier, the k-edge of iodine is 33.2 keV, and therefore, iodine attenuation (and consequently attenuation of enhancing structures such as tumor on contrast enhanced neck CT) increases at lower keVs approaching the iodine k-edge. At the same time, this comes at the expense of increased image noise on lower energy VMIs, as would be expected. Nonetheless, different studies using either a quantitative and/or subjective approach have demonstrated that there is increased tumor conspicuity and soft tissue contrast (compared to muscle) on VMIs reconstructed at energies lower than the SECT equivalent 65 or 70 keV VMIs. There is debate regarding the exact energy, and this partly depends on the acquisition platform and parameters as well. However, one study using a fast kVp switching technique suggests that this is best achieved on the 40 keV VMIs (Appendix 1: Figures 2 and 3; Appendix 2: Figures 5 - 7).

Other published studies, using a dual source scanner, suggest higher energy reconstructions. One study using a dual source scanner reported that while tumor attenuation was highest on 40 keV images, the 60 keV VMIs had the highest tumor to muscle contrast to noise ratio and subjective overall image quality. In a later study by the same group, it was reported that by creating an altered or “advanced” form of monoenergetic reconstructions, the objective contrast to noise ratio of tumors was highest on the “advanced” 40 keV images, but the 55 keV images were preferred subjectively. The algorithm used for generation of “advanced” 40 keV reconstructions combined the high signal data obtained at low energies with the superior noise properties seen at medium energies into one reconstructed image. At this time, there is not yet an absolute consensus on the optimal low energy reconstructions for tumor evaluation. This likely also depends on the acquisition parameters and there could possibly be a difference between different
types of scanners. There is also probably a component of user preference and getting used to interpreting the more noisy but greater contrast low energy VMIs. In addition to using low energy VMIs to improve tumor visualization, at least one study using a dual source scanner has reported using different weighting or blending factors for WA images for increasing tumor conspicuity.

Another proposed application of DECT is for the evaluation of thyroid cartilage invasion. Accurate determination of thyroid cartilage invasion is important for proper staging and consequently management of laryngeal and hypopharyngeal cancers. There are challenges for determination of thyroid cartilage invasion, and one of these is the variable ossification of the thyroid cartilage. This is unpredictable and the non-ossified parts of the thyroid cartilage can have attenuation similar to tumor. There are few studies suggesting that DECT can improve evaluation of the thyroid cartilage in HNSCC patients. At least one study has shown that addition of iodine overlay maps (Appendix 1: Figure 3) can improve accuracy for the determination of thyroid cartilage invasion. Using another approach, another study has demonstrated that non-ossified thyroid cartilage has different spectral Hounsfield unit curve characteristics compared to HNSCC (Appendix 3: Figures 3 and 5). Specifically, there is greater suppression of attenuation of enhancing tumor with relative preservation of attenuation of non-ossified thyroid cartilage on high energy VMIs. In a study of 30 different HNSCC patients, it was found that there was no overlap between the attenuation of non-ossified thyroid cartilage and HNSCC on VMIs reconstructed at 95 keV or higher (Appendix 3: Figures 3 – 5). This suggests that high energy VMIs can also be useful for the evaluation of thyroid cartilage invasion (Appendix 1: Figure 5; Appendix 3: Figures 4 and 5). There are also some practical advantages of using high energy VMIs with some DECT platforms that will be discussed during the presentation.
As discussed above, other DECT reconstructions in addition to the SECT equivalent 65 or 70 keV VMIs may have value for the evaluation of HNSCC. However, considering the physics and trade-offs of different reconstructions, it is unlikely that any of these can be used in isolation to replace all other reconstructions. Instead, one approach is a multi-parametric approach to DECT evaluation of the neck. Using this approach, the 65 or 70 keV reconstruction is used as the standard reference with additional reconstructions targeted to supplement and enhance evaluation of the tumor and invasion of critical structures.

In addition to what is discussed above, there are other potential applications of interest to head and neck imaging. For example, another role of high energy VMIs is to reduce metallic and dental artifact. There are multiple studies demonstrating that high energy VMIs can reduce dental artifact, although there is also a reduction in the attenuation of enhancing/iodine containing tumor and therefore, this needs to be balanced when evaluating head and neck pathology (Appendix 1: Figures 6 and 7). There are limited studies suggesting potential utility of DECT for evaluation of lymphadenopathy, and virtual unenhanced images reconstructed from a contrast enhanced acquisition have the potential to replace true unenhanced images in the evaluation of sialolithiasis. These and other potential emerging applications of DECT, including combination of spectral data with advanced image processing, will be briefly discussed during the presentation.

**Selected References:**


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Received: 1 September 2015; Accepted: 27 October 2015; Published: 6 November 2015

Abstract: There is an increasing body of evidence establishing the advantages of dual-energy CT (DECT) for evaluation of head and neck squamous cell carcinoma (HNSCC). Focusing on a single-source DECT system with fast kVp switching, we will review the principles behind DECT and associated post-processing steps that make this technology especially suitable for HNSCC evaluation and staging. The article will review current applications of DECT for evaluation of HNSSC including use of different reconstructions to improve tumor conspicuity, tumor-normal soft tissue interface, accuracy of invasion of critical structures such as thyroid cartilage, and reduce dental artifact. We will provide a practical approach for DECT implementation into routine clinical use and a multi-parametric approach for scan interpretation based on the experience at our institution. The article will conclude with a brief overview of potential future applications of the technique.

Keywords: head and neck squamous cell carcinoma; dual energy CT; fast kVp switching; virtual monochromatic image; iodine overlay map; thyroid cartilage invasion; dental artifact reduction; lymphadenopathy

1. Introduction

Although there has been interest in dual-energy computed tomography (DECT) since the 1970s, it is not until recent technological advances permitting almost simultaneous image acquisition at two different energy levels in a single scan that DECT has become possible for routine clinical use. Since the introduction of clinical DECT scanners in 2006 [1–3], there has been increasing literature on potential applications of DECT in all major subspecialties in radiology [4–7]. In particular, there is increasing evidence supporting the advantages of using DECT for evaluating head and neck pathology, with specific applications for head and neck squamous cell carcinoma (HNSCC) [8–17].

Squamous cell carcinoma is the most common malignancy of the head and neck, other than non-melanoma skin cancers [18]. Conventional, single-energy CT (SECT) is often the first line imaging modality used for characterization, staging, and follow-up of HNSCC below the level of the hard
palete [11,13,19,20]. Because of the often infiltrative growth of HNSCC and the potential for image degradation secondary to various artifacts, achieving images with high lesion contrast, high image quality, and low noise, is essential for optimal delineation of lesions from surrounding tissue and consequently accurate tumor staging and treatment planning [11]. While the technical innovations of multidetector CT (MDCT) have led to substantial improvements in image quality in the last decade, the advent of DECT and its unique post-processing capabilities has now made possible additional tissue characterization and image processing beyond what is possible with conventional, SECT scanners [6,11,15].

In this article, we will review the basic principles behind DECT and the use of DECT reconstructions for improving HNSCC evaluation and staging, focusing on a single-source DECT system with fast kVp switching. We will review the use of different DECT reconstructions for enhancing tumor conspicuity, tumor interface with surrounding normal soft tissues, accuracy of invasion of critical structures such as thyroid cartilage, and dental artifact reduction. We will also provide a practical, multi-parametric approach for scan interpretation and implementation into clinical use based on current evidence and the experience at our institution. Finally, we will provide a brief overview of advanced DECT analysis and other potential future applications for head and neck cancer evaluation.

2. Basic Principles of DECT

Conventional, SECT uses X-rays generated from a rotating tube at a single fixed potential to expose digital detectors after passing through and being attenuated by the patient. The signal that is detected reflects the intensity of the X-ray after attenuation through the patient. Thus, CT images are pictorial representations of the relative attenuation values of tissues, quantified in Hounsfield units (HU) [6,21–23].

Tissue attenuation depends not only on the energy spectrum of the x-ray beam, but also on the density and elemental composition of the material through which it passes [22,23]. While images obtained with SECT provide excellent structural information, material-specific information can sometimes be limited. At a fixed tube potential, different materials can have the same attenuation, and consequently be difficult to distinguish [5].

With DECT, the same anatomic structure is imaged at two different peak energy levels, typically 140 kVp and 80 kVp, providing high and low energy spectra for imaging [3]. The two resulting image datasets allow for analysis of energy-dependent changes in attenuation of different materials, enabling spectral evaluation of tissues at different energy levels [3,5]. Since certain materials or tissues may attenuate x-ray beams differently at different energy levels, spectral evaluation using DECT may be used to accentuate clinically relevant characteristics of the tissue of interest, or improve differentiation of certain tissues. Spectral characterization using DECT is highly dependent on the atomic number (Z) of tissues. For example, many common constituents of normal tissues in the human body have low atomic numbers and would be difficult to distinguish based on their spectral properties. However, iodine has a much higher atomic number (Z = 53), which results in a strong spectral contrast between the heavy atoms of iodinated contrast agents used in CT scanning, and the light atoms of the tissues in the body [3,24]. This property can be exploited to improve evaluation of enhancing lesions such as HNSCC, as will be described and illustrated later in this article.

3. Types of DECT Scanners

There are currently three major types of DECT scanners that use different techniques to acquire high energy and low energy datasets: a dual-source dual-energy scanner, a single-source dual-energy scanner with fast kilovoltage peak (kVp) switching, and a single-source dual-energy scanner with a dual-layer detector (Figure 1).
A dual-source DECT scanner uses two x-ray tubes with corresponding detectors aligned at a 90° angle (Figure 1). Each x-ray tube operates at a different potential, one at higher energy, and the other at lower energy (typically 140 kVp, and 80 kVp, respectively) (Siemens AG, Forchheim, Germany) [3,25]. A single-source DECT scanner with fast kVp switching uses a single X-ray tube and detector combination. With this technique, the tube voltage follows a pulsed curve, and projection data is collected twice for every projection, one at high and one at low tube voltage, during rapid kVp switching; (C) Illustration of a dual layer DECT, consisting of a single source and single (but layered) detector. The detector is composed of two scintillation layers enabling separation of high and low energy spectra produced by a single source.

Figure 1. Different dual-energy CT (DECT) scanners currently in clinical use. (A) Illustration of a dual source DECT, consisting of two source x-ray tubes with corresponding detectors; (B) Illustration of a single source DECT with rapid kVp switching. With this type of scanner, the tube voltage follows a pulsed curve, and projection data are collected twice for every projection, one at high and one at low tube voltage, during rapid kVp switching; (C) Illustration of a dual layer DECT, consisting of a single source and single (but layered) detector. The detector is composed of two scintillation layers enabling separation of high and low energy spectra produced by a single source.

4. Radiation Dose Considerations

The potential harmful effects of radiation exposure from occasionally performed diagnostic imaging studies is debatable [30,31], particularly in the adult head and neck cancer population, who may undergo radiation therapy as a part of their treatment. Nonetheless, radiation exposure from medical imaging must always be considered, and the radiation dose should be as low as reasonably achievable while obtaining scans of high diagnostic quality. It should also be noted that image quality and radiation exposure from a CT scan are inter-related. Therefore, any comparison of dose made between different acquisition techniques must also take into account effects on image quality.

Early after the introduction of clinical DECT scanners, concerns were raised regarding increased radiation exposure to the patient, reported as up to three times compared to a conventional SECT acquisition [32]. However, subsequent improvements in acquisition and post processing techniques have largely overcome these concerns. An initial study in 2007 by Johnson et al. [2] that primarily evaluated material differentiation, demonstrated radiation doses well below reference dose values for the respective body regions. A subsequent study performed on phantoms by Schenzle et al. [33]
compared the radiation doses of first- and second-generation dual-source systems to conventional CT, using different pulmonary CT angiography protocols. The authors found that dose was similar between DECT and SECT protocols, and that lower contrast-to-noise (CNR) ratio with one of the DECT protocols could be overcome, and even improved compared to SECT, by using blended images. More recent studies evaluating various anatomic regions have shown that DECT may even result in a lower radiation dose than SECT, while maintaining similar image quality [33]. These improvements have been attributed to advances in CT technology and software [34].

One of the earliest studies using a single-source DECT scanner with fast-kVp switching considered radiation dose in abdominal imaging protocols. Longer gantry revolution time on first-generation software resulted in significantly higher radiation doses than those of conventional SECT [32]. However, more recent studies with this type of scanner have shown radiation dose levels closer or similar to those of SECT. Using this DECT technique, Li et al. [35] reported 14% higher dose for DECT compared to SECT for a body exam or 22% higher dose for an examination of the head. However, Zhang et al. [36] observed that at equal doses, the diagnostic performance of DECT and SECT were equivalent in abdominal imaging.

Tawfik et al. [37] directly evaluated radiation doses in the head and neck using a dual-source scanner. They reported that both quantitatively and qualitatively, image quality of DECT was comparable to that of SECT, but with a 12% lower radiation dose. Since then, other studies evaluating the head and neck, while not primarily studying radiation dose, have also stated that DECT radiation dose was similar to or less than that of SECT [13]. At our institutions using fast kVp switching scanners, we also routinely obtain neck CTs in dual energy mode without a significant dose penalty compared to SECT scans.

DECT enables multiple additional reconstructions through post-processing that are not possible with SECT. Therefore, if the DECT acquisition can be performed with a similar dose and at least equivalent quality to a SECT, then any additional information obtained from other DECT-specific reconstructions or analysis would represent a relative advantage compared to SECT, since this additional information is essentially obtained for “free”. In addition, because DECT can be used to create virtual unenhanced images for detection of stones, or iodine overlay maps providing a quantitative estimate of tissue iodine content, DECT may under some circumstances result in a reduced number of acquisitions needed as compared to SECT. For example, in abdominal imaging, generation of virtual unenhanced images using DECT post-processing techniques can eliminate the need to perform a true unenhanced acquisition in some CT protocols. As a result, radiation exposure is significantly reduced, which is an additional potential advantage of DECT relative to SECT, for carefully selected applications [38].

5. Improved HNSCC Evaluation and Soft Tissue Boundary Delineation Using Low Energy Reconstructions

CT is often the first line imaging modality for initial staging and follow-up of most HNSCC. Unless contraindicated, CT scans of the neck performed for evaluation of head and neck cancer should be performed after administration of intravenous contrast. Contrast is administered in order to improve soft tissue contrast and to help distinguish tumor from normal tissues or vital structures such as vessels. Administration of iodinated CT contrast agents improves detection and delineation of tumors because of differences in tumor vascularity and enhancement patterns compared to normal soft tissues. However, even on contrast-enhanced scans, tumor can have similar attenuation to certain normal tissues, such as muscle and non-ossified thyroid cartilage, and at times making a distinction can be challenging [16,19,39,40].

When a DECT scan is obtained, one type of image that can be generated is the virtual monochromatic image (VMI). These images represent simulated tissue attenuation as it would appear if the patient was imaged with a monochromatic X-ray beam at the specified energy level. When imaging with a single-source dual-energy CT scanner with fast kVp switching, data can be processed
to obtain images at any energy level between 40 and 140 kiloelectron volts (keV) [26]. With a dual source type scanner, images may also be reconstructed at energy levels higher than 140 keV.

The main physical interactions at X-ray energies being considered (60–150 keV), and those required for spectral tissue characterization, are the photoelectric effect and Compton scattering. However, spectral tissue characterization is particularly dependent on the photoelectric effect. The photoelectric effect is highest just above the k-edge of an atom, which represents the binding energy of the innermost, or K-shell, electrons. The k-edge of iodine is 33.2 keV [3]. As such, the conspicuity or attenuation/density of iodine containing tissues such as enhancing tumor becomes higher on lower energy VMIs approaching the iodine k-edge. However, this comes at the expense of increased image noise on lower keV VMIs. The reason for this is an increased proportion of scatter relative to signal generating photons at lower energies, and this trade-off needs to be taken into consideration.

The increased attenuation of iodine at lower energies can be taken advantage of in order to increase the visual conspicuity and measured attenuation/density of tumor using DECT. In a study performed using a single-source DECT scanner with fast kVp switching, Lam et al. [17] evaluated optimal VMI reconstructions for assessment of normal anatomy and HNSCC. The authors concluded through objective analysis of signal-to-noise ratio (SNR) that 65 keV VMIs had the best overall image quality and suggested that it should be used as the default reconstruction for assessment of the neck. The optimal, highest SNR at 65 keV was closely followed by the 70 keV VMIs, the typical default reconstruction believed to most closely resemble the standard 120-kVp SECT acquisition, based on data extrapolated from body imaging [41,42]. In the same study, it was also shown that tumor conspicuity/attenuation is highest on 40 keV VMIs [17] (Figures 2 and 3). Furthermore, it was shown that the attenuation difference between tumor and muscles was also highest on the 40 keV VMIs, despite the higher image noise on these reconstructions [17] (Figures 2 and 3). We have recently expanded on these observations using data obtained at our two different institutions and also demonstrated that subjectively, 40 keV is the preferred VMI for targeted tumor evaluation by both general radiologists and those who specialize in head and neck imaging [43].

![Figure 2](image_url)

**Figure 2.** Increased tumor attenuation on 40 keV virtual monochromatic images (VMIs). (A) 70 keV single energy equivalent CT image of a right base of tongue tumor (large black arrow) and pathologic right level IIA lymph node (small white arrow) is shown. Note the similar density of both lesions compared to the normal right sternocleidomastoid muscle (M); (B) On the 40 keV image displayed using the same window-level settings, note the higher lesion density as well as higher relative contrast compared to muscle (M). Also note the increased image noise on the 40 keV VMI (B) compared to 70 keV VMI (A).
Higher tumor attenuation on 40 keV VMIs has also been reported using a dual-source DECT scanner [15,44]. However, at least in one study by Wichmann et al., the 60 keV VMIs, rather than the 40 keV VMIs were reported as having the highest tumor contrast to noise ratio and subjective overall image quality [15]. At this time, it is not clear whether the discrepancy between optimal VMI energy level described in the study by Lam et al., using a fast kVp switching scanner, and the study by Wichmann et al., using a dual source scanner, is secondary to technical differences between the scanners or secondary to differences in image acquisition (the acquisition dose was lower in the study by Wichmann et al.). In a later study by Albrecht et al., it was reported that by creating an altered or "advanced" form of monoenergetic reconstructions, the objective contrast to noise ratio of tumors was highest on the "advanced" 40 keV images, but the 55 keV images were preferred subjectively [44]. The algorithm used for generation of “advanced” 40 keV reconstructions combined the high signal data obtained at low energies with the superior noise properties seen at medium energies into one reconstructed image. In addition to using low energy VMIs to improve tumor visualization, other studies have reported using different weighting or blending factors for WA images to improve tumor conspicuity [11]. At this time, there is not yet consensus on the optimal reconstructions for tumor evaluation using a dual-source scanner. There are currently no published reports evaluating HNSCC using a dual layer scanner type.

![Virtual monochromatic images (VMIs) and iodine overlay map of a laryngeal tumor (T) invading the left thyroid cartilage.](image)

**Figure 3.** Virtual monochromatic images (VMIs) and iodine overlay map of a laryngeal tumor (T) invading the left thyroid cartilage. (A) 65 keV VMI; (B) 40 keV VMI; and (C) iodine-water (iodine overlay) material decomposition maps are shown. Note the increased tumor conspicuity on the 40 keV (B) compared to the 65 keV (A) VMIs. The iodine overlay map provides a quantitative estimate of iodine content of different tissues and demonstrates iodine containing tumor transgressing the left thyroid cartilage (arrow). It is noteworthy that the tumor edge of the extralaryngeal component (arrow) is more clearly seen on the 40 keV VMI (B) and iodine overlay map (C) than on the SECT equivalent 65 keV VMI (A).

### 6. Evaluation of Thyroid Cartilage Invasion

Accurate determination of thyroid cartilage invasion is important for proper staging and consequently management and treatment of laryngeal and hypopharyngeal tumors [8,19,45,46]. Both CT and MRI can be used to evaluate cartilage invasion, and each imaging modality has advantages and limitations for staging of laryngeal and hypopharyngeal cancer [19,39,47]. Using a combination of specific diagnostic criteria (sclerosis, erosion, lysis, and extralaryngeal spread) for the evaluation of laryngeal cartilages, Becker et al. have reported that CT can have an overall sensitivity of 82%, specificity of 78%, and negative predictive value of 91% [20,39]. When focusing on thyroid cartilage, sensitivity and specificity were 71% and 83% respectively [48]. MRI can also be used to evaluate thyroid cartilage invasion and is reported to have a very high negative predictive value (94%–96%), but a lower specificity (74%–88%). When considering invasion of the thyroid cartilage specifically,
at least some studies suggest that there is a greater potential for false positives on MRI because of reactive inflammation, edema and fibrosis that may mimic invasion by tumor [20,39]. Obtaining high diagnostic quality MRI examinations can also be problematic in the head and neck cancer population who may have difficulty clearing their secretions and remaining motionless during the much longer examination times for this modality compared to CT.

DECT acquisitions enable creation of reconstructions based on two material or even three material decomposition [3,24]. These reconstructions can be used to isolate materials of interest relative to a reference material, assuming that the two materials have sufficiently different spectral properties. Two common types of reconstructions generated using material decomposition are maps reflecting the iodine content of different tissues, called iodine overlay maps, and virtual unenhanced images [3,24,38]. Iodine overlay maps are of interest in the assessment of HNSCC since they provide a quantitative estimate and a visual representation of the iodine content of different tissues, such as enhancing tumor (Figure 3).

In a study performed using a dual-source DECT, Kuno et al. [9] used iodine maps to help differentiate areas of tumor invasion from normal laryngeal cartilage (Figure 3). The authors showed that the addition of iodine overlay maps to the weighted-average (WA) equivalent of standard SECT 120-kVp images resulted in increased specificity (96% vs. 70%) for the diagnosis of invasion of laryngeal cartilage, without compromising the sensitivity (86% vs. 86%). These values show an improvement over those previously reported in the literature (83% specificity and 71% sensitivity) [48]. Furthermore, Kuno et al. also reported improved inter-observer reproducibility with the addition of iodine maps. Improved specificity and inter-observer reproducibility result in reduced overestimation of tumor invasion, and may help reduce unnecessary laryngectomies [9,46].

Another type of reconstruction that may be useful for evaluating thyroid cartilage invasion is the high energy VMI. Although the attenuation of tumor is very different from that of ossified thyroid cartilage (cortical bone and bone marrow), attenuation of tumor can be similar to that of non-ossified thyroid cartilage (NOTC) [8,16,19,39,40,49,50]. This similarity in attenuation can make detection of small or early invasion problematic in cases where tumor abuts NOTC. In a study using a single-source DECT with fast kVp switching, Forghani et al. [16] compared the spectral attenuation values of HNSCC to normal NOTC. Although this study did not directly evaluate thyroid cartilage invasion, the authors demonstrated that the spectral Hounsfield unit attenuation curves of tumor and NOTC are different, especially at high energies (Figure 4). Specifically, there was progressive separation of the attenuation curves of tumor and NOTC at high energies, without overlap of the curves on VMIs of 95 keV or higher in that patient population [16]. The findings suggest that high energy VMIs may also be helpful for evaluating thyroid cartilage invasion. Based on these observations, tumor invading cartilage would appear as a relatively low density gap, whereas normal NOTC would preserve a relatively high attenuation on the high energy reconstructions (Figure 5). It is noteworthy that since tumor attenuation is suppressed on high energy VMIs, these should be used in conjunction with the 65 and 40 keV VMIs. High energy VMIs are not meant to be used in isolation.
7. Dental Artifact

There is a high prevalence of dental restorations in the general and HNSCC patient population and depending on the type and amount of dental material present, there can be significant associated
artifact and image degradation. This can in turn reduce the diagnostic accuracy of exams and obscure lesions such as tumors, particularly in the oral cavity but also to a lesser extent at other sites, including in the oropharynx. High-density objects like metal create artifact through several mechanisms: photon starvation, beam hardening, and scatter [51,52]. Because of the high density of metal, the entire spectrum of the X-ray beam is absorbed, so-called photon starvation, resulting in zero-transmission, which complicates the filtered back-projection. Beam hardening occurs because of the polychromatic nature of the X-ray beam. As the beam passes through the tissue, the lower energy photons are absorbed disproportionately as compared to the higher energy photons. The X-ray beam that is detected therefore contains photons from the higher energy portion of the spectrum, which manifests as dark streaks [51–55]. Scatter results from the high x-ray attenuation coefficient of bone and metal [51].

Though the extent of artifact can be a function of factors intrinsic to the object causing the artifact, such as shape, size and material composition, modifying the acquisition parameters of the CT scan can reduce artifact [56]. Increasing the peak voltage and the tube current, narrowing the collimation, and optimizing image reconstruction are ways to reduce artifact [51,57,58]. However, the application of these methods may result in a greater radiation exposure or decreased spatial resolution [58]. Certain interpolation techniques may even result in the creation of new artifacts [52,53]. Iterative reconstruction algorithms or sinogram inpainting methods have also been shown to reduce metallic artifact, but not all of these techniques are commercially available for routine use in clinical practice, at least in part because of the large computational power required for some of the algorithms [6,57,59,60].

In clinical practice, imaging at higher peak voltage reduces the magnitude of artifacts, and may potentially represent an approach to improving the quality of CT imaging in patients with dental hardware. Using DECT to reconstruct VMIs that simulate imaging at higher energy levels may therefore reduce metallic artifact [53] (Figures 6 and 7). This effect has been investigated in a number of in vivo and ex vivo studies using orthopedic hardware, and high energy VMIs have been shown to reduce metallic artifact significantly, both quantitatively and qualitatively, improving assessment of the implant, the surrounding bone, and soft tissue interface [51–53,56–58,61].

![Figure 6](image_url). Use of high energy DECT virtual monochromatic images (VMIs) for dental artifact reduction. (A) 65 keV and (B) 140 keV VMIs are shown from the same level in the neck. Note significant reduction of artifact such as in the region of retromolar trigone (black arrow) or oral tongue (white arrow) on the higher energy, 140 keV VMI compared to the 65 keV VMI.
In clinical practice, imaging at higher peak voltage reduces the magnitude of artifacts, and there was less artifact on VMIs than on standard SECT images. Overall, through decreased image contrast, negatively affecting image quality. The study also evaluated different artifact reduction techniques compared to SECT. The authors concluded that overall, model-based iterative reconstruction was most promising, with significant improvement of image quality without loss of image contrast. High energy VMIs (140 keV) obtained with a DECT scanner using fast kVp switching also showed good reduction of artifact, but with lower image contrast at higher energy levels. The authors found that the concomitant use of metal artifact reduction software actually decreased image contrast, negatively affecting image quality. The study also evaluated different materials used in dental hardware, confirming that titanium caused the least amount of artifact on CT, with cobalt-chromium contributing slightly more, and zirconium the most.

There is not yet consensus on the optimal VMI energy level for reduction of dental artifact. Studies evaluating orthopedic hardware have found the optimal VMI to be greater than 90–110 keV on single-source DECT [51,57,61], while optimal VMI on dual-source DECT was between 95 and 150 keV [52,53,56,58]. Pilot studies evaluating VMIs for reduction of dental artifact show similar values, with reported energy levels greater than 88–100 keV for dual-source DECT [55,62], and 140 keV for single-source DECT using fast kVp switching. One of the challenges in dealing with dental artifact is that there can be significant variation depending on the type and amount of material used. The other variable that must be considered is the target lesion being evaluated. For example, if the objective is to better assess bone detail (or invasion) in an area obscured by artifact, there may be much greater leeway or benefit for significantly higher energy VMIs, approaching or even exceeding
140 keV. However, if the objective is to better visualize the actual enhancing tumor, then more intermediate energy VMIs may have to be considered that balance the increased artifact reduction with decreased tumor attenuation and contrast on higher energy VMIs (Figure 7). This is currently being investigated by our group. Nonetheless, so far the evidence shows that high energy DECT VMIs are promising and have the potential for improving lesion assessment in areas obscured by artifact, such as the oral cavity. Further refinements in applications of DECT for artifact reduction, and how they compare to other methods that are being developed using SECT [60,63], are an interesting topic for future research.

8. Other Potential DECT Applications for the Evaluation of HNSCC

There are a few studies suggesting that DECT can improve evaluation of pathologic lymph nodes. In the study by Lam et al. [17], it was demonstrated that in addition to improving visibility of the primary lesion, 40 keV VMIs also improve conspicuity of metastatic lymph nodes. We are currently investigating potential use of these reconstructions for evaluation of nodal heterogeneity. Tawfik et al. [12] have reported that contrast content of metastatic HNSCC lymph nodes is less than that of normal lymph nodes, as quantified by iodine content calculation through the use of iodine overlay maps produced by DECT. Liang et al. [64] have also shown that there can differences in spectral characteristics of metastatic lymph nodes compared to non-metastatic lymph nodes. In their study, they evaluated the slope of lymph node attenuation with respect to the energy level, and calculated the ratio relative to the primary lesion. They reported that the ratio of the slopes was greater for metastatic lymph nodes than for normal lymph nodes, which may not be in agreement with observations from Tawfik’s group. Optimal evaluation of lymph nodes using DECT requires further investigation and is an interesting topic for future research.

9. Practical, Multi-Parametric DECT Approach for HNSCC Evaluation

One of the major advantages of imaging with DECT is that through sophisticated post-processing, different reconstructions can be generated without the need for additional patient scanning or radiation exposure. Although one approach may be to try to find a single best reconstruction that captures all the clinically relevant information, it may not be possible to do so because there is often a trade-off between different key parameters of interest. For example, low energy reconstructions improve lesion conspicuity but at the expense of image noise. High energy reconstructions appear to improve evaluation of thyroid cartilage and reduce dental artifact, but suppress iodine density and therefore result in decreased visibility of the tumor itself. Iodine overlay maps also contain important information regarding the iodine content of the tumor and have been shown to improve accuracy for determination of thyroid cartilage invasion, but lack the complete anatomic information that is available on standard CT reconstructions.

Therefore, instead of relying on a single set of reconstructions, based on our experience and current literature, we recommend a multi-parametric approach to HNSCC evaluation using DECT. Our recommended approach is to supplement the standard single energy CT equivalent VMIs with additional reconstructions targeted for evaluation of specific characteristics of clinical interest, similar to the use of different MRI sequences for lesion characterization. Based on our experience, the high SNR 65 (or 70) keV VMIs should be used for standard evaluation of the neck and as reference images for normal anatomy. These should be supplemented with low energy (40 keV) VMIs for targeted evaluation of the tumor and tumor-soft tissue boundary in all HNSCC cases. For laryngeal and hypopharyngeal tumors, we also recommend complementary evaluation with high energy VMIs (95 keV or greater) and iodine overlay maps, in order to increase accuracy for evaluation of thyroid cartilage invasion. Lastly, the use of high energy VMIs should also be considered for evaluation of oral cavity and possibly oropharyngeal tumors, in order to reduce dental artifact. However, the optimal energy for dental artifact reduction in tumor containing areas is yet to be determined. These recommendations are for a single energy DECT with fast kVp switching and are summarized in
Table 1. It is our opinion that the same overall approach is likely to be beneficial using a dual source scanner (and presumably a dual layer scanner), although there is no clear consensus at this time on the exact reconstruction energies that are best for a dual source scanner.

Table 1. Recommended\(^1\) multi-parametric approach for the evaluation of head and neck squamous cell carcinoma using a single source fast kVp switching dual energy CT scanner.

<table>
<thead>
<tr>
<th>Reconstructions for all dual energy CT scans of the neck:</th>
<th>65 and 40 keV VMIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstructions for evaluation of laryngeal tumors:</td>
<td>65 and 40 keV VMIs + Iodine overlay maps; High energy VMIs (95 keV or greater)</td>
</tr>
<tr>
<td>Reconstructions for evaluation of oral cavity and possibly oropharyngeal tumors:</td>
<td>65 and 40 keV VMIs + Consider supplemental high energy VMIs for dental artifact reduction</td>
</tr>
</tbody>
</table>

\(^1\) Recommendations are based on the current published evidence and the practice at the author’s institutions and are not meant to be exclusive or all encompassing. These are based on a small number of studies and it is likely that there is room for additions or small adjustments according to specific institutional protocols and preferences.

10. Future Prospects and Concluding Remarks

Dual energy CT spectral tissue characterization is an exciting and active area of research. It is likely that additional refinements in technique and recommendations for use of different reconstructions for HNSCC evaluation will emerge for the different DECT platforms in the near future. One of the important considerations for routine clinical use is workflow friendly implementation. Depending on the scanner type and version of the console, different energy VMIs and iodine overlay maps can be generated by the technologists and sent to PACS for clinical use. Some of the newer consoles for certain types of scanners also enable automatic generation of both high and low energy VMIs. Furthermore, some DECT platforms have post-processing software integrated with the clinical PACS, allowing workflow friendly integration. These should facilitate and increase the use of this exciting technology. Implicit in this set up is increased use of resources, including technologist and potentially radiologist time, as well informatics resources such as PACS/IT storage. Therefore, widespread and continuing use of DECT and its spectral capabilities is contingent on the additional value provided for the diagnostic work up and treatment planning for our patients. As such, continued research in this area is of paramount importance, in order to further advance and demonstrate the potential additional value of DECT for tumor characterization. In this regard, in addition to what has been discussed in this article, spectral data from DECT scans contain a wealth of quantitative information that could be potentially be utilized for more advanced tissue and image analysis and these represent exciting topics for future investigations in the era of personalized medicine.

**Author Contributions:** All authors have made substantial contributions to this review article, have expertise in the field of dual energy CT and/or applications to head and neck. All authors agree to be listed and have approved the submitted version of the publication.

**Conflicts of Interest:** R.F. has received a research grant from the Rossy Cancer Network titled “Spectral dual energy CT and textural radiogenomic analysis for optimal tumor delineation, patient staging, and biomarker for head and neck squamous cell carcinoma” and was a speaker at a lunch and learn session titled “Dual-Energy CT Applications in Neuroradiology and Head and Neck Imaging” sponsored by GE Healthcare at the 27th Annual Meeting of the Eastern Neuroradiological Society in Sept 2015.

**References**


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APPENDIX 2:
Optimal Virtual Monochromatic Images for Evaluation of Normal Tissues and Head and Neck Cancer Using Dual-Energy CT

S. Lam, R. Gupta, M. Levental, E. Yu, H.D. Curtin, and R. Forghani

ABSTRACT

BACKGROUND AND PURPOSE: Dual-energy CT is not used routinely for evaluation of the head and neck, and there is no consensus on the optimal virtual monochromatic image energies for evaluating normal tissues or head and neck cancer. We performed a quantitative evaluation to determine the optimal virtual monochromatic images for visualization of normal tissues, head and neck squamous cell carcinoma, and lymphadenopathy.

MATERIALS AND METHODS: Dual-energy CT scans from 10 healthy patients and 30 patients with squamous cell carcinoma were evaluated at different virtual monochromatic energy levels ranging from 40 to 140 keV. The signal-to-noise ratios of muscles at 6 different levels, glands (parotid, sublingual, submandibular, and thyroid), 30 tumors, and 17 metastatic lymph nodes were determined as measures of optimal image quality. Lesion attenuation and contrast-to-noise ratios (compared with those of muscle) were evaluated to assess lesion conspicuity.

RESULTS: The optimal signal-to-noise ratio for all the tissues was at 65 keV ($P < .0001$). However, tumor attenuation ($P < .0001$), attenuation difference between tumor and muscles ($P = .03$), and lesion contrast-to-noise ratios ($P < .0001$) were highest at 40 keV.

CONCLUSIONS: The optimal image signal-to-noise ratio is at 65 keV, but tumor conspicuity compared with that of muscle is greatest at 40 keV. Optimal evaluation of the neck may be best achieved by a multiparametric approach, with 65-keV virtual monochromatic images providing the best overall image quality and targeted use of 40-keV virtual monochromatic images for tumor evaluation.

ABBREVIATIONS: CNR = contrast-to-noise ratio; DECT = dual-energy CT; HNSCC = head and neck squamous cell carcinoma; keV = kiloelectron volt; kVp = kilovoltage peak; VMI = virtual monochromatic image
Summary of primary HNSCC tumor sites evaluated

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (n = 22), primary site</td>
<td>11</td>
</tr>
<tr>
<td>Larynx</td>
<td>7</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>1</td>
</tr>
<tr>
<td>Retromolar trigone, anterior tonsillar pillar</td>
<td>10</td>
</tr>
<tr>
<td>Oral cavity–other</td>
<td>12</td>
</tr>
<tr>
<td>Oropharynx–other</td>
<td>1</td>
</tr>
<tr>
<td>Sinuses, nose</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent or metastatic (n = 8)</td>
<td>6</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>2</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>

*Head and neck squamous cell carcinoma invading the parotid gland, n = 2; parapharyngeal space metastasis, n = 1; cheek, n = 1; and neopharynx, n = 1.

CT750HD; GE Healthcare, Milwaukee, Wisconsin). In this system, spectral separation is achieved on the basis of projection-based material decomposition by using the fast sampling capabilities of a proprietary scintillator detector with low afterglow. Although the broad principles behind both DECT acquisition systems are similar, there are significant differences in hardware, acquisition, and postprocessing. As a result, any cross-platform application of observations made by using either system requires validation. Furthermore, there is currently no consensus on the optimal VMIs for the evaluation of HNSCC or the approach to incorporate DECT into routine clinical use.

The hypothesis behind our investigation was that VMIs acquired at energies other than 70 keV, either alone or in combination, can enhance the conspicuity of HNSCC. The objective of this investigation, therefore, was to determine the optimal VMI that provides the highest image quality and the VMI that enables optimal tumor visualization by using a single-source DECT scan with rapid kVp switching. This determination was made by objectively and quantitatively analyzing normal structures at different levels in the neck and tumors at different primary sites. Spectral evaluation was performed by using different VMI energy levels ranging from 40 to 140 keV in 5-keV increments, and mean attenuation, SNR, and CNR were used as end points for evaluation.

**MATERIALS AND METHODS**

**Patients**

This study was approved by the institutional review board at the Jewish General Hospital (Montreal, Quebec, Canada). A total of 40 patients who had undergone DECT between June 2013 and July 2014 were evaluated retrospectively. There were 10 consecutively healthy patients and 30 consecutive patients with histopathologically proven (by biopsy and/or surgery) HNSCC who met the selection criteria discussed below. Normal cases consisted of normal or near-normal scan results with minor incidental findings (dental periapical lucencies, benign reactive lymph nodes or tonsillar enlargement, and incidental cutaneous lesions such as sebaceous cysts) in patients without known malignancy or major systemic disease. To have a broad and representative sample of HNSCC, patients with primary untreated or recurrent/metastatic tumors from different sites were included (Table). Exclusion criteria included suspected HNSCC not confirmed by biopsy or surgery and any tumor that was too small for sampling by the minimum preset ROI size and numbers (see below).

**CT Technique**

Each patient was scanned with the same 64-section dual-energy scanner (Discovery CT750HD; GE Healthcare). Examinations were performed after the administration of 80 mL of iopamidol (Isovue 300; Bracco Diagnostics, Princeton, New Jersey) injected at a rate of 2 mL/s and the patients were scanned after a delay of 65 sec. All scans were acquired in dual-energy rapid 80- to 140-kVp switching mode by using the following gemstone spectral imaging protocol: gemstone spectral imaging preset at 15, a large-scan field of view (up to 50 cm), a 40-mm beam collimation, a 0.6-second rotation time, and a 0.984:1 helical pitch. Images were reconstructed into 1.25-mm sections in a 25-cm display field of view and a 512 × 512 matrix. The average CT dose index volume for the main acquisition (entire neck to carina) was 17.3 mGy.

**Postprocessing and Image Analysis**

**Postprocessing and General Analysis.** A 70-keV reconstruction is generated automatically by the scanner for standard clinical use. Quantitative image analysis was performed at an Advantage 4.6 workstation (GE Healthcare). Normal structures or lesions were evaluated with circular ROIs, and CT attenuation in Hounsfield units and standard deviation were measured within the ROIs. In each case, quantitative spectral analysis was performed in identical ROIs at different VMI energy levels ranging from 40 to 140 keV, in 5-keV increments, for a total of 21 energy levels per ROI. Each normal structure or lesion was evaluated with multiple ROIs (described in greater detail below). For each patient, the mean attenuation of a given structure or lesion was determined on the basis of the average Hounsfield units of the respective ROIs in that structure or lesion. Image noise was based on the SD in an ROI, and the average noise for each structure or lesion was calculated by obtaining the average SD in their respective ROIs. As described in greater detail below, because of different sizes of normal structures and lesions, different-sized ROIs had to be used. So that the results would not be biased toward larger structures (eg, larger tumors), the average ROI for a given normal structure or lesion for each patient was given equal weight when pooling data from multiple patients.

**Spectral Evaluation of SNR in Normal Tissues.** In the first part of the study, the SNR of muscles and major glands was evaluated. Because of changes in tissue composition and the shape of the neck in the craniocaudal plane, muscles were evaluated at 6 different levels in the neck. From cranial to caudal, the lateral pterygoid (level of fossa of Rosenmüller), masseter (level of parotid), genioglossus (oral cavity), sternocleidomastoid muscle at the level of the submandibular glands, sternocleidomastoid muscle at the level of true vocal cords, and sternocleidomastoid muscle at the level of the thyroid gland were evaluated. In addition, the parotid, submandibular, sublingual, and thyroid glands were evaluated. For consistency, the right side of the neck was evaluated, except for the sublingual gland and genioglossus muscle. In these cases, because of their relatively small sizes, the side with the larger gland or both sides were evaluated. Normal-structure ROIs were iden-
tified by S.L. (diagnostic radiology resident with 3 years of training) and reviewed by R.F. (attending physician with fellowship training and 4 years postfellowship experience in neuroradiology and head and neck radiology) before recording the data for further analysis. For each structure, 3 nonoverlapping ROIs were placed. When possible, all 3 ROIs were placed on the same section, except those for small structures (sublingual and genioglossus), for which the ROIs had to be placed on more than 1 section to obtain good coverage and avoid overlaps or artifacts. ROI sizes that enabled good sampling without overlapping or volume averaging with adjacent structures were used. Areas of visible artifacts, such as from dental amalgam, were avoided. For this part of the study, 30 ROIs per patient were evaluated. Depending on the size of the structure being evaluated, the minimum individual ROI diameter used was 3.3 mm (corresponding to a sampled area per ROI of 8.6 mm²), and the maximum diameter used was 5.8 mm (corresponding to a sampled area per ROI of 26.4 mm²). The SNR was calculated for each structure, in each patient, by dividing the mean CT attenuation for the 3 ROIs by the mean noise (SD) for the ROIs.

Spectral Evaluation of Tumors and Pathologic Lymph Nodes. For tumors, the mean attenuation and tumor–muscle CNR were calculated. In each patient, the tumor and a nearby normal muscle (completely separate from tumor without contact or invasion of any part of that muscle) were evaluated. Each tumor or normal muscle was evaluated with a total of 9 ROIs, placed on at least 3 separate sections (Fig 1). In addition, 17 pathologic lymph nodes in 9 of the patients were evaluated, and each node was evaluated with 9 ROIs. Only grossly pathologic nodes were evaluated on the basis of either 1) biopsy or neck dissection, when such results were available, or 2) an abnormal-appearing node in the primary or secondary drainage area of the primary tumor by at least 2 criteria among the following: abnormal short-axis diameter, internal necrosis/heterogeneity, rounded contour, or irregular contour. For tumors and lymph nodes, the ROIs were placed in the homogeneous-appearing enhancing part of the lesion, avoiding areas of cystic change/necrosis or visible artifacts. For muscles, the ROIs were placed in areas without visible artifacts. For each normal-appearing structure or lesion, the mean attenuation was determined on the basis of the average Hounsfield units of the respective ROIs in that structure or lesion. Image noise was calculated as the SD in the ROI, and the average noise for each structure or lesion was calculated by obtaining the average SD in their respective ROIs. For tumors, the minimum individual ROI diameter used was 1.7 mm (sampled area per ROI, 2.3 mm²), and the maximum diameter used was 5.5 mm (sampled area per ROI, 23.8 mm²). For lymph nodes, the ROI size range was 2.3–4.7 mm (area, 4.2–17.3 mm²), and for muscles it was 2.3–4.8 mm (area, 4.2–18.1 mm²). To select an ROI size that provided good sampling and could be applied to different structures in each patient, the size of the ROIs varied because of differences in lesion or muscle size, tumor or lymph node homogeneity, and presence of artifacts. All ROIs in this section were placed by the attending head and neck radiologist (R.F.). The CNR was calculated individually for tumor or lymph node in each patient by using the formula CNR = (average lesion attenuation – average muscle attenuation)/√(variance [lesion] + variance [muscle]).

Statistical Analysis
The results are reported as mean ± SD. All comparisons between patients were performed by using the mean attenuation and/or noise from the structure or lesion of interest from each patient (and not by simply pooling all individual ROIs among all patients, which would have artificially inflated the statistical power of the study). Means from 2 different groups were compared by using a Student t test. For comparisons of multiple (>2) groups, 1-way ANOVA with the Dunnett multiple-comparisons test was used. Data from different ROI samples were compared by using an un-
paired test. Spectral data at different keVs derived from the same ROIs were analyzed by using paired analysis. Variance was calculated by using the standard formula variance = SD^2. A P value of <.05 was considered statistically significant. We used GraphPad Prism software for statistical analysis (version 6.005; GraphPad Software, San Diego, California).

RESULTS

DECT scans from 10 healthy subjects and 30 subjects with HNSCC with a total of 993 ROIs were evaluated. The mean patient age was 66 years (range, 37–97 years; 20 women, 20 men). In healthy subjects, a total of 6 muscle levels and 4 glands per patient were evaluated, each with 3 ROIs, corresponding to a total of 300 ROIs. The average ROI area evaluated per structure was 62.7 mm^2 (range, 27.2–75.6 mm^2).

Spectral Attenuation Characteristics and Optimal SNR of Muscles and Normal Glands

Muscle and gland attenuation progressively increased on lower-keV VMIs. However, the highest SNR for all the muscle groups and glands was at 65 keV. For all muscles combined, the mean SNR was 8.0, and for all glands combined the mean SNR was 9.5 at 65 keV. At this energy, the SNR was significantly greater than those at all other energies (1-way ANOVA with Dunnett multiple-comparisons test; Figs 2 and 3). This SNR was closely matched by the SNR at 70 keV (muscles, 7.9; glands, 9.0), followed by that at 60 keV (muscles, 7.1; glands, 8.8; Figs 2B and 3B). In addition to normal tissues, we also evaluated the SNRs of 30 tumors and 17 pathologic lymph nodes, and the optimal SNR was also at 65 keV (Fig 4).

Optimal VMIs and CNR for Evaluation of HNSCC

Similar to muscle, tumor attenuation increased at lower keVs. Tumor attenuation was highest on 40-keV VMIs, significantly different from those at all other energy levels (1-way ANOVA with Dunnett multiple-comparisons test; Fig 5). However, the slope of the increase in tumor attenuation was greater than that in muscles, resulting in greater attenuation separation in the low-keV range (Fig 5A). The greatest difference between tumor and muscle attenuation was at 40 keV. On VMIs reconstructed at this energy level, the mean tumor attenuation was 207.9 ± 46.8 and the mean muscle attenuation was 115.2 ± 31.3 (P = .03, unpaired 2-tailed t test; Fig 5). Because there is a progressive increase in image noise on lower-keV images, we also calculated tumor-muscle CNR as a quantitative index for lesion conspicuity. The tumor CNR was likewise highest at 40 keV, despite the increase in image noise, and significantly higher than those at other keVs.
energy levels (1-way ANOVA with Dunnett multiple-comparisons test; Fig 5).

**Optimal VMI for Evaluation of Metastatic Lymphadenopathy**

A total of 17 metastatic lymph nodes were evaluated, and lymph node–muscle CNRs were calculated as measures of conspicuity. Similar to those of tumors, the lymph node–muscle CNR was highest at 40 keV and significantly different from those at other energy levels (1-way ANOVA with Dunnett multiple-comparisons test; Fig 5). Although tumor–muscle and lymph node–muscle CNRs were highest at 40 keV, the optimal SNR was at 65 keV, similar to that of normal tissues (Fig 4).

**Comparison of 40-keV VMIs with Other Key DECT VMIs**

Mean tumor attenuation on 40-keV VMIs was significantly higher than that on 60-keV VMIs, 65-keV VMIs (optimal tissue SNR), and 70-keV VMIs (current standard reconstruction) (*P* < .0001; Fig 6A). Tumor–muscle CNRs were likewise significantly higher on 40-keV VMIs than on 60-, 65-, and 70-keV VMIs (*P* < .0001; Fig 6B). Qualitatively, the higher attenuation and CNR are result in increased tumor conspicuity at 40 keV (Fig 7).

**DISCUSSION**

In this investigation, we evaluated the optimal VMI energy levels for evaluation of the neck. Normal structures and lesions were evaluated by a general quality index, the SNR. In addition, the VMI energy level that provided optimal HNSCC and pathologic lymph node conspicuity was quantitatively evaluated by measuring lesion attenuation and calculating the CNR. Currently, the default reconstruction on the single-source dual-energy scanner with rapid kVp switching used in this study for neck CTs is 70 keV, the VMI believed to simulate the standard 120-kVp single-energy acquisition by extrapolation from abdominal CT studies. On the basis of our results, the 65-keV VMI has the optimal SNR and can be used as the default reconstruction for assessment of the neck. Similar observations have been made for head DECT scans by using this type of scanner.5 By extrapolation, one would expect that the 65 keV VMI also provides the optimal SNR for evaluation of other normal soft-tissue structures in the neck, such as small normal-appearing lymph nodes, but this could be validated in future studies targeted at the evaluation of those structures.

Although the 65-keV VMIs yielded the best SNR, both absolute tumor attenuation and contrast (by using normal muscles as reference) were highest on 40-keV VMIs. The increase in attenuation on lower-keV VMIs is expected, because these energies approach the *k* edge of iodine. Although image noise increases with decreasing VMI energy levels, the tumor–muscle CNR was still highest on the 40-keV reconstructions. This observation is different from that in a recently published study in which 40-, 60-, 80-, and 100-keV VMIs were evaluated, and it was reported that the highest tumor–muscle CNR was achieved at 60 keV.10 The reason for the difference is not entirely clear, but a number of explanations need to be considered. In the aforementioned study, a dual-source scanner was used. Apart from differences in acquisition, the methods of postprocessing for that scanner are different. Therefore, one possibility is that the differences are technical, related either to the different modes of acquisition and/or postprocessing algorithms. It is also noteworthy that noise was measured differently by using an ROI outside the patient, placed in air. We prefer using the SD within the tissues of interest as an indicator of noise and believe that it is more pertinent to clinical evaluation, similar to the method used by Pomerantz et al.5 This represents another potential source of variation, though we believe that it is less likely to account for the differences between the 2 studies. Future studies using larger sample sizes and comparing both systems would be of interest.

In our study, we evaluated normal structures at multiple levels...
in the neck and tumors at different subsites to make sure that our conclusions can be applied generally to the evaluation of the neck. However, one limitation is that the number of HNSCC tumors for each specific subsite was small, and our study did not evaluate lesions centered at the skull base. Therefore, it is possible that additional adjustments may further improve evaluation at a given cancer subsite. Furthermore, we focused on the enhancing part of the tumor rather than the hypoenhancing core, which is pertinent for distinguishing the tumor–normal tissue interface. However, there are additional parameters of clinical interest that were not evaluated in this study, such as distinguishing enhancing and hypoenhancing parts of a lesion, which can potentially be relevant for the evaluation of lesions such as small pathologic lymph nodes. These topics are of interest for future research.

We also focused on quantitative objective evaluation, which we believe is more robust and reliable than subjective evaluation. It has been our experience that similarly windowed low-keV VMIs are clearly distinguishable from the standard-energy VMIs at 70 keV, which makes a blinded subjective comparison nearly impossible. Furthermore, we have found that user acceptance of noise levels changes with exposure and experience. Therefore, although subjective evaluation is an interesting topic of future investigation, any such study needs to be designed carefully with well-defined end points and by taking into account the above-mentioned considerations and pitfalls. Last, our study did not address the optimal assessment of areas obscured by artifacts. Artifact reduction is a complex topic that merits a separate dedicated investigation.

CONCLUSIONS

The optimal image SNR is at 65 keV, but tumor conspicuity, compared with that of other soft tissues, is greatest at 40 keV. Therefore, on the basis of our observations, we recommend that standard neck reconstructions using this type of scanner be made with a 65-keV VMI and in addition, a 40-keV VMI reconstruction generated for the evaluation of patients with HNSCC. We do not advocate replacing the 65-keV reconstruction with the 40-keV VMI. Instead, we recommend that both the standard 65-keV VMI reconstructions and the 40-keV VMIs be automatically generated and sent to the PACS for evaluation of patients with cancer. Optimal evaluation of the neck may then be performed by a multiparametric approach. Using the proposed approach, the 65-keV VMIs providing the best overall image quality are used for general evaluation of the neck, supplemented with the targeted use of 40-keV VMIs for tumor detection and optimal HNSCC–soft tissue boundary visualization.

ACKNOWLEDGMENTS

We thank Ms. Veronika Glyudza for her assistance in data preparation and processing.

Disclosures: Rajiv Gupta—UNRELATED: Board Membership: Actelion Corp. Comments: advising the company on imaging in their drug trials; Grants/Grants Pending: Siemens Medical Solutions.ª Comments: research grant to Massachusetts General Hospital; the principal investigator on the grant (Udo Hoffman, MD) is not an author on this paper; Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Siemens Medical Solutions, Comments: travel support for an educational symposium on photon-counting CT organized by Siemens Medical Solutions. Mark Levental—UNRELATED: Consultancy: Biogen Idec. Comments: honorarium for attending a training seminar; Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Royal College Examiner, Comments: reimbursement of expenses; Hugh Curnin—UNRELATED: Royalties: Elsevier, Comments: royalties for textbook; Reza Forghani—UNRELATED: Consultancy: Biogen Idec, Collège des médecins du Québec, Comments: one-time honorarium for attending a training seminar; expert consultant for Collège des médecins du Québec (telemedicine committee, quality assurance); Expert Testimony: Collège des médecins du Québec, Comments: quality assurance and reviews; Payment for Lectures (including service on Speakers Bu-
quality assurance committee. *Money paid to the institution.


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APPENDIX 3:
Different Spectral Hounsfield Unit Curve and High-Energy Virtual Monochromatic Image Characteristics of Squamous Cell Carcinoma Compared with Nonossified Thyroid Cartilage

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ABSTRACT

BACKGROUND AND PURPOSE: The attenuation of normal nonossified thyroid cartilage can be similar to that of head and neck squamous cell carcinoma on CT. We compared dual-energy CT spectral Hounsfield unit attenuation characteristics of nonossified thyroid cartilage with that of squamous cell carcinoma to determine the optimal virtual monochromatic image reconstruction energy levels for distinguishing tumor from normal nonossified thyroid cartilage.

MATERIALS AND METHODS: Dual-energy CT scans from 30 patients with histopathology-proved squamous cell carcinoma at different primary sites (laryngeal and nonlaryngeal) and 10 healthy patients were evaluated. Patients were scanned with a 64-section single-source scanner with fast-kilovolt (peak) switching, and scans were reconstructed at different virtual monochromatic energy levels ranging from 40 to 140 keV. Spectral attenuation curves of tumor and nonossified thyroid cartilage were quantitatively evaluated and compared. Any part of the tumor invading the cartilage, when present, was excluded from ROI analysis to avoid cross-contamination from areas where there could be a mixture of cartilage and invading tumor.

RESULTS: Normal nonossified thyroid cartilage had a characteristic, predictable spectral attenuation curve that was different from that of tumors. The greatest difference in attenuation of nonossified cartilage compared with tumor was on virtual monochromatic images of $\geq 95$ keV ($P < .0001$), with sharp contrast between the relatively high attenuation of nonossified cartilage compared with that of tumor.

CONCLUSIONS: Head and neck squamous cell carcinoma has significantly different attenuation on virtual monochromatic images of $\geq 95$ keV, compared with nonossified thyroid cartilage.

ABBREVIATIONS: CNR = contrast-to-noise ratio; DECT = dual-energy CT; HNSCC = head and neck squamous cell carcinoma; NOTC = nonossified thyroid cartilage; SHUAC = spectral Hounsfield unit attenuation curve; VMI = virtual monochromatic image

Head and neck squamous cell carcinoma (HNSCC) is a common malignancy of the larynx and hypopharynx. Imaging plays a key role in staging of laryngeal and hypopharyngeal cancers, and accurate staging is necessary to help determine whether a patient will undergo organ-preserving treatment or laryngectomy. An important aspect of staging is to determine whether there is thyroid cartilage invasion. CT is typically the first-line technique for evaluation of laryngeal cancer, but evaluation of thyroid cartilage invasion remains a challenge on CT, in large part due to variable ossification of the thyroid cartilage. Although tumor has a different appearance from both the cortex and the fat-filled medullary space of ossified cartilage, the attenuation values of tumor and nonossified thyroid cartilage (NOTC) are very similar. Several criteria have been evaluated and proposed to improve the accuracy of CT for detection of cartilage invasion, but none are perfect.

Dual-energy CT (DECT) evaluates tissues at different x-ray energies, enabling spectral evaluation and material tissue characterization. With DECT, projection data are typically obtained simultaneously or near-simultaneously at 80 and 140 kilovolts (peak) (kVp). The measured values at the different acquisition energies can then be normalized to specific combinations of 2 different reference materials, such as iodine, water, or calcium. Furthermore, with sophisticated reconstruction algorithms, the

Published March 5, 2015 as 10.3174/ajnr.A4253

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information obtained from the different acquisitions can be combined to generate images at different predicted energy levels (kiloelectron volt [keV]), referred to as virtual monochromatic images (VMI). Depending on their elemental properties, different tissues have distinct attenuation, signal to noise, and contrast at different VMI energy levels, enabling spectral evaluation of tissue attenuation.\textsuperscript{16-17} Although currently there is only limited evidence, emerging data demonstrate advantages of DECT for head and neck imaging, with the potential for improved tumor visualization and material characterization.\textsuperscript{18-21} Kuno et al\textsuperscript{22} have also demonstrated that the addition of iodine overlay maps can increase interobserver reproducibility and improve the specificity of CT for determination of cartilage invasion without decreasing sensitivity compared with conventional CT images alone.

On contrast-enhanced CT, NOTC has relatively high intrinsic attenuation without measurable blood supply or iodine, whereas HNSCC demonstrates increased attenuation secondary to increased iodine content after administration of IV contrast. Therefore, because of their different compositions, we hypothesized that DECT virtual monochromatic images reconstructed at different energy levels may be useful in distinguishing tumor from nonossified thyroid cartilage, and in this investigation, we compared the spectral Hounsfield unit attenuation curve (SHUAC) characteristics of HN

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Primary Site & No. of Patients \\
\hline
Untreated tumors (n = 22) & 7\textsuperscript{a} \\
Larynx & 1 \\
Hypopharynx & 3 \\
Retromolar trigone, anterior tonsillar pillar & 5 \\
Oral cavity, other & 3 \\
Oropharynx, other & 3 \\
Sinuses, nose & 3 \\
Recurrent or metastatic tumors (n = 8) & \\
HNSCC invading parotid (n = 2), parapharyngeal space metastasis, oral cavity (n = 2), base of tongue, cheek, neophraynx & \\
\hline
\end{tabular}
\caption{Summary of primary HNSCC tumor sites evaluated}
\end{table}

\textsuperscript{a} Three of 7 laryngeal tumors had pathologically proven thyroid cartilage invasion.

\textbf{MATERIALS AND METHODS}

\textbf{ Patients}

The study was approved by the institutional review board. Thirty patients with proved HNSCC (by biopsy and/or surgery) and 10 healthy patients who had undergone DECT between June 2013 and July 2014 were retrospectively evaluated. Tumors from different primary sites were evaluated and are summarized in the Table. They included 7 patients with laryngeal carcinoma and 1 patient with hypopharyngeal carcinoma. Healthy patients were selected ad hoc from the same period (please refer to On-line Appendix for additional details on patient selection).

\textbf{ Image Acquisition}

All patients were scanned with the same 64-section dual-energy scanner (Discovery CT750 HD; GE Healthcare, Milwaukee, Wisconsin). All examinations were acquired after administration of IV contrast. Eighty milliliters of iopamidol (Isovue 300; Bracco, Princeton, New Jersey) was injected at a rate of 2 mL/s, and the patient was scanned after a delay of 65 seconds. Scans were acquired in dual-energy rapid 80- to 140-kV[p] switching mode by using the Gemstone Spectral Imaging (GE Healthcare) protocol. These were acquired with a Gemstone Spectral Imaging preset 15, with a large scan FOV (\(\leq 50 \text{ cm}\)), 40-mm beam collimation, 0.6-second rotation time, and 0.984:1 helical pitch. Images were reconstructed into 1.25-mm sections in a 25-cm display FOV and 512 \(\times\) 512 matrix. The average CT dose index volume for the main acquisition (entire neck to the carina) was 17.3 mGy.

\textbf{ Image Postprocessing and Analysis}

Quantitative image analysis was performed at the Advantage Workstation 4.6 (GE Healthcare). Scans were retrospectively reconstructed into different VMI energy levels ranging from 40 to 140 keV in 5-keV increments. Tumor and NOTC evaluation was performed by measuring mean CT attenuation (in Hounsfield unit \pm SD) within ROIs across the entire range of VMI energy levels.

First, NOTC was evaluated in healthy patients. Eighteen ROIs were placed in the NOTC in each patient, 9 on each side, to compare and confirm similarity of the 2 sides. Thereafter, normal NOTC and tumors were evaluated in 30 patients with HNSCC. In this population, the NOTC and tumor were each evaluated with 9 ROIs placed on at least 3 separate sections. For tumors, the ROIs were placed in the homogeneous-appearing enhancing part of the tumor, avoiding areas of cystic change or necrosis. For NOTC, ROIs were placed in the nonossified part of the thyroid cartilage, avoiding the area immediately adjacent to a site of ossification. In healthy patients and in patients with tumor who had primary tumors outside the larynx, ROIs were placed bilaterally within the NOTC. In patients with laryngeal cancers, ROIs were placed in either the contralateral normal NOTC, or if placed in the ipsilateral NOTC, they were placed in an area separated by at least 5 sections (6 mm) from any area of contact between tumor and cartilage. For evaluation of tumor in patients with laryngeal cancer, any part of the tumor adjacent to or invading the cartilage, when present, was excluded from quantitative ROI analysis to avoid cross-contamination from areas where there could potentially be a mixture of cartilage and invading tumor.

A total of 693 ROIs were evaluated. The sizes of the ROIs varied because of differences in thickness of the NOTC, tumor size, and tumor homogeneity among patients. The minimum individual ROI diameter used was 1.5 mm (corresponding to a sampled area per ROI of 1.77 mm\(^2\)), and the maximum diameter used was 5.5 mm (corresponding to a sampled area per ROI of 23.76 mm\(^2\)). As discussed earlier, multiple, at least 9, ROIs were used per structure, and the average ROI area evaluated per structure (normal cartilage or tumor) was 86.8 mm\(^2\) (range, 21.2–212.1 mm\(^2\)). The ROIs were averaged for each structure. So that the results are not biased toward larger structures (eg, larger tumors),
the average ROI for each patient’s NOTC or tumor was given equal weight when pooling data from multiple patients. Care was taken to avoid overlap of the ROI with adjacent tissues or necrotic parts of tumor to avoid volume averaging. All ROIs were placed by an attending physician with fellowship training and 4 years’ postfellowship experience in neuroradiology and head and neck radiology (R.F.). Additional information on the ROI analysis is provided in the On-line Appendix.

For each patient, the mean tumor and/or normal NOTC attenuation was determined on the basis of the average Hounsfield unit of the respective ROIs in that patient. Image noise was calculated as the SD in the ROI, and the average noise for each tumor or NOTC was calculated by obtaining the average SD in their respective ROIs. Comparisons of tumor and NOTC attenuation were performed by obtaining the average Hounsfield unit in all patients across the VMI range (40–140 keV). Tumor and NOTC contrast-to-noise ratios (CNRs) were calculated individually for each patient by using the following formula: CNR = \( \frac{(\text{Average Tumor Attenuation} - \text{Average Cartilage Attenuation})}{\text{Square Root} \left[ \text{Variance (Tumor)} + \text{Variance (Cartilage)} \right]} \). In 3 patients with HNSCC, the thyroid cartilage was completely ossified. In this subgroup, the CNR calculation was performed by using the average normal NOTC attenuation from the other 37 patients (27 with HNSCC and 10 healthy patients).

**Statistical Analysis**

Results were reported as mean ± SD. Pooled average SHUAC curves were generated from 40 to 140 keV, in 5-keV increments for comparison of NOTC and tumor. For comparison of means from 2 different groups, an unpaired 2-tailed t test was used. For comparison of multiple (>2) groups, 1-way ANOVA with the Tukey multiple comparison test was used. Variance was calculated by using the standard formula: variance = SD². A P value < .05 was statistically significant. We used GraphPad Prism software, Version 6.005, for statistical analysis (GraphPad Software, San Diego, California).

**RESULTS**

We first evaluated the spectral Hounsfield unit characteristics of normal NOTC in a group of 10 healthy patients (Fig 1A). The NOTC attenuation was highest at 40 keV and progressively decreased on higher kiloelectron volt VMIs (Fig 1A). There was no significant difference in the spectral Hounsfield unit characteristics of the right compared with the left NOTC. We then evaluated normal or unaffected NOTC in 30 patients with HNSCC (average age, 72 years; range, 56–97 years; 15 men, 15 women). Their primary tumor sites are summarized in the Table. Of the patients from the tumor group, 27 normal (or unaffected) NOTCs were included. In 3 patients, the entire thyroid cartilage was ossified and, therefore, was excluded from the analysis. There was no significant difference in NOTC between healthy subjects and those with normal or unaffected NOTC in the group of patients with HNSCC (Fig 1B). Subgroup analysis of normal/unaffected NOTC in the healthy patient group, patients with laryngeal cancer, those with untreated primaries outside the larynx, and those with recurrent/metastatic tumors was also performed with 1-way ANOVA with Tukey multiple comparison tests. There was no significant difference in the attenuation of normal NOTC between any of the groups, at any of the kiloelectron volts evaluated between 40 and 140 keV. The normal and unaffected NOTC spectral Hounsfield unit attenuation measurements from healthy patients and those
with tumor were combined and pooled from hereon for other comparative analyses (Fig 1C).

We next evaluated and compared the spectral attenuation characteristics of HNSCC and NOTC. Untreated primaries from the larynx \( (n = 7) \), extralaryngeal sites \( (n = 15) \), and recurrent/metastatic tumors \( (n = 8) \) were evaluated (Fig 2). All tumor subgroups had overall similar SHUAC characteristics (Fig 2). As expected, the attenuation of tumors was highest at 40-keV VMI, the kiloelectron volt closest to the k-edge of iodine. Given the similarity in their SHAUCs, the tumors were all combined and compared with NOTC (Fig 3A). The SHUAC of tumors differed from that of NOTC, with a statistically significant difference in the mean attenuation of all tumors combined compared with NOTC at all kiloelectron volts except 50, 55, and 60 keV (Fig 3A, \( P < .001 \)).

At 70 keV, the VMI energy level typically considered to be similar to that obtained with conventional single-energy CT, there was a small difference between mean tumor and NOTC attenuation, with overlap between the 2 groups on the scatterplot (Fig 3B). At the lowest extreme of the curve, at 40 keV, both tumor and NOTC had the highest average attenuation. However, the difference between tumor and NOTC was best seen on the higher kiloelectron volt VMIs, due to a combination of differences in attenuation and reduced variation (SD) of the measured values in different patients (Fig 3A, B). Indeed, in the groups evaluated in this study, there was no overlap between individual mean tumor and NOTC attenuation on VMIs reconstructed at \( \geq 95 \) keV (Fig 3B).

**FIG 2.** Comparison of spectral Hounsfield unit characteristics of different tumor subgroups: untreated larynx primaries \( (n = 7) \), untreated nonlarynx primaries \( (n = 15) \), and recurrent/metastatic tumors \( (n = 8) \). Note that the spectral Hounsfield unit attenuation curves of all the HNSCC tumor groups follow a similar trend, with increased attenuation of enhancing tumor at lower kiloelectron volts and decreased attenuation at higher kiloelectron volts. Values shown are mean \( \pm \) SD.

**FIG 3.** Spectral Hounsfield unit characteristics of head and neck squamous cell carcinoma compared with normal nonossified thyroid cartilage. A, Spectral Hounsfield unit curve of HNSCC at different primary sites \( (n = 30) \) compared with normal (or unaffected) NOTC \( (n = 37; 27 \) normal/unaffected NOTCs from the patients with tumor group and 10 NOTCs from healthy patients). B, Scatterplot of individual tumor densities at selected VMIs shows overlap between tumor and NOTC densities at many VMIs but complete separation at high-energy VMIs. C, Contrast-to-noise analysis performed at different kiloelectron volt VMIs demonstrating the higher absolute CNR at high-energy VMIs. D, Subgroup analysis of the laryngeal \( (n = 7) \) and nonlaryngeal (including a case of hypopharyngeal tumor; \( n = 23 \) ) primary sites. Three asterisks denotes \( P < .001 \); 4 asterisks denotes \( P < .0001 \); and ns, not significantly different.
Subgroup analysis of the laryngeal \((n = 7)\) primaries demonstrated similar trends in SHUAC, with persistent clear separation from the normal NOTC curve in the high kiloelectron volt range (Fig 3D). Subgroup analysis comparing NOTC with the untreated laryngeal primaries, untreated primaries outside the larynx, and recurrent/metastatic tumors also demonstrated a statistically significant difference between NOTC and all tumor subgroups on VMIs reconstructed at \(\geq 70\) KeV \((P < .0001, 1\text{-}way ANOVA)\), with the greatest difference at \(\geq 95\) KeV.

We also calculated the CNR to factor in differences in noise levels at different VMI energy levels. As in the previous observations, the absolute CNR was highest on high kiloelectron volt images (Fig 3C). Note that the negative values in Fig 3C indicate that tumor has a lower attenuation than NOTC at these kiloelectron volts. Therefore, tumor invasion of NOTC would be expected to appear as a low-attenuation defect in the otherwise high-attenuation NOTC (Figs 4 and 5).

**DISCUSSION**

Accurate determination of thyroid cartilage invasion is important for proper staging and treatment planning of laryngeal and hypopharyngeal cancers.\(^1\)\(^-\)\(^8\) Evaluation of thyroid cartilage invasion on imaging remains a challenge because of variable ossification and appearance of thyroid cartilage and similarities in attenuation of tumor and NOTC on CT.\(^1\)\(^,\)\(^2\)\(^,\)\(^10\)\(^,\)\(^11\) While tumor preferentially invades the ossified part of the cartilage, the similarity in appearance of NOTC and tumor can make definitive assessment for invasion challenging in cases in which tumor abuts the nonossified part of thyroid cartilage. Clear distinction of invasive tumor and focal nonossification of the cartilage may not be possible.

Kuno et al.\(^22\) demonstrated that DECT iodine overlay images improved the specificity of detection of laryngeal cartilage invasion. In our investigation, we compared the spectral Hounsfield unit characteristics of tumor and NOTC by using a single-source DECT with rapid kiloelectron volt switching to determine the utility of VMIs reconstructed at var-

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**FIG 4.** Differences in attenuation of NOTC (arrows) and tumor (T) on different kiloelectron volt VMIs. Axial contrast-enhanced CT images are shown from a patient with a supraglottic squamous cell carcinoma with the same section reconstructed as a virtual monochromatic images at 70, 40, and 140 keV. A, Seventy-kiloelectron volt VMI shows tumor abutting the inner surface of the right NOTC. B, Forty-kiloelectron volt VMI shows greater attenuation of the tumor than on the 70-keV VMI due to iodine content, increased contrast between tumor and NOTC, and somewhat better depiction of tumor-NOTC interface. C, One hundred forty–kiloelectron volt VMI shows suppression of tumor attenuation but preserved high attenuation in the NOTC. Note the qualitative contrast improvement with clear distinction of tumor-NOTC interface.

**FIG 5.** Quantitative spectral Hounsfield unit attenuation characterization of tumor and NOTC in a patient with pathologically proved tumor invasion into the thyroid cartilage. VMIs reconstructed at 40 keV (A) and 140 keV (B) demonstrate tumor invasion into the anterior left thyroid cartilage (white arrows). Note variable ossification of the left thyroid cartilage and minimal focal nonossification of the right thyroid cartilage. On the 140-keV VMI, attenuation due to invasion of the left thyroid cartilage (white arrows) is suppressed, appearing as a defect, compared with the normal ipsilateral NOTC and contralateral NOTC (red arrows). C and D, An example of quantitative analysis is shown, demonstrating individual spectral Hounsfield unit attenuation curves for different ROIs. Note the differences in spectral attenuation characteristics of tumor (T) compared with normal ipsilateral and contralateral NOTC. The spectral curve shows clear attenuation separation in the higher kiloelectron volt range. Please note that the curves shown in this figure are those for individual ROIs. In earlier figures, the average from multiple ROIs (at least 9) per structure, per patient, was used to calculate pooled mean attenuation for each group or subgroup (in addition, areas of invasion were not included in the earlier pooled analysis).
ious kilo-electron volt levels for distinguishing tumor from NOTC. Our study expands on observations by Kuno et al that DECT can be helpful in the evaluation of laryngeal cartilage in patients with HNSCC. In our study, we evaluated another aspect of DECT, VMIs reconstructed at different kilo-electron volt energy levels, to characterize and compare HNSCC and unaffected NOTC.

Although in this investigation we did not directly evaluate thyroid cartilage invasion, the observations in this study are a step toward application of VMIs and SHUAC analysis for assessment of NOTC and proceeding to studies evaluating NOTC invasion. We demonstrate that HNSCC has a very different spectral Hounsfield unit attenuation curve than normal NOTC. Although there was some difference in mean attenuation between NOTC and tumor at 70 keV, the VMI energy level similar to that of a standard single-energy CT acquisition, the difference was small and there was overlap between individual tumor and NOTC attenuation. This finding reflects the challenges that can be encountered in distinguishing NOTC from tumor on conventional CT.

On the other hand, there were significant differences in attenuation at either extreme of the VMI energy curve, with the distinction between tumor and NOTC best achieved on VMIs of $\geq 95$ keV. On high kilo-electron volt VMIs, iodine attenuation in enhancing tumor is partially suppressed, whereas the normal NOTC retains a relatively high and fairly uniform attenuation and would therefore be distinct from adjacent tumor (Fig 4). Against the high-attenuation background of NOTC, tumor would be expected to appear as a relatively low-attenuation defect that stands out from the normal thyroid cartilage (Fig 5). Normal NOTC has uniform attenuation without gaps or defects. On the basis of the results of our study, one would expect that VMIs may be used qualitatively to assess NOTC integrity (Figs 4 and 5). In cases where there is ambiguity, supplemental evaluation with quantitative ROI analysis and SHUAC analysis may also be helpful. A potential example of such application, demonstrating individual ROI curves, is shown in Fig 5. On the basis of the observations in this study, we believe that future investigations directly evaluating applications of high-energy VMI and SHUAC for thyroid cartilage invasion are warranted. Because many patients without thyroid cartilage invasion or with minor invasion may not be treated surgically, such studies will be designed to correlate imaging findings with long-term patient outcome rather than on the basis of histopathologic correlation alone.

Compared with iodine overlay maps, high kilo-electron volt–reconstructed VMIs are similar to standard sequences to which radiologists are accustomed, possibly providing an advantage for implementation and user acceptance. In addition, high kilo-electron volt VMIs can result in decreased artifacts associated with metallic implants and other materials. At this time, both high-energy kilo-electron volt VMIs and iodine overlay maps are likely to be useful for increasing the accuracy of CT for determination of laryngeal cartilage invasion, and a comparison of the 2 and evaluation of potential complementary application in thyroid cartilage assessment is an interesting topic for future research.

Because this work is a general characterization of HNSCC, we used both primary laryngeal tumors and tumors outside the larynx. In addition, we evaluated recurrent/metastatic tumors. Although there were small differences in mean attenuation among the different tumor subgroups, all of the tumor groups had similar spectral attenuation characteristics (Fig 2). Furthermore, similar differences in NOTC and tumor attenuation with the greatest difference on high kilo-electron volt VMIs were observed when NOTC was compared with either the entire group of 30 tumors and specific subgroups.

Limitations of this study include the retrospective design and small number of cases. In addition, there was no pathologic confirmation of uninvaded NOTC. Nonetheless, our study demonstrates clear qualitative and quantitative differences in spectral Hounsfield unit attenuation curves of HNSCC compared with NOTC. We believe that our investigation and that by Kuno et al provide the basis for future, ideally prospective, studies to evaluate the advantages of DECT, including high kilo-electron volt VMIs, for detecting thyroid cartilage invasion and predicting patient outcome.

**CONCLUSIONS**

HNSCC has different spectral Hounsfield unit attenuation characteristics with significantly different attenuation on VMIs of $\geq 95$ keV compared with noncystified thyroid cartilage. Therefore, DECT has the potential to improve accuracy for distinguishing tumor and NOTC and to improve evaluation of cartilage invasion by laryngeal cancer.

**ACKNOWLEDGMENTS**

We thank Veronika Glyudza for her assistance in data preparation and processing.

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