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Evaluation of cervical lymph nodes with CT perfusion in patients with hypopharyngeal and laryngeal squamous cell cancer

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Summary

Background: In patients with head and neck squamous cell cancer, metastases in cervical lymph nodes still remain the single most important negative predicting factor. Their presence reduces overall 5-year survival by 50%.

The aim of the study was to evaluate the role of computed tomography perfusion (CTP) for differentiation between metastatic and non-metastatic cervical lymph nodes in patients with squamous cell cancer of hypopharynx and larynx.

Material/Methods: This was a prospective single center study of 18 consecutive patients. Eleven patients with squamous cell cancer of the hypopharynx and seven patients with laryngeal cancer underwent CT examination of the neck followed by CTP. Group II, III, and V of lymph nodes were evaluated. Perfusion maps of basic parameters (blood flow [BF], blood volume [BV], mean transit time [MTT] and permeability surface [PS]) were reconstructed for all patients. In all patients resection of primary tumour along with neck dissection was performed. Lymph nodes underwent histopathological examinations for presence of metastases. CTP parameters were related with histological analysis of resected nodes.

Results: CTP and histological findings of 65 nodes were correlated. 24 of them were metastatic and 41 were non-metastatic. Metastatic nodes showed significant hyperperfusion, comparing to non-metastatic ones. An average value of BF in metastatic nodes was 136.4 ml/100 g/min, BV was 7.7 ml/100 g, MTT was 4.4 s and PS was 19.4 ml/100 g/min. The average values for non-metastatic nodes were: BF was 80.7 ml/100 g/min, BV was 4.7 ml/100 g, MTT was 5.6 s and PS was 12.8 ml/100 g/min. The differences were significantly higher for BF, BV and PS values ($p<0.05$).

Conclusions: CTP may be useful in differentiation between metastatic and non-metastatic lymph nodes, based on evaluation of the value of BF, BV and PS.

Key words: CT perfusion • squamous cell cancer • laryngeal cancer • lymph nodes

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Background

Metastases in cervical lymph nodes are common in head and neck cancer, especially in supraglottic and hypopharyngeal manifestation of the disease.The presence of a metastatic node on one side of the neck reduces the 5-year survival rate by 50%, and the presence of a metastatic node on both sides of the neck reduces the survival rate by further 25% [1,2]. Therefore, evaluation of cervical lymphadenopathy is crucial for patients with head and neck cancer as it helps in the assessment of patient prognosis and the selection of appropriate treatment method. Evaluation of the morphology of the lymph node in order to detect possible metastatic involvement represents one of the most challenging problems for surgeons and radiologists [3–5].

Two most frequently used imaging methods, contrast-enhanced computed tomography (CT) and magnetic resonance (MR) allow detection of enlarged nodes often with necrosis and extracapsular spread [6], but neither method can accurately differentiate non-metastatic from metastatic, non-enlarged lymph nodes [7].

Ultrasound (US) and US-guided fine-needle aspiration cytology (FNAC) have been extensively used for many years, their sensitivity and specificity are very high [8,9], but those techniques are operator-dependent. FNAC is an invasive method and there is a risk of false negative results arising from aspiration of the wrong node or its necrotic part.

Metabolic imaging with single photon emission CT (SPECT) and positron emission tomography (PET) can help in this differentiation, but they are expensive, less readily available and most important have low specificity [10].

Since diagnosis of metastatic lymph nodes has an important clinical impact, new functional imaging technologies, CTP and magnetic resonance diffusion studies (DWI-MRI) are being employed [11–13].

Diffusion-weighted MRI allows visualisation of Brownian motion of water molecules (molecular diffusion) in examined tissue. Cancer metastasis to the lymph nodes usually are associated with decrease in water diffusivity thus resulting in lower signal attenuation [14,15].

CTP is a technique that allows quick qualitative and quantitative evaluation of tissue blood perfusion by generating maps of blood flow (BF), blood volume (BV), and mean transit time (MTT). CTP has been found to be useful for non-invasive diagnosis of many diseases like cerebral ischemia and infarction, tumoral neo-angiogenesis, differentiation between malignant and benign process and for evaluation of tumor response to radio- and chemotherapeutic treatment [16,17].

Recent studies, based on doppler ultrasound imaging of tumor vascularization showed that CT perfusion parameters may provide valid information on angiogenic activity induced by neoplastic cells invasion of lymph nodes [18].

Aim

The aim of the study was to evaluate the usefulness of computed tomography perfusion examination for the differentiation between metastatic and non-metastatic cervical lymph nodes in patients with hypopharyngeal and laryngeal squamous cell cancer.

Material and Methods

This was a prospective single-center study. The study group included 18 consecutive patients, previously untreated, with hypopharyngeal or/and laryngeal squamous cell cancer confirmed on biopsy.

There were 14 men and 4 women, mean age was 52 years. Eleven patients had hypopharyngeal cancer and seven had laryngeal cancer. A detailed clinical characteristics of the group is presented in (Table 1).

Prior to surgery all patients underwent standard contrast-enhanced CT imaging of the neck followed by perfusion examination at the level of tumor. The examination was performed using a 64-row spiral CT unit, VCT (GE Medical Systems).

First, CT examination was performed from the level of skull base to thoracic inlet, in 1.25 mm slices (125 kV, automatically modulated mA), before and after contrast medium (iodine concentration of 320 mg/dl (Visipaque, GE Healthcare, USA)) administration (80 ml + 20 ml of saline flush, flow – 1 ml/s, with 100 s delay), using soft tissue and bone reconstruction kernels.

Afterwords (7–10 minutes), CTP acquisition was performed according to soft tissue tumor protocol. The scanning range was 8 cm and in all cases it was enough to include the whole tumor and lymph nodes from II, III and V group (according to Memorial Sloan-Kettering Cancer Center guidelines).

Sixteen 5-mm CT sections of continuous (cine) scanning (80 kV, 190 mA) were obtained, with a total acquisition time of 45 s. CT was initiated 4 s after the intravenous infusion (injection rate of 4.5 ml/s) of iodinated contrast medium with an iodine concentration of 320 mg/dl (Visipaque, GE Healthcare, USA). The contrast agent was injected into an antecubital vein with a power injector (Medrad, Pittsburgh, USA).

BF (ml/min/100 g tissue), BV (ml/100 g tissue), MTT (s) and PS (ml/min/100 g tissue) maps were generated using commercially available software (Perfusion 3, AW 4.2, GE Healthcare, Millwaukee, USA). This algorithm allows deconvolution of the parenchymal time-concentration curves by a reference arterial-curve. The region of interest (ROI) was placed in common carotid artery. The venous outflow ROI was manually selected. In each evaluated lymph node ROI was placed centrally to include the entire node and tailored to minimise partial volume effect artifacts.

Nodes smaller than 4mm in long axis were excluded from the study due to increased partial volume effect errors.

Table 1. Location and staging of primary tumour and number of lymph nodes evaluated in individual patients.

Patient	Primary site of cancer	TNM	Number of lymph nodes evaluated
1	Hypopharynx – pyriform sinus	T3 N1 M0	3
2	Hypopharynx – pyriform sinus	T4 N2c M0	4
3	Hypopharynx – pyriform sinus	T4 N2b M0	4
4	Hypopharynx – pyriform sinus	T4 N2c M0	3
5	Hypopharynx – pyriform sinus	T4 N2c M0	5
6	Hypopharynx – pyriform sinus	T3 N2a M0	2
7	Hypopharynx – pyriform sinus	T3 N1 M0	2
8	Hypopharynx – pyriform sinus	T1 N2b M0	4
9	Hypopharynx – pyriform sinus	T4 N2b M0	6
10	Hypopharynx – pyriform sinus	T4 N2c M0	4
11	Hypopharynx – postcricoid	T4 N2b M0	2
12	Larynx – supraglottic	T3 N1 M0	3
13	Larynx – supraglottic	T3 N2c M0	6
14	Larynx – supraglottic	T4 N2c M0	3
15	Larynx – supraglottic	T4 N2c M0	4
16	Larynx – glottic	T4 N1 M0	5
17	Larynx – glottic	T3 N1 M0	3
18	Larynx – subglottic	T4 N1 M0	2

Nodes with central necrosis visible in CT examination were directly diagnosed as harbouring metastases and were also excluded since necrosis has almost no vascularity hence very low perfusion.

The value of each perfusion parameter was calculated for every node separately.

All patients underwent surgery for resection of primary tumour along with unilateral or bilateral selective or radical modified neck dissection. Nodes located in surgically easily identifiable places i.e. carotid bifurcation, facial vein junction, immediate proximity of submandibular gland, hyoid bone were individually resected and sent for pathological examination in separate marked containers. All specimens underwent standard histopathological examinations for presence of metastases. Pathological results were related to perfusion parameters in each node. Results were analysed using two-sample independent t-test.

Results

All resected primary tumors were confirmed to be squamous cell cancers.

Histologically confirmed metastatic nodes (n=24) revealed the following average perfusion values: BF was 136.4 ml/100 g/min, BV was 7.7 ml/100 g, MTT was 4.4 s and PS was 19.4 ml/100g/min (Figure 1).

The average perfusion values for non-metastatic nodes (n=41) were: BF was 80.7 ml/100g/min, BV was 4.7 ml/100 g, MTT was 5.6 s and PS was 12.8 ml/100 g/min (Figure 2).

Differences between the values of BF, BV and PS between metastatic and non-metastatic nodes were proven to be statistically significant with $p<0.05$ (Figure 3).

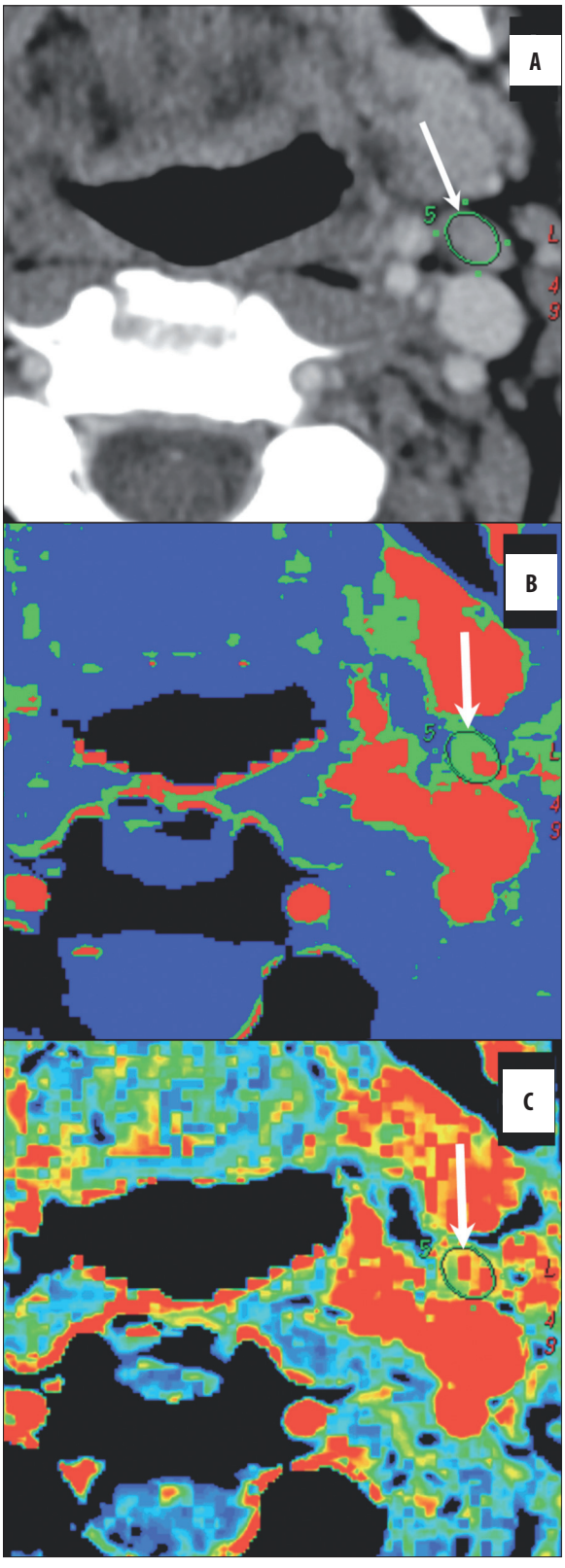
Discussion

The role of imaging in head and neck cancer is to determine the extent of the primary tumor as well as involvement of cervical lymphatic system.

A determinant of paramount importance in diagnostic usefulness of an imaging modality is an ability to detect the presence of metastatic lymph nodes, particularly where this is not clinically evident or there are doubts based on physical examination.

Perfusion CT is known to offer quantitative assessment of tissue hemodynamics, nevertheless, the examination of a restricted slab of tissue and the use of ionising radiation and iodinated contrast agent are some drawbacks of the method [19,20].

Dynamic CT and perfusion parameters mirror tissue vascularization and might reflect angiogenic activity and thus, theoretically, may be able to differentiate neoplastic from non-neoplastic tissue.



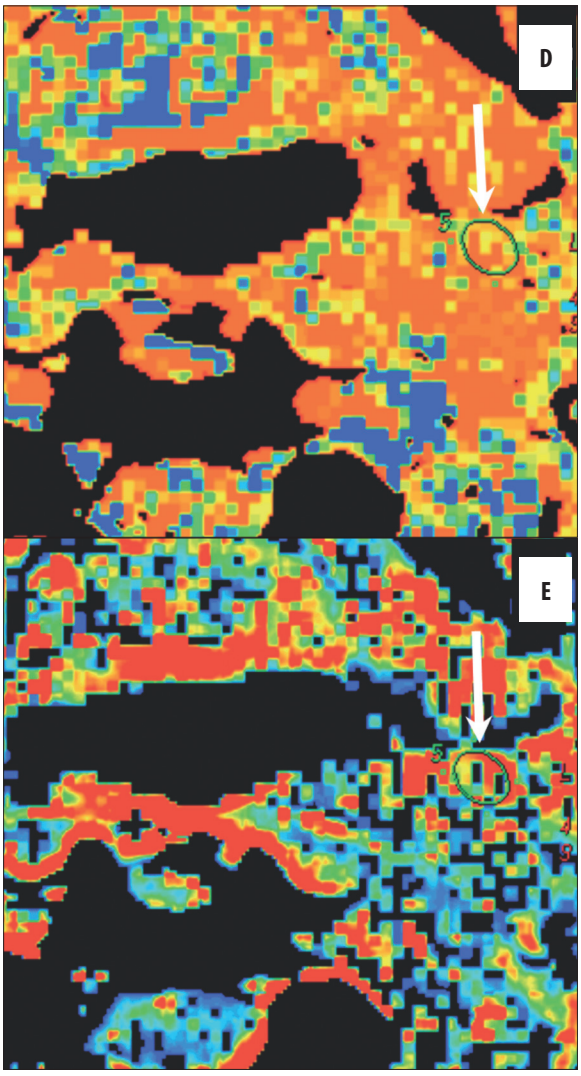


Figure 1. Lymph nodes in patient with laryngeal cancer. There is one node laterally to the carotid bifurcation, on the left side (group II). High values of blood flow and blood volume were suggestive for metastatic character. This node on histological examination was proven to be metastatic. (**A**) ROI is placed over the node; (**B**) blood flow map (BF). BF 152 ml/100g/min; (**C**) blood volume map (BV). BV 8, 07 ml/100 g; (**D**) mean transit time map (MTT). MTT 3, 77 s; (**E**) permeability surface map (PS). PS 16, 96 ml/100 g/min.

A recent paper by Kapse and colleagues demonstrated that the inflammation of the intestinal wall is characterised by higher perfusion parameters than normal tissue, but by lower perfusion parameters than neoplastic tissue. The increased perfusion and permeability of inflamed tissue may be due to the effect of cytokines, which provokes vasodilatation and increases endothelial permeability, but not at such high levels as neoplastic tissue, where angiogenesis plays an important role [21].

The results obtained in this study show an almost double value of BF in metastatic versus non-metastatic cervical lymph nodes. There was also a significant increase in BV and PS, except for MTT value. Similar relations were reported in axillary nodes with breast cancer metastases [22]. PS reflects the rate of iodinated contrast medium leakage from vessels to extracellular space and MTT reflects its transit time through the nodal vascular bed. In metastatic nodes BF is increased by newly developed vessels, while MTT is usually increased by the presence of pathologic

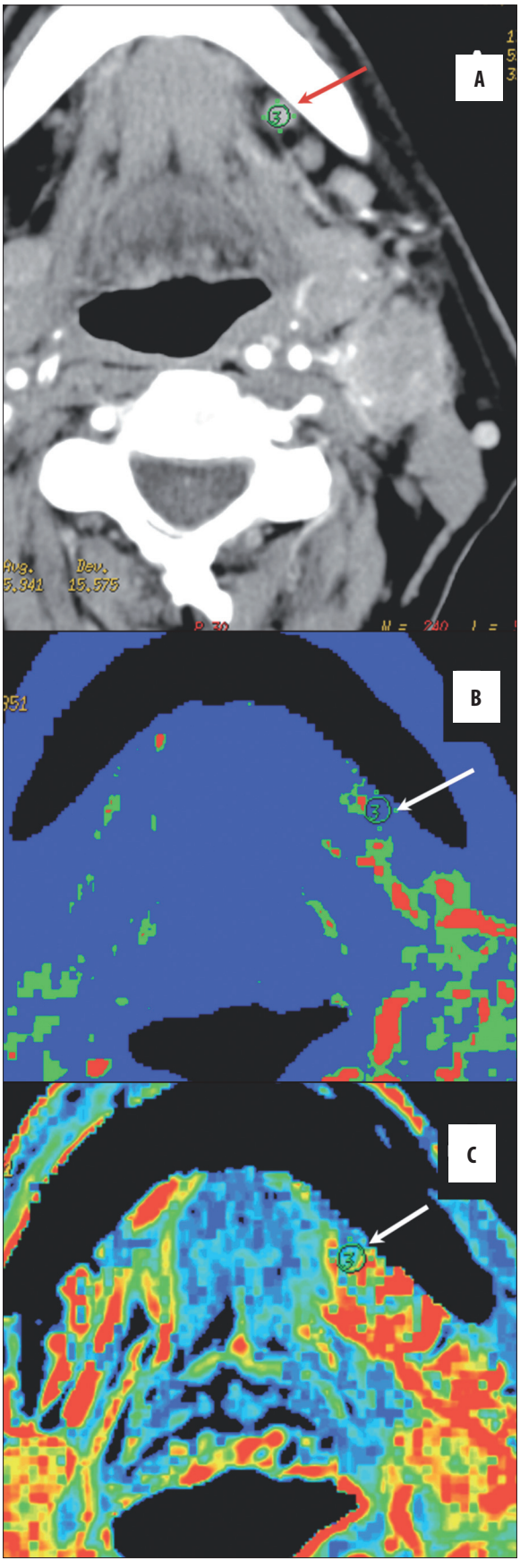


Figure 2. Lymph nodes in patient with hypopharyngeal cancer. There are several small round submandibular nodes (group IB) on the left side. Value of CTP parameters speaks for their non-metastatic character. All these nodes were proven to be non-metastatic on histological examination. (**A**) ROI is placed over small 5 mm node; (**B**) blood flow map (BF). BF 35 ml/100g/min; (**C**) blood volume map (BV). BV 4, 06 ml/100 g; (**D**) mean transit time map (MTT). MTT 3, 95 s; (**E**) permeability surface map (PS). PS 4, 15 ml/100g/min.

arterio-venous shunts. Changes in vascular endothelium and in the function of vessels induced by neo-angiogenesis and by cytokine-mediated inflammation elevate the PS value. BV was also increased in metastatic nodes as a result of vasodilatation and neovascularistion.

A recent paper by Bisdas and colleagues reports no significant difference in CTP parameters between normal and metastatic nodes in patients with oropharyngeal cancer [18]. This may result from inclusion of all metastatic nodes even those with signs of central necrosis characterised by very low perfusion values.

Results of this study are in keeping with the observations by Yuen and colleagues, who described a higher CT contrast enhancement of metastatic axillary nodes than that of

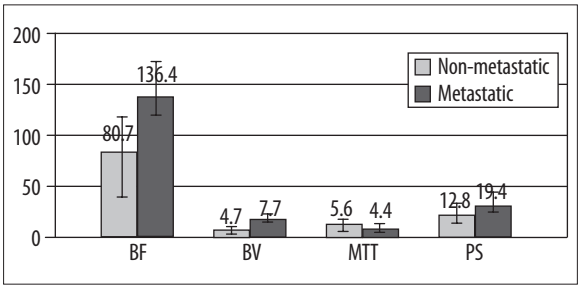


Figure 3. Perfusion parameters for metastatic and non-metastatic lymph nodes.

non-metastatic ones [23]. The early enhancement shown in their series of metastatic nodes probably reflects the higher blood volume due to angiogenesis, even if the simple protocol used was unable to study the contrast and blood dynamics.

As speculated by Lurie and colleagues the contrast enhancement in lymph nodes starts in the subcapsular cortical sinus and progresses to the medullar space. Both neoplastic and inflammatory infiltration mainly occur in subcapsular sinus and the enlargement of this area may be one of the factors responsible for an increased blood uptake, mirrored by an increase of BF in the first place [22].

FDG-PET/CT may also detect small metastases in lymph nodes. However it has resolution limitations. An inflammation in the non-metastatic nodes may be misinterpreted as metastatis. Nodal necrosis may cause false-negative diagnoses on PET because of the low glycolytic activity of the necrotic area. False results also may be anchored in the visual or semi-quantitative operator dependent PET/CT evaluation. A study by Bisdas showed that ROC (region of contrast) curves of SUV (standard uptake value) of 3.25 yielded satisfactory sensitivity and specificity but did not surpass the physician's performance with visual interpretation [24]. Limitations of PET/CT in nodal staging has been among others attributed to the almost equal tracer uptake in reactive nodes as that in metastatic lesions [25].

Dynamic contrast-enhanced MR imaging has been applied in primary cancers of the head and neck diagnosis and has been also successfully utilised to distinguish metastatic from non-metastatic lymph nodes in squamous cell carcinoma of the head and neck. Lack of absolute perfusion quantification, unlike in the CTP, as well as the dependence on the sequence parameters, and the lack of evidence-based reproducibility is a well-known drawback of the method [26].

Besides conventional contrast-enhanced MR, much effort has been exerted in detecting nodal metastases using diffusion-weighted imaging (DWI). Cancer metastases to the regional lymph nodes are associated with alterations in water diffusivity and microcirculation in the node. High signal intensity in the DWI (in b-values ≥150 s/mm^2) that corresponds to low ADC (apparent diffusion coefficient) values reflects the changes in the proportion of extracellular to intracellular water protons mobility expected in the nodal metastases. Therefore, ADC maps provide helpful information on the necrotic areas and help differentiate metastatic from non-metastatic nodes [13,27]. Cut-off values of ADC for metastatic nodes of 1.38×10^{-3} mm^2/s yielded 96% accuracy, 98% sensitivity, and 88% specificity in a study by Hermans [28], while other authors suggest lower cut-off values [29].

The reported sensitivity of MRI for lymph node metastases detection ranges from 64 to 92%, whereas the reported specificity ranges from 40 to 81% [28,29].

According to the recent study of Liao et al. 124 patients with SCCA of the oral cavity the specificity of PET alone was 93% and together with CT/MRI was 94.5% [30].

Conclusions

Blood Flow, Blood Volume and Permeability Surface in Computed Tomography Perfusion (CTP) have significantly increased values in metastatic cervical lymph nodes in comparison to non-metastatic nodes in patients with hypopharyngeal/laryngeal squamous cell cancer.

Computed Tomography Perfusion might be useful in differentiation between metastatic and non-metastatic cervical lymph nodes however this requires further validation.

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