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Detection of Cartilage Invasion in Laryngeal Carcinoma with Dynamic Contrast-Enhanced CT

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Objective: Staging of laryngeal cancer largely depends on cartilage invasion. Presence of cartilage invasion affects treatment choice and prognosis. On MRI and contrast-enhanced CT (CECT) it may be challenging to differentiate cartilage invasion from inflammation. The purpose of this study is to compare the diagnostic properties of dynamic contrast-enhanced CT (DCECT) and CECT for visual detection of cartilage invasion in laryngeal cancer.

Study Design: Prospective cohort study.

Methods: Patients with T3 or T4 laryngeal squamous cell carcinoma treated with total laryngectomy were evaluated using 0.625 mm slice CT. DCECT derived permeability and blood volume maps and CECT images were visually evaluated for the presence of invasion of the cartilaginous T-stage subsites of laryngeal cancer, by detecting continuity with the tumor-bulk of increased permeability, increased blood volume, and enhancement. Histological evaluation of the surgical total laryngectomy specimen served as the gold standard. Sensitivity, specificity, negative predictive value, and positive predictive value were calculated and compared using the McNemar and Chi-squared test.

Results: From 14 included patients, a total of 462 subsites were available for T-stage analysis, of which 84 were cartilage. The median time between CT imaging and total laryngectomy was 1 day (range 1–34 days). There was no significant difference in the detection of cartilage invasion between DCECT and CECT. The sensitivity of CECT was better for all subsites combined (0.85 vs. 0.75; $p < 0.01$).

Conclusion: DCECT does not improve visual detection of cartilage invasion in T3 and T4 laryngeal cancer compared to CECT.

Key Words: Laryngeal carcinoma, cartilage invasion, DCECT, CT perfusion, total laryngectomy.

Level of Evidence: 2b, individual cohort study.

INTRODUCTION

Cancers of the head and neck account for 3–5% of all cancers in the United States and for about 10% in Europe.[1] About one-fifth of head and neck cancers occur in the larynx.[2] Depending on the tumor (T) stage of the disease at the time of presentation, head and neck cancer is treated with radiotherapy alone, chemoradiation, or with surgery usually followed by radiotherapy. In laryngeal cancer, the T-stage and thereby the treatment is strongly influenced by the presence of cartilage invasion. The staging guidelines of the American Joint Committee on Cancer state that minor thyroid cartilage erosion is classified as T3, whereas invasion through the thyroid cartilage is T4. Cartilage invasion affects the type of surgery and has been shown to affect the response to radiotherapy.[3–5] To detect cartilage invasion, MRI can be used with high sensitivity (around 90%) and good specificity (around 80%).[6] However, MRI may be less suited to visualize sclerosis or cortical sclerosis of non-ossified cartilage, which is variably present in the larynx and may represent tumor invasion.[7] In addition, MRI can be affected by motion in the region of the larynx due to its relatively long imaging time. Therefore, contrast-enhanced CT (CECT) is often preferred over MRI although the specificity may be lower (around 70%) depending on the used imaging criteria.[8–10] Both on MRI and CECT, it often remains challenging to differentiate inflammation and edema from cartilage invasion.[8,9,11] In addition, CECT has limited accuracy for detection of early extra laryngeal spread of laryngeal cancer (ie, stage T4a).[12] To better differentiate between inflammation and cartilage invasion, there has been a growing interest in the use of dynamic contrast-enhanced CT (DCECT).[13] DCECT is a non-invasive tool to assess the microcirculatory properties of malignant tissue.[14] Contrast leakage, which can be estimated with DCECT, may be an indicator of neoangiogenesis and

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thereby local invasiveness. An additional advantage of the use of DCECT is that differences in perfusion parameters, like blood volume and blood flow, may predict therapeutic response.[13,15] However, results are still limited to small trials and more evidence for the usefulness of DCECT in the evaluation of head and neck cancer is needed.

In our institution, we evaluated a series of patients with T3 or T4 laryngeal squamous cell carcinoma with 128 detector-row DCECT who were subsequently treated with total laryngectomy. The purpose of this study is to compare the value of DCECT and CECT for the visual detection of tumor invasion of the different subsites described in the T-stage classification of laryngeal carcinoma and especially invasion of cartilage.

MATERIALS AND METHODS

Patient Selection

All patients were selected from a prospectively collected series of patients with primary T3 or T4 histologically proven squamous cell carcinoma of the larynx who were primarily treated with total laryngectomy (TLE) at our institution between June 2009 and December 2011.[16] Patients were included if they had pre-surgical DCECT imaging available with a maximum of 5 weeks (35 days) between imaging and surgery. DCECT was obtained in patients that gave informed consent after standard imaging workup to determine the T-stage and tumor biopsy. This study was approved by the local institutional ethical review board.

Imaging Protocol

All imaging was performed with the patient positioned in a radiotherapy mask using a Philips Brilliance iCT scanner (Philips Healthcare, Best, the Netherlands). The imaging protocol consisted of non-contrast CT (NCCT), DCECT and CECT.

The NCCT was acquired using 128x0.625 mm collimation, 80 kVp, 100 mAs, a rotation time of 0.75s, 220 mm FOV, and a 512x512 matrix.

The DCECT slab was centered to the level of the tumor as identified on the NCCT. For the acquisition three consecutive series were made: the first series with 20 frames each 3 seconds, the second series with 10 frames every 6 seconds, and the third series with 10 frames every 20 seconds. The first series were acquired without post-injection delay during injection of 50 ml non-ionic iodine contrast agent (Ultravist 300, Bayer-Schering Pharma AG, Berlin, Germany) into the antecubital vein at a rate of 5 ml/s, followed by a 40-ml saline flush. The first frames were therefore unenhanced. Scans were acquired in axial mode using 128x0.625 mm collimation, 120 kVp, 200 mAs, a rotation time of 0.4s, 180 mm FOV, and a 512x512 matrix.

Subsequently the CECT images were acquired 65 seconds after injection of another 90 ml of non-ionic iodine contrast agent at a rate of 5 ml/s followed by a 30-ml saline flush using 128x0.625 mm collimation, 120 kVp, 150 mAs, a rotation time of 0.4s, 220 mm FOV, and a 512x512 matrix.

Image Post-Processing and Analysis

From the acquired 0.625 mm CECT data three different reconstructions were made: 1) 3 mm slice thickness perpendicular to the vocal cords; 2) 3 mm slice thickness coronal to the vocal cords; and 3) 1 mm slice thickness in the axial plane for multi-planar viewing and detailed evaluation.

TABLE I.
List of T-Stage Subsites that Were Evaluated.

Supraglottis:
- mucosa of base of tongue
- vallecula left/right
- suprahyoid epiglottis
- infrahyoid epiglottis
- hyoid invasion
- medial wall of pyriform sinus left/right
- pre-epiglottic tissues
- paralaryngeal space left/right
- aryepiglottic folds left/right
- laryngeal ventricle left/right
- arytenoid cartilage left/right
- ventricular bands (false cords) left/right

Glottis:
- anterior commissure.
- posterior commissure
- true vocal cords left/right
- minor thyroid cartilage erosion (eg, inner cortex) left/right
- thyroid cartilage invasion
- cricoid cartilage invasion
- postcricoid area
- paraglottic space left/right

Subglottis:
- >5 mm below true vocal cord

Extra laryngeal:
- deep extrinsic muscle of the tongue
- trachea
- strap muscles
- esophagus
- encases carotid artery (>270°) left/right
- mediastinal structures

To correct for patient motion between DCECT time frames a non-rigid second order b-spline multi resolution registration was done using the Elastix toolkit.[17] To reduce noise the registered data were filtered using a temporal Gaussian filter (SD = 5s) and the bilateral TIPS filter.[18]

The perfusion parameters permeability (K^{trans}), blood volume (BV), and delay (T_d) were estimated by nonlinear regression using the plug-flow tissue-uptake model.[19,20] The arterial input function (AIF) was measured in the external carotid artery.

The DCECT derived K^{trans} and BV maps and CECT images were evaluated in a randomized order by two observers (JD with 7 years of experience in DCECT imaging, and FP with 20 years of experience in head and neck imaging) in consensus with a 3-month interval between the DCECT and CECT studies. The observers were blinded for the result of the first evaluation and the pathology data. Tumor invasion into laryngeal subsites that are described for T-staging of laryngeal cancer (Table I) was determined visually as being positive or negative.

On the DCECT map, any region with K^{trans} or BV similar to and continuous with the non-necrotic part of the tumor-bulk was considered to be invaded. Since all patients had T3 or T4 carcinoma the tumor bulk could be easily identified as a mass lesion with increased K^{trans} or BV.

TABLE II.
Imaging Criteria for Cartilage Invasion.

Thyroid:

- Extralaryngeal spread: Major cartilage destruction with tumor on inner and outer aspect of cartilage
- Erosion or lysis: Punched out lesion or focal lytic defect within sclerotic bone marrow comparable to osteolysis

Cricoid:

- Extralaryngeal spread: Major cartilage destruction with tumor on inner and outer aspect of cartilage
- Erosion or lysis: Punched out lesion or focal lytic defect within sclerotic bone marrow comparable to osteolysis
- Sclerosis: obvious thickening of the ossified inner or outer cortex or increased ossification of the medullary cavity.

Arytenoid:

- Extralaryngeal spread: Completely surrounded by tumor or not visible anymore owing to tumor invasion
- Erosion or lysis: Punched out lesion or focal lytic defect within sclerotic bone marrow comparable to osteolysis
- Sclerosis: obvious thickening of the ossified inner or outer cortex or increased ossification of the medullary cavity.

On CECT images any region with enhancement similar to the enhancing non-necrotic part of the tumor-bulk was considered to be invaded. Cartilage involvement was assessed using the CT criteria of Becker et al[10] (Table II).

Pathology Procedure

The fresh TLE specimen from the operating room was fixed in 4% buffered formaldehyde for $\geq$48 hours and thereafter put in agarose. The agarose block was sliced in 3-mm-thick slices and photographed. For further histological processing the agarose was then removed manually. The slices were decalcified (17.5% formic acid + 17.5% sodium formate) and embedded in paraffin. For each 3-mm-thick slice, a 4-μm section was obtained and stained with haematoxylin and eosin (H&E). A dedicated head and neck pathologist (SW), blinded to the imaging results, used a light microscope to delineate the tumor on the H&E sections with a permanent marker pen. Subsequently, the delineations were digitized and used to assess which subsites in the T-stage were invaded by the tumor (Table I).

Since visual inspection of the imaging data and the pathology specimens was used to determine subsite involvement the data did not need to be registered.

Statistical Analysis

The primary endpoint is tumor invasion of any T-stage subsite and the secondary endpoint is cartilage invasion.

To evaluate the diagnostic value of DCECT and CECT for the detection of tumor involvement of the T-stage subsites two-by-two contingency tables were created to calculate the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) with 95% confidence intervals. The delineations on the H&E sections of the surgical TLE specimen served as gold standard. From the different sensitivities, specificities, likelihood ratios graphs were created.[21] These graphs are comparable to standard ROC-curves, with the difference that they are constructed from only one point. The slopes of the lines in the graph are directly related to PPV and NPV, facilitating a visual comparison of all diagnostic properties of binary tests.

Differences in sensitivity and specificity between DCECT and CECT were calculated using the McNemar test. Differences in PPV and NPV between DCECT and CECT were calculated using a Chi-squared test.

Subsites that were never involved in the surgical TLE specimen and that were never labeled as tumor invasion in the DCECT or CECT evaluation were excluded from further analysis in order not to artificially increase the number of observations.

The analyses were done for all subsites together and for cartilage subsites alone.

RESULTS

Sixteen patients matched the inclusion criteria. One patient was subsequently excluded because the image quality of the scans was compromised by severe motion. Another patient was excluded because a large biopsy was taken between the DCECT scan and laryngectomy, causing significant tissue loss and deformation. The remaining 14 patients were included for further analysis. All 14 patients were diagnosed with squamous cell carcinoma. Thirteen patients were male. The median age was 61 years (range 50–78). The median time between the CT imaging study and surgery was 1 day (mean 6.2; range 1–34).

Subsites that were excluded from analysis because they were never involved in the surgical TLE specimen or DCECT or CECT evaluation were: base of tongue, hyoid bone, carotid encasement, and extrinsic muscles of tongue. Finally, a total of 462 subsites were available for further analyses. Of these 462 subsites, 84 involved cartilage.

The diagnostic properties of DCECT and CECT for the detection of involvement of cartilage subsites and all T-stage subsites are summarized in Table III. As illustrated by the likelihood ratio graphs in Figure 1, CECT seems to have overall better diagnostic properties than DCECT, both for cartilage subsites and all subsites. However, only the difference in sensitivity for all subsites was statistically significant.

There was a discrepancy between DCECT and CECT in 50 (11%) of all subsites. This discrepancy was spread over all subsites with a percentage ranging between 2% and 21%. The highest number of discrepant cases was in the true vocal cords (6 of 28 true vocal cords). Nine discrepant subsites were cartilage subsites (11% of all cartilage subsites). Forty-one discrepant subsites were non-cartilage subsites (11% of all non-cartilage subsites).

In 27 subsites (of which 3 were cartilage subsites) both DCECT and CECT showed false positive results. In 22 subsites (of which 3 were cartilage subsites) both DCECT and CECT showed false negative results.

The detection of involvement of the individual cartilage subsites is summarized in Table IV. For the individual subsites, no statistical analysis is performed, due to the limited number of patients included in this study. The largest percentage of missed cartilage involvement was for arytenoid cartilage (43%).

Figures 2, 3, and 4 show examples of false negative, false positive, and true positive DCECT findings for

TABLE III.
Diagnostic Properties of DCECT and CECT.

All Cartilage	Positive	Negative	Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)
Pathology	21	63				
DCECT	20	64	0.67 (0.47–0.87)	0.90 (0.83–0.98)	0.70 (0.50–0.90)	0.89 (0.81–0.97)
CECT	23	61	0.86 (0.71–1.01)	0.92 (0.85–0.99)	0.78 (0.61–0.95)	0.95 (0.90–1.01)
p-value			0.13	1.00	0.73	0.33
All subsites	Positive	Negative	Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)
Pathology	165	297				
DCECT	163	299	0.75 (0.68–0.81)	0.87 (0.83–0.90)	0.75 (0.69–0.82)	0.86 (0.82–0.90)
CECT	181	281	0.85* (0.79–0.90)	0.86 (0.82–0.90)	0.77 (0.71–0.83)	0.91 (0.88–0.94)
p-value			<0.01	1.00	0.70	0.07

CECT = contrast-enhanced computed tomography; CI = confidence interval; DCECT = dynamic contrast-enhanced computed tomography.

arytenoid invasion, together with CECT and H&E sections at the same level.

DISCUSSION

Our results show that the diagnostic properties of CECT and DCECT derived K^{trans} and BV maps for the visual assessment of cartilage invasion in patients with T3 and T4 laryngeal carcinoma are not significantly different. However, if all subsites are evaluated together, CECT showed significantly higher sensitivity for detection of tumor invasion.

Previous studies in CT and MRI have shown that determining tumor invasion and especially cartilage invasion of laryngeal carcinoma remains difficult. To our knowledge, our paper is the first to study visual assessment of K^{trans} and BV maps derived from DCECT for the evaluation of cartilage invasion in laryngeal carcinoma. Visual assessment allows for expert interpretation, incorporating knowledge of anatomy, patterns of tumor spread, and technique dependent artefacts. Although we used advanced filtering methods, high spatial resolution, and robust perfusion estimation algorithms, DCECT was still not better than CECT for the detection of cartilage invasion. DCECT may therefore not be suited for this purpose. Visual assessment with DCECT proved especially difficult for the arytenoid cartilage, with a detection rate of 57%. This was most likely caused by imperfect registration between the images in the time series of the DCECT in this relatively small structure, resulting in artefacts at the edges. In addition, ossification could have played a role. The increased attenuation from the ossification combined with partial volume effects may have resulted in erroneous tissue attenuation curves and thereby misinterpretation of the DCECT parameter maps.

A major strength of our study is the availability of a total laryngectomy specimen.

A previous study evaluating tumor infiltration with DCECT showed a sensitivity of 33.3%, specificity of 96.5%, PPV of 66.6%, and NPV of 87.5% for cartilage.[22] Only infiltration of thyroid cartilage was analyzed in this study. The analysis was based on regions of interest (ROIs) drawn on CECT images of different structures in the neck to differentiate tumor from normal tissue. Quantitative differences in DCECT measurements between ROIs were used to determine tumor invasion.

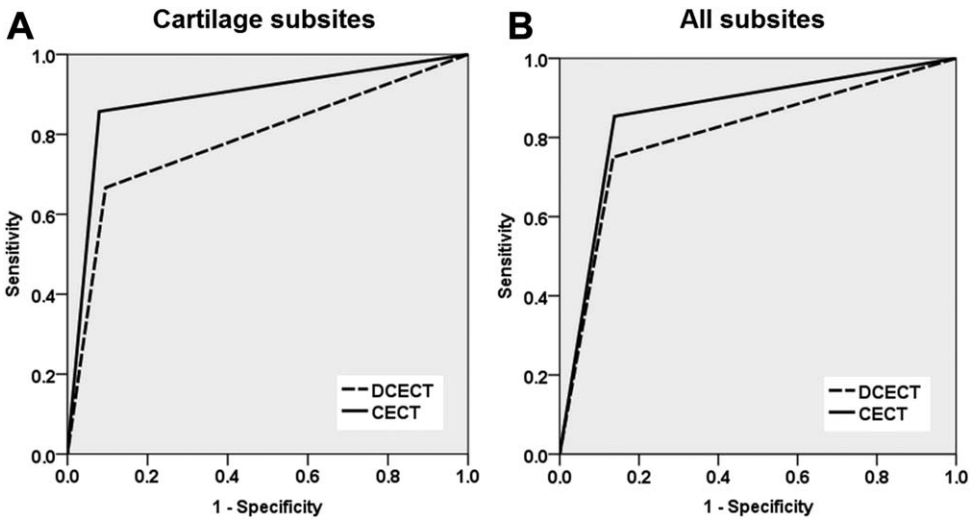

Fig. 1. Likelihood ratio graphs of (A) cartilage subsites, and (B) all subsites. From these graphs, it can be easily appreciated that CECT appears to have overall better diagnostic properties than DCECT. CECT = contrast-enhanced computed tomography; DCECT = dynamic contrast-enhanced computed tomography.

TABLE IV.
Detection of Cartilage Invasion with DCECT and CECT.

Thyroid erosion (T3)	True Positive	False Positive	True Negative	False Negative
DCECT	0	1	26	1
CECT	0	0	27	1
Thyroid invasion (T4a)				
DCECT	9	3	0	2
CECT	11	2	1	0
Arytenoid invasion				
DCECT	4	1	20	3
CECT	5	2	19	2
Cricoid invasion				
DCECT	2	1	11	0
CECT	2	1	11	0

CECT = contrast-enhanced computed tomography; DCECT = dynamic contrast-enhanced computed tomography.

ROI placement is therefore crucial for this method since the site of tumor invasion needs to be within the ROI. Several other studies have shown that squamous cell carcinoma of the head and neck can be differentiated from normal muscles with quantitative DCECT analyses.[23–25] However, due to the variability in quantitative perfusion estimations with DCECT thresholds to delineate tumor have not yet been published.[26] Our approach to use visual assessment of the DCECT parameter maps intended to overcome this problem.

The diagnostic properties of CECT found in our study are higher than in other previously published results. The imaging criteria for CECT defined by Becker et al[10] showed an overall sensitivity of 82% (compared to 85% in our study), specificity of 79% (compared to 86%), positive predictive value of 62% (compared to 77%), and negative predictive value of 91% (compared to 91%) for cartilage subsites. The applied criteria were: extra laryngeal tumor and erosion or lysis in the thyroid, cricoid, and arytenoid cartilages; and sclerosis in the cricoid and arytenoid (but not the thyroid) cartilages.[10] In comparison to our study, Becker et al evaluated a larger population (111 patients) with inclusion of patients with smaller lesions (ie, T1/T2), and larger slice thickness of the CECT reconstructions. Both in the study by Becker et al and our study, 140 ml of iodine contrast was injected prior to the CECT study. A previous study with MRI found a sensitivity of 91%, specificity of 79%, positive predictive value of 58%, and negative predictive value of 97%, for cartilage invasion on T1 weighted gadolinium enhanced fast spin echo sequences.[6] Smaller lesions were also included in that study.

The current study has several limitations. Firstly, all patients had either T3 or T4 laryngeal carcinoma. Therefore, most tumors were fairly large with gross infiltration of laryngeal and extra laryngeal structures. Our results may thus not represent the true diagnostic value of DCECT in a clinical setting, since smaller masses with less obvious infiltrative growth on both CECT and DCECT were not included. The lesions evaluated in our study may show superficial cartilage erosion in some areas while there is invasion in other areas. This was not evaluated separately. In our population, only one patient had erosion of the thyroid cartilage without invasion. Secondly, the size of the studied population is small. Thirdly, the use of DCECT has several limitations that need to be considered. Since the DCECT acquisition takes a couple of minutes, motion effects can influence

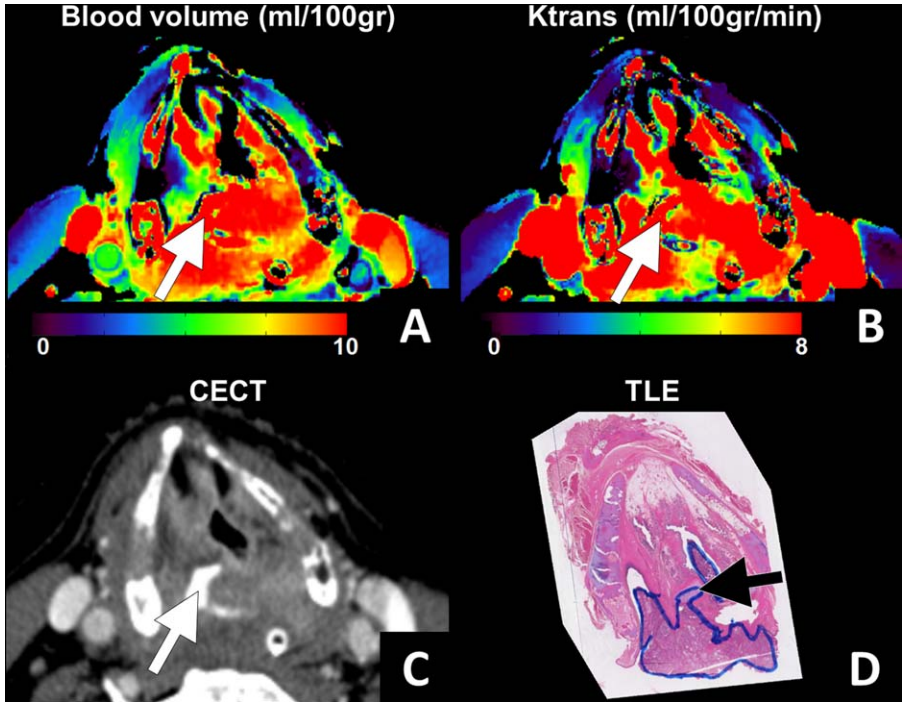

Fig. 2. Example of true positive DCECT derived Blood volume (A) and K^{trans} (B) maps and true positive CECT image (C) for arytenoid invasion of laryngeal cancer (white arrows). The images show a completely surrounded right arytenoid, increased blood volume and increased K^{trans} on DCECT, and sclerosis on CECT. The laryngectomy (TLE) haematoxylin and eosin (H&E) slice (D) clearly shows that the tumor invades the arytenoid cartilage (black arrow). CECT = contrast-enhanced computed tomography; DCECT = dynamic contrast-enhanced computed tomography.

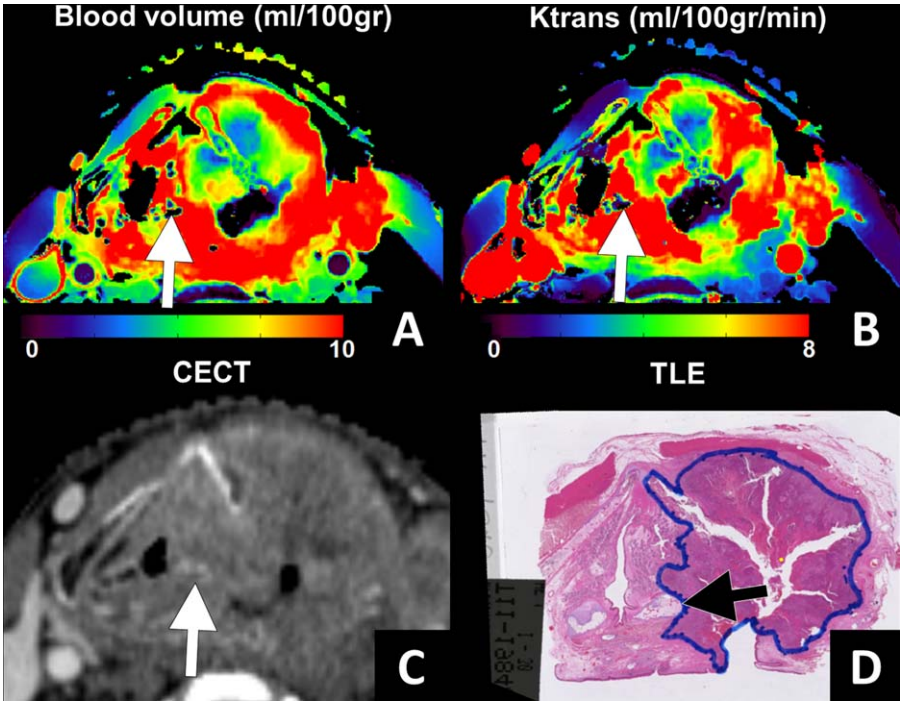

Fig. 3. Example of false positive DCECT derived Blood volume (A) and K^{trans} (B) maps and false positive CECT image (C) for arytenoid invasion of laryngeal cancer (white arrows). The images show a completely surrounded right arytenoid and were also interpreted as having punched out lesions and sclerosis. The laryngectomy (TLE) haematoxylin and eosin (H&E) slice (D) shows that the tumor folds around the arytenoid cartilage without infiltrating it (black arrow). CECT = contrast-enhanced computed tomography; DCECT = dynamic contrast-enhanced computed tomography.

perfusion estimates and therefore the imaging characteristics. We used the Elastix toolbox to correct for motion artefacts as much as possible.[17] However, slight movement can still result in erroneous estimates of DCECT parameters especially at the interface between different tissue types such as bone or air. In addition, streak artefacts from high concentration of contrast agent or bone can influence perfusion estimates. The DCECT analysis we used is not commercially available. Perfusion estimates obtained with different software packages and

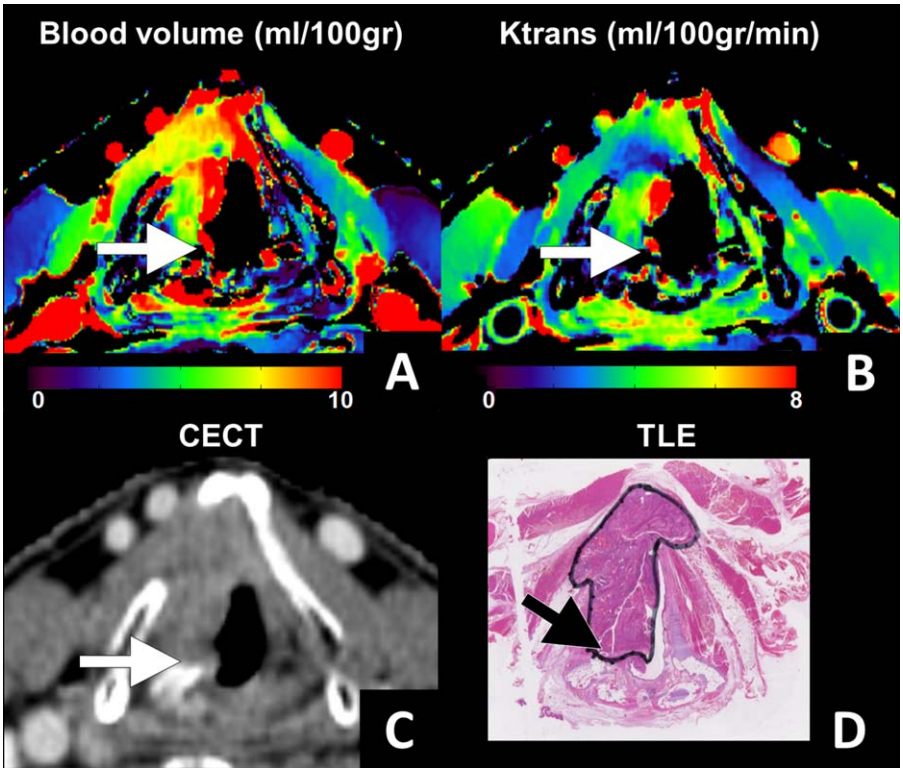

Fig. 4. Example of false negative DCECT derived Blood volume (A) and K^{trans} (B) maps and false negative CECT image (C) for minimal arytenoid invasion of laryngeal cancer, visible on the total laryngectomy (TLE) haematoxylin and eosin (H&E) slice (D; black arrow). CECT = contrast-enhanced computed tomography; DCECT = dynamic contrast-enhanced computed tomography.

analysis methods differ significantly and are not directly interchangeable.[27] This has to be taken into account if the results are applied to other platforms. Another drawback of DCECT is the radiation dose, which, however, may not be relevant for the evaluated population of patients with T3 and T4 carcinoma who all received post-surgical radiotherapy.

CONCLUSION

In conclusion, in our study CECT and DCECT derived BV and K^{trans} maps display similar diagnostic properties for visual detection of cartilage invasion in T3 and T4 laryngeal cancer. The sensitivity for detection of tumor invasion is significantly higher for CECT than DCECT if all subsites are evaluated together.

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