Objectives: To assess the utility of dynamic imaging namely, wash-in and wash-out characteristics through multidetector contrast-enhanced computed tomography in differentiating benign and malignant pulmonary masses.

Materials and Methods: Seventy-three patients who were suspected to have malignant pulmonary mass on the basis of clinical symptoms and chest radiograph were included in the study. All the patients underwent multidetector computed tomography scanning, and three series of images were obtained for each patient-noncontrast, early enhanced, and 15 min delayed enhanced scans. Computed tomography (CT) findings were assessed in terms of washin, absolute, and relative percentage washout of contrast. Biopsy of the mass was done and sent for histopathological evaluation. Sensitivity, specificity, and area under curve for diagnosing malignancy in the lung masses were calculated by considering both the wash-in and wash-out characteristics at dynamic CT and plotting the receiver operating curve after the final diagnosis which was obtained by histopathological evaluation. Results: Threshold net enhancement (washin) value of >22.5 HU had sensitivity, specificity, and diagnostic accuracy of 88.5%, 57.1%, and 82%, respectively, in predicting malignancy. Threshold relative percentage washout of <16.235% had 98.1%, 85.7%, and 94% sensitivity, specificity, and diagnostic accuracy, respectively, and threshold absolute percentage washout of <42.72% had 98.1%, 95.2%, and 95% sensitivity, specificity, and diagnostic accuracy, respectively, in predicting malignancy. Conclusion: Threshold net enhancement (washin), absolute and relative washout percentages can be used to predict malignancy with very high diagnostic yield, and possibly obviate the need of invasive procedures for diagnosis of bronchogenic carcinoma.

Keywords: Contrast wash-in, contrast wash-out, histopathology, lung mass, multidetector computed tomography
With the advent of newer techniques such as helical dynamic CT, multidetector row CT using contrast material, more accurate and useful characterization of pulmonary masses can be done by utilizing their hemodynamic differences, as degree of enhancement of malignant lesions is significantly more than benign lesions.[12-15]

Earlier studies using dynamic-enhanced multidetector row CT mainly considered the early enhancing phase of the lung lesion, which revealed high sensitivity in diagnosing malignant nodules albeit low specificity.[4]

Recent studies have been done for the imaging characterization of adrenal lesions by assessing the washout properties of the adrenal lesions at delayed contrast-enhanced CT (CECT).[6-10] Washout of the contrast material is defined as a decrease in the attenuation of the lesion at delayed CECT after the intravenous administration of contrast.[11]

However, very few authors have studied combined wash-in and wash-out properties at delayed CECT in imaging characterization of malignant and benign pulmonary nodules.[11-13] Although these studies evaluate the standard wash in–wash out characteristics, they are only in solitary lung nodules instead of lung masses that we are evaluating in this study. The purpose of the present study was to assess the sensitivity, specificity, and accuracy of a dedicated lung CT protocol using attenuation values at unenhanced CT and CECT in early and delayed phases to study wash-in and wash-out characteristics (by calculating both absolute and relative percentage washout) in the imaging of suspicious pulmonary masses and their correlation with histopathological examination.

**Materials and Methods**

**Patient inclusion criteria**

Seventy-three patients who were suspected to have malignant pulmonary mass (diameter >3 cm) on the basis of clinical and chest radiographic evaluation were included in the study. Ethical committee clearance was taken for the study protocol and written informed consent was taken from all the patients.

**Multidetector computed tomographic scanning**

All the patients underwent multidetector CT (MDCT) scanning using 384-slice CT scanner (Siemens SOMATOM Force®). Scanning of the suspicious lesion was first done to obtain thin-section unenhanced CT scan images (2.5 mm collimation, 0.8 s gantry rotation time, 120 kVp, 90 mA), followed by dynamic and delayed enhanced scanning. With the help of a high-pressure injection apparatus (Meadrad, Pittsburgh), at a flow rate of 1.8 ml/s, 60–90 ml of a nonionic contrast agent (Ultravist, 370 mg/ml) was injected through the cubital vein. The amount of the contrast agent was calculated based on the body weight (1.5 ml/kg). In each patient, three series of images were obtained – unenhanced noncontrast (from the lung apices through the adrenal glands), early enhanced postcontrast scanning of the entire lung at 15–20 s, and delayed scanning limited to the lung mass only, were done approximately 15 min after the administration of contrast material using similar scanning parameters. After scanning, images were reconstructed into slices 2 mm thick using standard algorithm. All images were then transferred to the workstation for further evaluation, and both mediastinal (window width, 400 HU; window level, 20 HU) and lung (window width, 1500 HU; window level, −700 HU) window images were then viewed.

A circular or ovoid region of interest (ROI) was placed over the lesion on each image of the nonenhanced CT scan and both dynamic and delayed scans. The section with the largest surface area of tissue was selected. Calcified and necrotic regions were not included in the assessment. Then, the mean attenuation value was calculated.

Using the mean Hounsfield unit value in each ROI of the suspicious pulmonary masses on the dynamic and delayed CT scans, following dynamic characteristics of tumor enhancement using wash-in and wash-out values of the contrast were calculated and assessed: peak enhancement, net enhancement (washin), and absolute and relative percentage loss (washout). Peak enhancement was defined as the attenuation value of the mass in the early enhancement phase. Net enhancement was calculated by subtracting the pre-enhancement attenuation value from the peak enhancement attenuation value. Absolute loss of enhancement at delayed imaging was calculated by subtracting the attenuation value at 15 min (HU_{delayed}) from the peak enhancement attenuation value (HU_{early}). Absolute percentage loss was calculated using the formulae:[11]

Absolute washout (absolute percentage loss of enhancement) = \([\text{HU}_{\text{early}} - \text{HU}_{\text{delayed}}]/\left[\text{HU}_{\text{early}} - \text{HU}_{\text{noncontrast}}\right]\) × 100.

Relative washout (relative loss of enhancement) = \(((\text{HU}_{\text{early}} - \text{HU}_{\text{delayed}})/\text{HU}_{\text{early}})\) × 100.

**Pathologic evaluation**

CT-guided biopsy was performed on MDCT scan (Siemens Somatom force® 384 slice).

Bronchoscopy (Biopsy) was performed by OLYMPUS flexible fiber-optic bronchoscope-TYPE TE2®.
Biopsy samples were kept in formalin and sent to the pathology department for the histopathological analysis.

**Statistical analysis**

Statistical analysis was performed with SPSS Software (Version 15.0, Chicago, IL: SPSS Inc.). The values were compared between malignant and benign pulmonary masses after final diagnosis by histopathological evaluation by the use of Student’s t-test. Receiver operating characteristic analysis was performed to determine a threshold for differentiating malignant from benign lesions.

Sensitivity and specificity were calculated by varying the level of enhancement that signified a positive finding (cut-off value).

Diagnostic characteristics – that is sensitivity, specificity, and area under curve – were calculated by considering both the wash-in (net enhancement) and washout (absolute and relative percentage loss of enhancement) characteristics at dynamic CT.

Student’s t-test and receiver operating curve analysis were used to analyze statistically significant differences between attenuation values for unenhanced imaging, net enhancement, and absolute and relative loss of enhancement in malignant and benign masses. $P < 0.05$ was considered statistically significant difference.

**RESULTS**

Out of 73 patients suspected to have malignant lung mass, 51 were males and 22 were females. Out of 73 lung masses suspicious for malignancy, 52 were proven to be malignant and 21 turned out to be benign on histopathological examination [Table 1].

The mean age for patients with diagnosed malignancy was $56.43 \pm 4.07$ years and for benign mass was $26.53 \pm 10.13$ years.

**Noncontrast computed tomography**

The mean CT attenuation value for benign lesions on noncontrast CT scan was $39.00 \pm 3.48$ HU (range 33-45). The mean attenuation value in 52 malignant lesions on noncontrast CT scans was $38.98 \pm 3.45$HU (range 34-46). The mean attenuation value of benign and malignant lesions on nonenhanced CT scans was not significantly different from each other (Student’s t-test, $P = 0.983$).

**Early enhanced computed tomography and washin of contrast material**

The mean attenuation of benign lesions on early CECT scans was $61.29 \pm 6.94$ HU (range 52–75) and net enhancement attenuation (washin) was $22.29 \pm 7.60$ HU (range 7–40). The mean attenuation of the malignant lesions on early enhanced CT scans was $69.94 \pm 10.88$ HU (range 58–84). Net enhancement attenuation (washin) for malignant lesion was $30.96 \pm 5.95$ HU (range 20–42). Significant differences were found between benign and malignant lesions with regard to the mean attenuation value (Student’s t-test, $P < 0.001$). Significant differences were found between benign and malignant lesions with regard to the net enhancement attenuation (washin) on early CECT scans.

Results of the receiver operating curve analysis [Figure 1] showed that a threshold net enhancement value of $22.5$ HU has a sensitivity of $88.5\%$ and specificity of $57.1\%$ to diagnose malignancy on early CECT scans.

**Delayed contrast-enhanced computed tomography with absolute and relative percentage washout of contrast material**

On delayed CECT scans, the mean absolute attenuation value for the benign lesions was $44.86 \pm 7.51$ HU (range 35–70). The mean absolute attenuation value

| Table 1: Characterization of lesions according to histopathological diagnosis |
|---------------------------------|-------------------------------|
| Histopathological diagnosis     | Number of lesions |
| Malignant                       | 52 |
| Adenocarcinoma                  | 25 |
| Squamous cell carcinoma         | 12 |
| Small cell carcinoma            | 9  |
| Sarcomatoid                     | 1  |
| Large cell                      | 3  |
| Metastasis                      | 2  |
| Benign                          | 21 |
| Tuberculosis                    | 10 |
| Pneumonic consolidation         | 9  |
| Hamartoma                       | 1  |
| Fungal ball                     | 1  |

Figure 1: The graph depicting results of the receiver operator characteristic analysis to differentiate between benign and malignant lesions with regard to net enhancement attenuation (wash-in) on contrast-enhanced computed tomography in early phase. The area under curve is $0.827$, $P < 0.001$. 
for 52 malignant lesions on delayed CECT scans was $64.58 \pm 5.93$ HU (range 54–82). The absolute attenuation values of malignant lesions were significantly larger than values of benign lesions on delayed CECT scans (Student’s $t$-test, $P < 0.001$).

Results of receiver operating curve analysis [Figure 2] showed that a threshold absolute attenuation value of $>56.5$ HU had 92.3% sensitivity and 90.5% specificity in diagnosing malignancy on delayed CECT scans.

On the MDCT scans, the mean absolute percentage washout value for benign lesions came out to be $75.76 \pm 20.69$ (range, 7.5–96.15).

The mean absolute percentage washout value for malignant lesions was $17.77 \pm 10.51$ (range, $-4.76–35.45$). The range is in negative as the Hounsfield unit of one lesion actually increased on delayed imaging than early enhanced CT.

The absolute percentage washout values of malignant lesions were significantly lower than the values of the benign lesions on delayed CECT scans (Student’s $t$-test, $P < 0.001$).

The results of receiver operating curve analysis [Figure 3] showed that a threshold absolute percentage washout of $<42.72\%$ had 98.1% sensitivity and 95.2% specificity for identifying malignant lesions.

On the MDCT scans, the mean relative percentage washout value for benign lesions came out to be $26.53 \pm 10.13$ (range, 4.11–44.59).

The mean relative percentage washout value for malignant lesions was $7.61 \pm 4.07$ (range $-1.67–18.99$). The range is in negative as the attenuation value of one lesion actually increased on delayed imaging than early enhanced CT.

The relative percentage washout values of malignant lesions were significantly lower than the values of the benign lesions on delayed CECT scans (Student’s $t$-test, $P < 0.001$).

The results of receiver operating curve analysis [Figure 4] analysis showed that a threshold relative percentage washout of $<16.235\%$ had 98.1% sensitivity and 85.7% specificity for identifying malignant lesions.

The results have been summarized in the following Tables 2 and 3. Two examples have been shown in Figures 5 and 6 which show the radiograph that served as inclusion criteria along with their MDCT and histopathological evaluation.

**DISCUSSION**

Enhancement of lung mass at CT is strongly predictive of malignancy and vascularity, as degree of enhancement

| Table 2: Summary of different characteristics of malignant and benign masses |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Malignant (n=52) | Benign (n=21)   |
| Noncontrast CT attenuation (HU) | 38.98±3.45       | 39.00±3.48      |
| Mean attenuation (HU)          | 69.94±10.88      | 61.29±6.94      |
| Net enhancement attenuation (washin) (HU) | 30.96±5.95       | 22.29±7.60      |
| Delayed contrast-enhanced CT (HU) | 64.58±5.93       | 44.86±7.51      |
| Absolute percentage washout    | 17.77±10.51      | 75.76±20.69     |
| Relative percentage washout    | 7.61±4.07        | 26.53±10.13     |

SD: Standard deviation, CT: Computed tomography

![Figure 2](image2.png)

**Figure 2:** The graph depicting results of the receiver operator characteristic analysis to differentiate between benign and malignant lesions with regard to absolute attenuation value on contrast-enhanced computed tomography in early phase. The area under curve is 0.950, $P < 0.001$.

![Figure 3](image3.png)

**Figure 3:** The graph depicting the results of the receiver operator characteristic analysis for differentiating between malignant and benign pulmonary masses with regard to mean absolute washout at contrast-enhanced computed tomography. The area under curve is 0.958, $P < 0.001$. 


of malignant lesions is significantly more than the benign lesions.\cite{2,4,14,15} Yamashita et al.\cite{16} reported that a maximum attenuation of 20–60 HU appears to be a good predictor of malignancy. In their study, Swensen et al.\cite{2} reported that a threshold value of 15 HU produced a sensitivity of 98\%, a specificity of 58\%, and an accuracy of 77\% for malignant nodules. Since then, the cutoff values for differentiating benign and malignant lesions have been set at 15 or 20 HU.

Cutoff values for differentiating benign and malignant lesions have increased since higher dynamic study peak enhancements were obtained with MDCT as compare to the earlier studies performed using conventional or single helical CT.\cite{4} Therefore, by keeping 30 HU or more of net enhancement as a cutoff value in differentiation of malignant and benign lesions, sensitivity for malignant lesions was 99\%, specificity was 54\%, positive predictive value was 71\%, negative predictive value was 97\%, and accuracy was 78\%. However, all of these previous dynamic CT studies\cite{2,4} mainly considered the early phase of dynamic CT scanning and showed low specificity ranging from 54\% to 77\% and showed false-positive results for active granulomas and thus did not help much to differentiate them from malignant lesions. In our study, a threshold net enhancement (washin) value of 22.5 HU (i.e., net enhancement more than 22.5 HU indicates malignancy) had a sensitivity of 88.5\%, specificity of 57.1\%, and accuracy of 82\% in diagnosing malignancy on early CECT scans. The results in our study also showed that wash-in features have higher sensitivity but lower specificity in diagnosing malignant lesions. In the present study, wash-in enhancement of 22.5 HU or more was achieved by all malignant lesions.

Wash-out features at delayed CECT have been assessed in imaging characterization of adrenal lesions.\cite{6-10} However, very few studies have studied combined wash-in and wash-out properties at delayed CECT in imaging characterization of malignant and benign pulmonary nodules.\cite{11-13}

To the best of our knowledge, in the available literature, this is the first study to focus on wash-in, absolute, and relative percentage washout values at delayed CECT in imaging characterization of skeptical lung masses and then their correlation with histopathological examination.

In our study, the relative percentage washout values of malignant lesions were significantly lower than the values of the benign lesions on delayed CECT scans ($P < 0.001$). We also found that a threshold relative percentage washout of $<16.235\%$ calculated through receiver operating curve had 98.1\% sensitivity, 85.7\% specificity, and 94\% accuracy in identifying malignant lesions. The absolute percentage washout values were also calculated and showed that malignant lesions have significantly lower absolute percentage washout values than the value of the benign lesions on delayed CECT scans ($P < 0.001$). We found out that a threshold absolute percentage washout of $<42.72\%$ had 98.1\% sensitivity, 95.2\% specificity, and 95\% accuracy in predicting malignancy. Our study showed that by the assessment of washout characteristics, specificity in identifying malignant lesions was higher than that for wash-in features in the early phase of dynamic CT. In a study done by Ye et al.,\cite{12} the relative percentage washout value was calculated for both malignant and benign lung nodules and showed a higher specificity in identifying malignant nodules than that for wash-in characterization in the early phase of dynamic CT scanning. However, Ye et al.,\cite{12} did not calculate the absolute percentage washout.

The basis for the noted difference in the washout characterization of malignant and benign lesions has

| Table 3: Sensitivity, specificity, and diagnostic accuracy of various contrast-enhanced computed tomography parameters |
|---------------------------------------------------------------|
| Threshold values | Predictive value | Sensitivity (%) | Specificity (%) | Diagnostic accuracy (%) |
|------------------|------------------|-----------------|-----------------|------------------------|
| Net enhancement  | 22.5 HU          | 88.5            | 57.1            | 82                     |
| Relative washout | $<16.23\%$       | 98.1            | 85.7            | 94                     |
| Absolute washout | $<42.72\%$       | 98.1            | 95.2            | 95                     |

Figure 4: The graph depicting the results of the receiver operator characteristic analysis for differentiating between malignant and benign pulmonary masses with regard to mean relative washout at contrast-enhanced computed tomography. The area under curve is 0.942, $P < 0.001$. 
been attributed to the difference in their pathologic and pharmacokinetic properties. Both intravascular and interstitial spaces are notably involved in the delivery of contrast material through the lung parenchyma.[17] In general, malignant pulmonary lesions are primarily supplied by the bronchial arteries with varying degree
of contribution from the pulmonary circulation.[18-21] Washout from the intravascular space takes place mainly through the pulmonary veins in the normal pulmonary tissue. However, in malignant lung lesions, outflow of contrast through the pulmonary veins is decreased, and the predominant venous outflow is through the bronchial veins into the right atrium.[18] Remarkably large interstitial space has been noticed in some human and experimental malignant tumors.[22] In the normal lung tissue, washout from the interstitial space takes place through the lymphatic vessels.[18] An extremely distinguishable feature of malignant lung lesions is the near complete absence or pronounced diminution of lymphatic outflow.[17] The impeded flow through pattern in the intravascular and the interstitial spaces leads to holding of contrast medium in the malignant lung lesions. The intravascular space is decreased in actively infectious and inflammatory lesions.[18] In majority of the inflammatory lung processes, there is diffuse thrombosis at the level of arterioles in the pulmonary circulation. Thus, the lesion is predominantly supplied by the bronchial arteries which appear to increase in number and size.[21] Washout of the contrast from the intravascular space in the inflammatory lesions occurs through comparatively straight vessels with a normal configuration and thus not hindered. Washout from the interstitial space of the inflammatory lung nodules is escalated by the active lymphatic flow.[17,24] Therefore, the retention of the contrast is improbable in majority of the inflammatory lung processes.

CONCLUSION

The assessment of suspicious pulmonary masses by calculating wash in and their absolute and relative percentage wash-out values through dynamic contrast-enhanced multidetector row computed tomography proved to be highly beneficial in the prediction of malignancy. The cutoff values obtained can be used for diagnosing malignancy with a very high diagnostic yield and can possibly obviate the need of biopsy or FNAC which require invasive procedures.

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Conflicts of interest

There are no conflicts of interest.

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