Original Article

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Radiology Section

# CT Perfusion in Evaluation of Cervical Lymph Node Metastasis in Head and Neck Malignancies: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Though, many cross-sectional modalities are available for evaluation of cervical lymph node metastasis but their results are highly variable. There is paucity of the literature in India, regarding lymph nodal assessment using Computed Tomography (CT) perfusion in head and neck malignancies even though, there is high incidence of oral cancer in India.

**Aim:** To assess the role of Computed Tomography Perfusion (CTP) in evaluation of cervical lymph nodes in head and neck malignancies, by using CT perfusion parameters as compared to histopathology.

**Materials and Methods:** This cross-sectional study was conducted in the Department of Radiodiagnosis in collaboration with the Department of Surgery and Pathology at Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi, India, from October 2017 to April 2019. The study included 30 newly diagnosed head and neck cancer patients, with 46 nodes planned for surgical neck dissection. Computed tomography scan of neck was acquired using Siemens Somatom Definition Flash 256CT scanner. Reconstruction and post processing was performed on workstation and perfusion parameters were obtained to generate the CT perfusion maps. Differentiation between benign and malignant lymph nodes was done, on the basis of CT perfusion parameters such as Blood Flow (BF), Blood Volume (BV), Mean Transit Time (MTT) and Permeability Surface (PS), which were compared with histopathological findings of resected lymph nodes. McNemar's test was applied for comparison and statistical analysis. Receiver Operating Characteristic (ROC) curve of quantitative parameters were obtained, for the detection of sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPP) and diagnostic accuracy.

**Results:** Out of 46 nodes, 23 were metastatic and 23 were non metastatic. The average value of BF in metastatic nodes was 174.61±71.76 mL/100g/min, BV was 16.32±11.9 mL/100g, MTT was 4.83±2.54 seconds and PS was 49.3±28.59 mL/100g/min. The average values for non metastatic nodes were: BF 88.06±34.4 mL/100g/min, BV: 9.89±7.63 mL/100g, MTT: 13.11±18.58 seconds and PS: 37.07±29.26 mL/100g/min. The differences between the parameters like blood flow (p-value <0.0001), blood volume (p-value=0.005) and MTT (p-value=0.002) in malignant and benign nodes were significant. In case of blood flow, sensitivity was 82.61% and diagnostic accuracy was 84.78%. In case of blood volume, sensitivity was 91.30% and diagnostic accuracy was 73.91%. In case of mean transit time, sensitivity was 56.52% and diagnostic accuracy was 73.91%. In case of permeability surface, sensitivity was 91.30% and diagnostic accuracy was 67.39%.

**Conclusion:** Blood flow and blood volume values were significantly increased in metastatic cervical lymph nodes as compared to non metastatic nodes, whereas MTT was significantly low. Permeability surface showed equivocal results.

**Keywords:** Blood flow, Blood volume, Computer tomography, Mean transitive, Permeability surface

## INTRODUCTION

Head and neck malignancies are one of the commonly encountered malignancies in Asian subcontinent. Head and neck malignancies include, those arising from oral cavity, larynx, pharynx and salivary gland, of which oral cavity malignancies are the most common [1]. In India, approximately 0.2 to 0.25 million new head and neck malignancy patients are diagnosed each year by the Indian Council of Medical Research (ICMR), out of which 90 % are squamous cell carcinoma [2-4]. Oral cavity squamous cell carcinoma is an invasive malignancy, shows perineural growth and commonly metastasize the cervical lymph nodes [5,6], and presence of metastatic cervical lymphadenopathy is associated with poor prognosis and reduces the survival rate [7]. Hence, early detection of cervical lymph node metastasis is very important step in cancer staging and its management.

The very first step of the nodal staging is to assess the anatomical level of pathological lymph node in patients with known head and neck malignancy. In 1938 Rouviere H, developed classification for cervical lymph nodes, based on anatomic location and drainage area [8]. In 1977 American Joint Committee on Cancer staging classifies the lymph nodes into seven levels, Level 1 to Level 7. This is the latest and most accepted classification [9].

Although Ultrasonography (USG) is extensively used, due to its wide availability and cost effectiveness, but alone it cannot precisely characterise the aetiology of cervical lymphadenopathy and it has to be accompanied with Fine Needle Aspiration Cytology (FNAC) to improve sensitivity and specificity [10]. Colour Doppler increases diagnostic accuracy of USG but its inconsistent results and poor repeatability decreases its routine usage. Recently, noninvasive USG techniques like sonoelastography has also gained value in differentiating benign versus malignant lymph nodes, but it is not widely used due to its operator dependence and qualitative nature [11].

There are multiple imaging modalities for evaluation of cervical lymph nodes. Commonly used are Ultrasonography (USG) and Computed Tomography (CT) scans. Other modalities are, Doppler, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). Recently developed imaging techniques that can be used are sonoelastography, CT perfusion, Contrast Enhanced Ultrasonography (CE-USG), MR perfusion and diffusion weighted-MRI [12].

Nowadays, Contrast Enhanced Computed Tomography (CECT) is the first line examination for evaluation of head and neck

malignancies, because of its accessibility and high reliability. Addition of CT perfusion in the same sitting will further add to value of study [13]. Computed Tomography Perfusion (CTP) is a functional dynamic study, which helps in quantification of the enhancement in tissue and blood at certain time points, following intravenous administration of iodinated contrast. It can obtain multiple quantitative CTP parameters like Blood Flow (BF), Blood Volume (BV), Mean Transit Time (MTT) and Permeability Surface (PS) with a single acquisition [13,14].

The CTP parameters provide valid information on angiogenic activity induced by metastatic cell invasion of lymph nodes [12]. CTP include higher spatial resolution, wider longitudinal coverage by new Multidetector Computed Tomography (MDCT) scanners, more extensive data sampling of large lesions. CT perfusion is a recent addition for the evaluation of lymph nodes and has shown encouraging but variable results in different study [13].

Hence, present study was conducted with the aim to assess the role of CTP in evaluation of cervical lymph nodes in head and neck malignancies by using CT perfusion parameters and compare with histopathology.

## MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Radiodiagnosis in collaboration with the Department of Surgery and Pathology at Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi, India, from October 2017 to April 2019. Approval of the Institutional Ethics Committee (IEC/VMMC/SJH/Thesis/October/2017-198) was taken for the study and written informed consent was obtained from all patients.

**Sample size calculation:** The sample size was calculated by Mcnamer test with the reference from Zhong 2014 [15]. Study included 30 untreated patients with squamous cell carcinoma confirmed on biopsy and planned for surgical neck dissection. Total 46 nodes planned for surgical neck dissection.

**Inclusion and Exclusion criteria:** All histopathology proven cases of head and neck malignancies, planned for neck dissection were included in the study. Previously treated patients of head and neck cancer, impaired renal function, pregnant females, nodes smaller than 4 mm in long axis (due to increased partial volume effect error), nodes with macrocalcification and necrosis (because nodes with central necrosis visible in CT examination were directly diagnosed as metastasis and necrosis has almost no vascularity hence very low perfusion) and age less than 18 years were excluded from the study.

### Procedure

Non Contrast Computerised Tomography (NCCT) and CT perfusion was performed with Siemens Somatom Definition Flash 256CT scanner. Non contrast CT scan of the neck was obtained from the base of skull to the thoracic inlet, in 0.6 mm slice thickness (120 KV and 35 mAS) with the help of prior scout imaging. Localisation, morphology, number, attenuation and calcification of lymph nodes were assessed on NCCT, thereafter considering the exclusion criteria, appropriate lymph node was selected as Region Of Interest (ROI).

**CT perfusion:** CT perfusion scan was planned accordingly, after selection of ROI in 5 mm slice thickness (100 KV and 150 mAS) were obtained, with a total acquisition time of 1.5 sec. Lymph node perfusion scan began with start of intravenous (IV) contrast administration. Total volume of 50-70 mL of iodinated contrast, with 30-40 mL normal saline was injected IV, using a power injector at rate of 4-5 mL/sec via 18-gauge cannula placed in the cubital vein. CTP data was acquired in dynamic mode simultaneous to contrast injection for Z-axis coverage of 10 cm. Manual postprocessing was done, to define arterial input function and venous outflow function for the automated CTP variable. Using automated threshold, based on deconvolution algorithm reconstruction and post processing was done to generate the CT perfusion maps processed on Siemens syngo via advanced multimodality workstation version VB 20. The analysis of CTP maps was done for parameters of BF (mL/100g/min), BV (mL/100g), MTT (sec), and PS (mL/100g/min). Differentiation between benign and malignant lymph node was done based upon higher BF, BV, PS and lower MTT values and compared with the standard values taken as reference of BF in metastatic nodes was 136.4 mL/100g/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.13.

**Histopathology:** These patients underwent elective neck dissection and the histopathological results of dissected lymph nodes were obtained, and these results were compared to perfusion parameters in each node.

## STATISTICAL ANALYSIS

The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Receiver operating characteristic curve was used to find out cut-off point of parameters for predicting malignancy. A p-value of <0.05 was considered statistically significant.

## RESULTS

There were 25 men and five women with mean age of 52.67±13.23 years. The mean age of the patients were 52.67±13.23 years. Maximum number of the patients (33.33%) belonged to age group >60 years with only 20.00% patients belonging to ≤40 years age group [Table/Fig-1]. Largest number of patients (n=7) had primary site of cancer in buccal mucosa, followed by tonsillar fossa (n=6), aryepiglottic fold (n=4) [Table/Fig-2]. More than half of the patients had one lymph nodes were found in 16 (53.33%) patients, two nodes were found in 13 (43.33%) patients and involvement of four lymph nodes was seen in 1 (3.33%) patient [Table/Fig-3]. According to distribution of lymph nodes levels, out of 46 lymph nodes most were level IIa (n=18) lymph nodes, followed by level Ib (n=13), level III (n=7) [Table/Fig-4]. CT perfusion parameters- BF, BV and MTT showed a significant difference between the benign and malignant lymph nodes (p-value <0.05). However, PS was comparable (p-value=0.06) [Table/Fig-5].

| Age distribution (years) | Frequency | Percentage |
|---|---|---|
| ≤40 | 6 | 20% |
| 41-50 | 8 | 26.67% |
| 51-60 | 6 | 20% |
| >60 | 10 | 33.33% |
| Total | 30 | 100% |
| Mean±SD | 52.67±13.23 | |
| Median (IQR) | 53 (42-62) | |

**[Table/Fig-1]:** Age distribution of the study participants.

CT perfusion images and corresponding histopathological images of two cases is shown in [Table/Fig-6a,b and 7a-c].

The study used receiver operating characteristic curve of quantitative parameters of CTP for prediction of malignancy (histopathology as gold standard), in the detection of sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and diagnostic accuracy. In case of blood flow, sensitivity was 82.61% and diagnostic accuracy was 84.78%. In case of blood volume, sensitivity was 91.30% and diagnostic accuracy was 73.91%. In case of mean transit time, sensitivity was 56.52% and diagnostic accuracy was 73.91%. In case of permeability surface, sensitivity was 91.30%

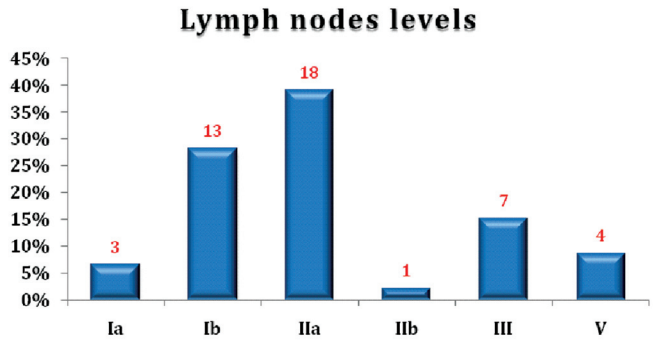
and diagnostic accuracy was 67.39% [Table/Fig-8]. The area under the curve for blood flow was maximum [Table/Fig-9,10].

| Squamous cell carcinoma | Frequency | Percentage |
|---|---|---|
| Buccal mucosa | 7 | 23.33% |
| Tonsilar fossa | 6 | 20% |
| Aryepiglottic fold | 4 | 13.33% |
| Hard palate | 3 | 10% |
| Submandibular region | 2 | 6.67% |
| Epiglottic and Aryepiglottic fold | 1 | 3.33% |
| Floor of mouth | 1 | 3.33% |
| Lower lip | 1 | 3.33% |
| Aryepiglottic fold and pyriform sinus | 1 | 3.33% |
| Base of tongue | 1 | 3.33% |
| Upper lip | 1 | 3.33% |
| Carcinoma tongue | 1 | 3.33% |
| Lateral tongue | 1 | 3.33% |
| Total | 30 | 100% |

**[Table/Fig-2]:** Distribution of subjects on the basis of site (N=30).

| Number of nodes | Frequency | Percentage |
|---|---|---|
| 1 | 16 | 53.33% |
| 2 | 13 | 43.33% |
| 4 | 1 | 3.33% |
| Total | 30 | 100% |

**[Table/Fig-3]:** Distribution of subjects based on frequency of the nodes.



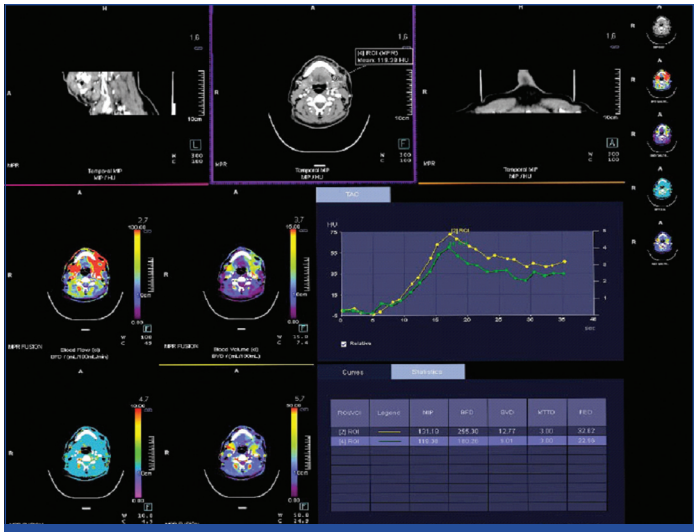

**[Table/Fig-4]:** Distribution of lymph nodes based on levels of lymph node.

| Quantitative parameters of CT perfusion | | Benign (n=23) | Malignant (n=23) | p-value (Unpaired t-test) |
|---|---|---|---|---|
| Blood flow (mL/100g/min) | Mean±SD | 88.06±34.4 | 174.61±71.76 | <0.0001 |
| | Median (IQR) | 79.1 (66.645-115.625) | 178.1 (131.750-190.700) | |
| Blood volume (mL/100g) | Mean±SD | 9.89±7.63 | 16.32±11.9 | 0.005 |
| | Median (IQR) | 7.4 (5.230-10.980) | 11 (9.225-20.475) | |
| Mean transit time (sec) | Mean±SD | 13.11±18.58 | 4.83±2.54 | 0.002 |
| | Median (IQR) | 7.3 (4.600-9.475) | 3.7 (3-7.520) | |
| Permeability surface (mIL/100g/min) | Mean±SD | 37.07±29.26 | 49.3±28.59 | 0.06 |
| | Median (IQR) | 30.3 (17.475-46.650) | 45.7 (28.425-64.250) | |

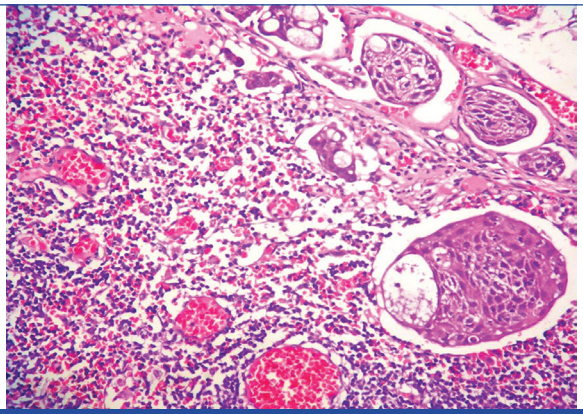
**[Table/Fig-5]:** Association of quantitative parameters of CT perfusion.
p-value <0.05 was considered statistically significant

## DISCUSSION

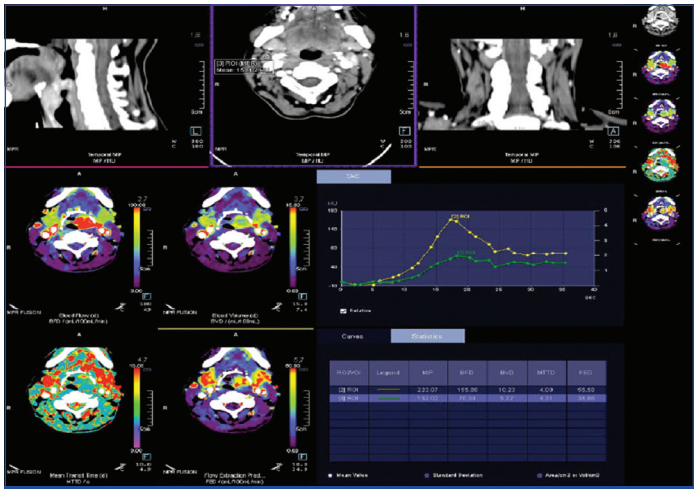
Compared to western world, the mean age of diagnosis of oral cancer in developing countries like India [16,17], is a decade less (65 years vs 52 years). This is primarily related to the high prevalence of the addiction to tobacco chewing among young population, explaining the stable trend in oral cancer incidence in



**[Table/Fig-6a]:** CT Perfusion image of a 51-year-old male patient with squamous cell carcinoma of left submandibular region reveals - Blood flow, blood volume and permeability surface is increased and mean transit time decrease of lymph nodes at left level IB and II (According to above CT Perfusion parameter, both nodes are metastatic).

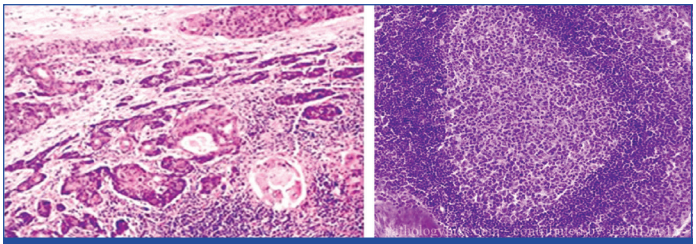


**[Table/Fig-6b]:** Histopathological examination revealed metastatic squamous cell carcinoma (H&E, 10x).



**[Table/Fig-7a]:** CT Perfusion image of a 46 year old female patient with squamous cell carcinoma of epiglottis and aryepiglottis region reveals - Blood flow, blood volume and permeability surface is increased and mean transit time decrease of lymph nodes at left level II and decrease blood flow, blood volume and increase mean transit time at right level II ( According to above CT Perfusion parameter, left level-II (Metastatic node) and right level-II (Benign node).

this group [15,17]. In the present study, in maximum number of the patients (23.33%) primary site of cancer was buccal mucosa; in 20.0% patients tonsillar fossa; in 13.33% patients aryepiglottic fold, in 10.0%, hard palate; in 6.67%. The present study results corroborated with the findings of Sharma P et al., who reported that the most common site was buccal mucosa, followed by the retro molar area, floor of mouth, lateral border of tongue, labial mucosa, and palate [18]. Histopathologically, in the present study 50% of



**[Table/Fig-7b,c]:** Histopathological examination revealed metastatic lymph node in squamous cell carcinoma ( left level-II) (H&E, 4x); Histopathological examination revealed benign lymph node in squamous cell carcinoma. (Right level- II) (H&E, 40x). (Images from left to right)

(114.62±14.26 vs 67.82±13.84, p-value=0.002); and significantly low MTT (5.56±0.39 vs 9.46±3.23, p-value=0.002); with higher but comparable BV [15].

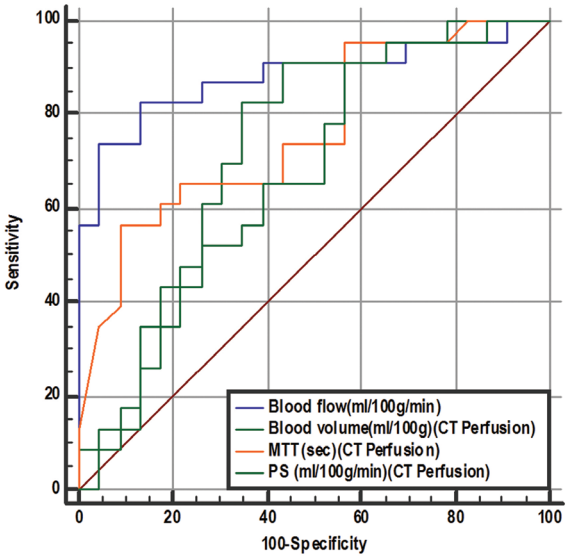
In contrast, Bisdas S et al., found that there is no significant difference in CTP parameters between non metastatic and metastatic nodes in patients with oropharyngeal cancer [12]. Results of the present study may have been due to the inclusion of all metastatic nodes, which shows signs of central necrosis; which would have given very low perfusion values. Interpretation of the area under the ROC curve showed that the performance of blood flow was excellent (AUC: 0.883; 95% CI: 0.754 to 0.959) with least standard error.

| Diagnostic test | Sensitivity | Specificity | Area under the curve | Positive predictive value | Negative predictive value | Diagnostic accuracy |
|---|---|---|---|---|---|---|
| Blood flow (mL/100g/min) | 82.61% (61.2%-95.0%) | 86.96% (66.4%-97.2%) | 0.883 (0.754 to 0.959) | 86.40% (65.1%-97.1%) | 83.30% (62.6%-95.3%) | 84.78% |
| Blood volume (mL/100g) | 91.30% (72.0%-98.9%) | 56.52% (34.5%-76.8%) | 0.741 (0.591 to 0.859) | 67.70% (48.6%-83.3%) | 86.70% (59.5%-98.3%) | 73.91% |
| Mean transit time (sec) | 56.52% (34.5%-76.8%) | 91.30% (72.0%-98.9%) | 0.765 (0.616 to 0.877) | 86.70% (59.5%-98.3%) | 67.70% (48.6%-83.3%) | 73.91% |
| Permeability surface (mL/100g/min) | 91.30% (72.0%-98.9%) | 43.48% (23.2%-65.5%) | 0.662 (0.507 to 0.794) | 61.80% (43.6%-77.8%) | 83.30% (51.6%-97.9%) | 67.39% |

**[Table/Fig-8]:** Determination of Sensitivity, specificity and accuracy of quantitative parameters of CTP.

| ROC for prediction of malignancy | Area under the ROC curve | Standard error | 95% Confidence interval | p-value | Cut-off |
|---|---|---|---|---|---|
| Blood flow (mL/100g/min) | 0.883 | 0.054 | 0.754 to 0.959 | <0.0001 | >122 |
| Blood volume (mL/100g) | 0.741 | 0.0758 | 0.591 to 0.859 | 0.0015 | >7.7 |
| Mean transit time (sec) | 0.765 | 0.0705 | 0.616 to 0.877 | 0.0002 | ≤3.74 |
| Permeability surface (mL/100g/min) | 0.662 | 0.0824 | 0.507 to 0.794 | 0.0497 | >22 |

**[Table/Fig-9]:** Receiver operating characteristic curve of quantitative parameters of CT perfusion for prediction of malignancy (HPE as gold standard). t-test was used




**[Table/Fig-10]:** ROC curve for the CT perfusion parameters.

the lymph nodes were benign and 50% were malignant. In disparity to the study done by Zhong J et al., in which out of the 65 lymph nodes, 48 nodes were proven to be histologically malignant, and 17 nodes were benign in concordance with selection bias depending on the number of cases, we get in our hospital [15].

On CT perfusion, authors found almost double value of BF and BV in metastatic versus non metastatic cervical lymph nodes. There was also a significant decrease in MTT value in metastatic lymph nodes as compared to benign nodes. However, PS was comparable (p-value=0.06). Trojanowski P et al., saw similar results in their study, who also showed an almost double value of BF in metastatic versus non metastatic cervical lymph nodes; with a significant increase in BV and PS, except for MTT value [13]. The BF, BV and MTT values in the current study is in congruence to the study of Zhong J et al., who showed that when compared to benign nodes, malignant nodes had a significantly higher BF

Both neoplastic and inflammatory infiltration mainly take place in subcapsular sinus and shows enlargement of this area, may be one of the factors that is responsible for an increased blood uptake and its reflected by an increase of BF in the first place.

The AUC of blood volume, mean transit time and permeability surface are also good for predicting malignancy. These findings were matching with the findings of Zhong J et al., who showed that in the ROC curves of BF, values used for differentiating benign from metastatic LNs, the areas under the curve were 0.605 [15].

The best threshold BF value for differentiating malignant from benign nodes was more than 122 mL/100g/min with least standard error, yielding a sensitivity of 82.61%, specificity of 86.96%, accuracy of 84.78%, PPV of 86.4%, and NPV of 83.3%. The accuracy of BF in our study, was slightly higher than the study of Zhong J et al., where the best threshold BF value for differentiating malignant from benign nodes was 100.36 mL/100 g/min, yielding a sensitivity of 68.18%, specificity of 52.94%, accuracy of 64.46%, PPV of 80.48%, and NPV of 37.50% [15].

Suryavanshi S et al., demonstrated that the best threshold MTT value for differentiating malignant from benign nodes was 5.4 sec, yielding a sensitivity of 90.5%, specificity of 93.4%, accuracy of 92.7%, PPV of 82.6%, and NPV of 96.6%. Computed tomography perfusion might be useful in differentiation between metastatic and non metastatic cervical lymph nodes however this requires further validation [19].

## Limitation(s)

The main limitation was the small sample size. The distribution of lymph nodes in the present study was unequal. Majority of the patients underwent ipsilateral neck dissection and therefore, the assessment of contralateral neck nodes could not be made.

# CONCLUSION(S)

Blood flow and blood volume has significantly increased values in metastatic cervical lymph nodes in comparison to non metastatic nodes, whereas MTT had significantly decreased values, however PS showed equivocal values. The CTP is a promising imaging tool

in the detection or exclusion of metastatic cervical nodes and has the potential for not only determining the extent of neck dissection but also planning radiation therapy.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Mar 15, 2022
- Manual Googling: Jul 23, 2022
- iThenticate Software: Aug 02, 2022 (25%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**

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