

Low-dose Computed Tomography Perfusion Study to Differentiate Between Benign and Malignant Ovarian Tumors

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ABSTRACT

OBJECTIVE: To assess the role of Low-dose perfusion computed tomography (PCT) in differentiating benign and malignant ovarian tumors.

STUDY DESIGN: Low-dose PCT (80 kVp and 120 mAs on a 256-slice CT scanner) was performed on fifty-one pathologically proven benign and malignant ovarian tumors. The PCT parameters calculated were blood flow (BF), blood volume (BV), time to maximum (T max), mean transit time (MTT), and flow extraction product (FED). Statistical analysis was performed to evaluate the association between these PCT parameters and histopathological diagnosis.

RESULTS: The study comprised 31 pathologically confirmed malignant and 20 benign ovarian tumors. The mean BF, BV, and FED values were elevated in malignant tumors and showed statistically significant association ($p < 0.001$). However, MTT and T max were not statistically significant. The average radiation dose for the entire study was 13.5 mSv, slightly lower than that of standard NCCT and CECT abdomen scans performed for staging purposes.

CONCLUSION: Low-dose PCT parameters (BF, BV, and FED) can play a significant role in differentiating benign from malignant ovarian tumors.

Keywords: Abdomen; Benign ovarian tumors; Blood; CT scanner; Malignant ovarian tumors; Perfusion computed tomography; Volume

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Introduction

Ovarian cancer is the 8th most common cancer in women and is also the 18th most common cancer globally (1). Ovarian cancer leads to significant morbidity and mortality and has a poorer survival rate than other gynecological malignancies, owing to its non-specific symptoms, making patients present in advanced stages (2).

According to The World Ovary Cancer Coalition Atlas, in 2012, there were about 239,000 cases and 152,000 deaths, and it is estimated that the incidence of ovarian cancers will increase by 55% and deaths by 67% by 2035 (2).

Histopathological examination is the gold standard for the characterization of ovarian tumors. Image-guided fine-needle aspiration and biopsy have diagnostic accuracy of about 87% (3). However, they can lead to peritoneal spread, hence, they are usually done for stage III/IV ovarian tumors as histopathology becomes the mainstay for proper regimen selection and neoadjuvant chemotherapy in such cases. Since these investigations are invasive and may lead to complications, imaging remains the mainstay for the initial diagnosis. Transvaginal ultrasound (TVS) is the first-line screening modality often followed by Computed Tomography (CT scan) or Magnetic Resonance Imaging (MRI). Since ultrasound is

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operator-dependent, CT scans and MRI are robust imaging modalities for the diagnosis and staging of ovarian tumors.

CT scan is very advantageous providing detailed analysis of the primary tumor, adjacent spread, peritoneal implantation, lymph nodal spread, and distant organs thus helping in the characterization of ovarian tumor (4). MRI is the preferred modality for follow-up of locally invasive malignant tumors, however, there are certain constraints of MRI like longer acquisition time, susceptibility artifacts, claustrophobia, cost, and limited availability (5,6). Furthermore, MRI cannot be performed in patients with cardiac pacemakers, cochlear implants, metallic implants, etc (7).

Malignant tumors are often more proliferative and associated with increased angiogenesis due to high metabolic demand (8). This can be detected by newer techniques such as CT perfusion, MR perfusion, and contrast-enhanced ultrasound (CEUS). The treatment response of malignant ovarian tumors to chemotherapy can also be assessed. These newer imaging techniques are emerging as promising tools for better characterization and follow-up of ovarian tumors. The present study endeavored to study the role of low-dose perfusion CT (PCT) parameters in differentiating benign and malignant ovarian tumors considering histopathology as the gold standard. We also aimed to establish the cut-off values of PCT parameters in differentiating benign and malignant ovarian tumors and analyzing their role in predicting the aggressiveness of malignant ovarian tumors.

Material and Method

This cross-sectional observational study included 51 untreated complex ovarian tumors, detected on ultrasound. The approval was obtained from an institutional ethical committee (S No. IEC/VMMC/SJH/Thesis/October/2020-11/CC-278 dt. 10.12.2020). All patients' written informed consent was also obtained. The patients with cystic ovarian tumors without any solid component, size <2 cm or >20 cm, who fail to undergo surgery or histopathology, pregnancy, severe respiratory or cardiac disease, deranged KFT, and known history of allergy were excluded from the study.

All the patients underwent CT perfusion on a 256-slice CT scanner (SIEMENS Somatom Definition Flash). 1500 ml of water was given orally over 45-60 mins, followed by 150 ml per rectum. A scout image was acquired to define the superior and the inferior extent of the tumor. Non-ionic iodinated contrast (400 mg/ml) was given intravenously (approximately 40 ml at the rate of 5.5 ml/sec). A 10 cm 4D range was set at the epicenter of the mass and perfusion scans were obtained: 23 passes; rotation time: 0.28 sec; acquisition time: 46.35 sec; scan delay: 5 secs, tube current: 120 mAs; voltage: 80 kV with an estimated radiation dose of 7 mSv (low dose scan). After this Porto-venous phase of the abdomen and pelvis was acquired and the estimated radiation dose of this entire study

was approx. 13.5 mSv. The raw perfusion data was evaluated and permeability maps were created with the arterial input in the internal iliac artery. For each mass, 5 ROIs were kept in different solid areas, and mean values were calculated for Blood flow (BF), blood volume (BV), time to maximum (T max), mean transit time (MTT), and flow extraction product (FED). (Figures 1 and 2) BF is the amount of blood (in mL) reaching the ROI per 100 of tissue with BV being blood flow per unit time (minute). MTT is the average transit time taken by the blood to cross from arterial supply to venous drainage with T max implying the maximum time taken by the contrast agent to reach peak attenuation in the ROI. FED is a parameter that assesses the interstitial permeability of the ROI (9). The parameters were also calculated for contralateral normal ovaries to serve as the control group. The confirmation of diagnosis was done by histopathology of the surgical specimen or an image-guided biopsy.

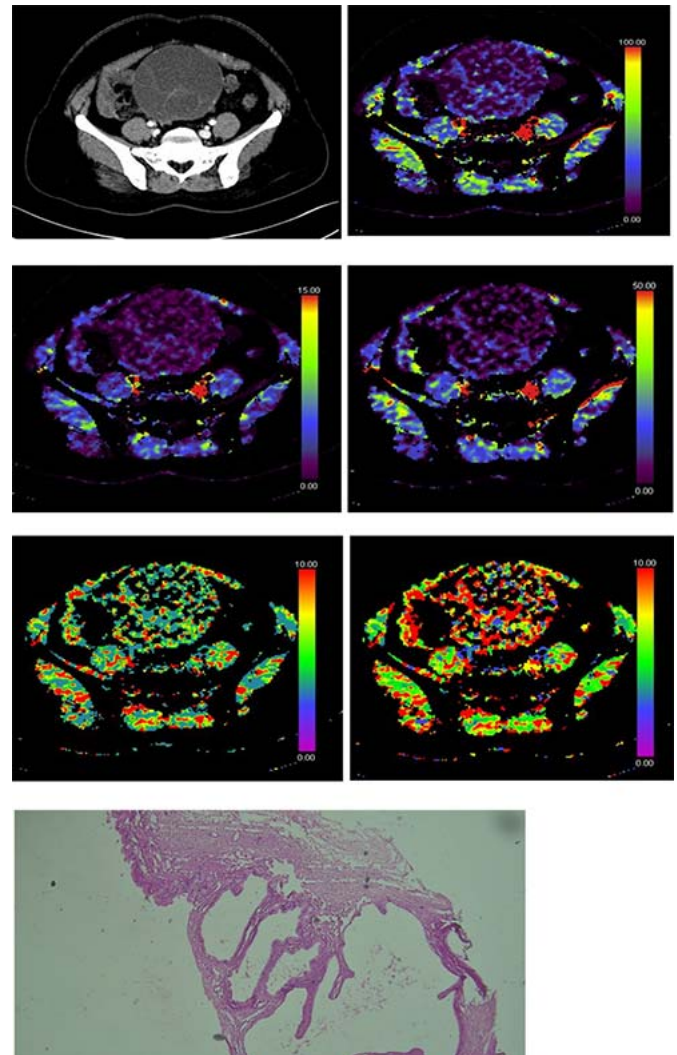


Figure 1: CT perfusion of left mucinous cystadenoma **a:** PCT image showing left ovarian multiseptated cystic lesion with septal enhancement **b:** BF 67.67 ml/100gm/min **c:** BV 3.48 ml/100gm **d:** FED 9.2 ml/100gm/min. **e:** MTT 3.19 sec **f:** T max 3.68-sec **g:** HE 10× showing mucinous cystadenoma with mucinous epithelial lining and fibro collagenous stroma.

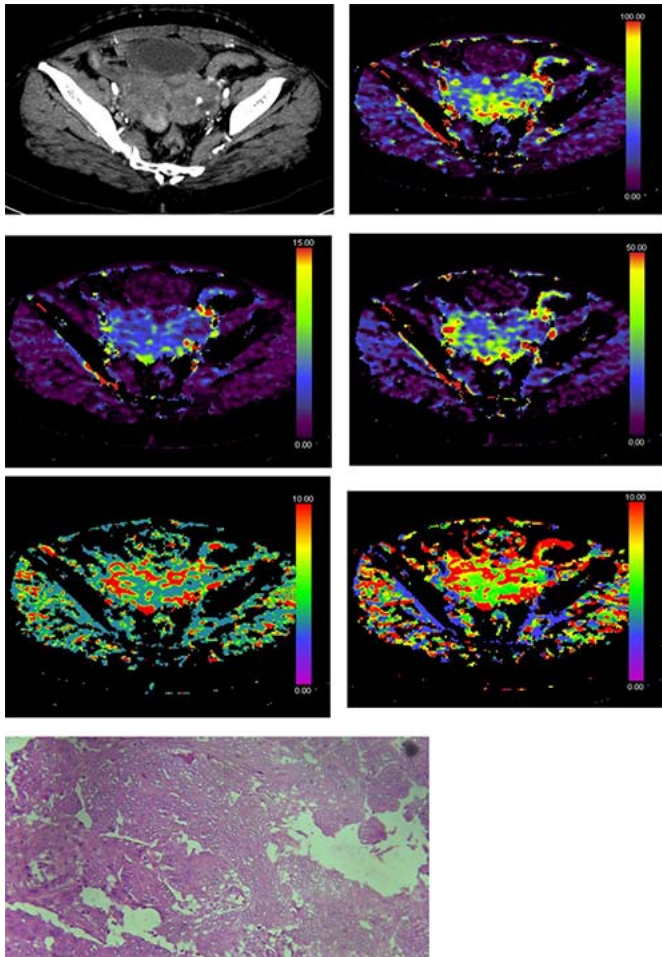


Figure 2: CT perfusion of bilateral high-grade serous cystadenocarcinoma **a:** PCT image showing bilateral solid vascular adnexal lesions **b:** BF right 97.84 and left 93.16 mL/100gm/min **c:** BV right 5.03 and left 4.98 mL/100gm **d:** FED right 27.74 and left 25.25 mL/100g/min. **e:** MTT right 3.09 and left 3.30-sec **f:** T max right 3.73 and left 5.31-sec **g:** HE 40x shows fused glands having pleomorphic nuclei with prominent nucleolus with focal areas of squamous differentiation.

Statistical analysis

Data were coded and recorded in the MS Excel spreadsheet program. SPSS v23 (IBM Corp.) was used for statistical analysis. The chi-square test and Fisher's exact test were used to compare categorical data between groups. Linear correlation between two continuous variables was explored using Pearson's correlation and Spearman's correlation. ROC analysis was performed to determine the area under the curve (AUROC), and a suitable cutoff was calculated using Youden's index. Statistical significance was set at a p-value <0.05.

Results

The study included 51 ovarian tumors (20 benign and 31 malignant). The mean age of patients was 38.63 yrs. (age range 21-70 yrs.). The maximum patients (17) were 18-30 years. Abdominal pain was the most common symptom. The surface epithelial carcinomas were most common (77%) among malignant tumors (61%). Mature cystic teratomas were found to

be the most common among the benign cases. All these 51 ovarian tumors were characterized based on their CT findings (CT impression). The CT impression and HPE showed agreement in 92.2% of cases (Cohen's Kappa=0.829, $p<0.001$).

The diagnostic performance of PCT parameters was analyzed statistically. The AUROC for BF was 0.919 (95% CI: 0.824-1, $p<0.001$), thus showing excellent diagnostic performance. A cut-off of $BF \geq 93.16$ predicted malignancy with a sensitivity of 97% and specificity of 80% (Figure 3a). The odds ratio (95% CI) for malignant HPE when $BF \geq 93.16$ was 58 (9.55-352.21) and the relative risk (95% CI) was 7.91 (2.65-28.46).

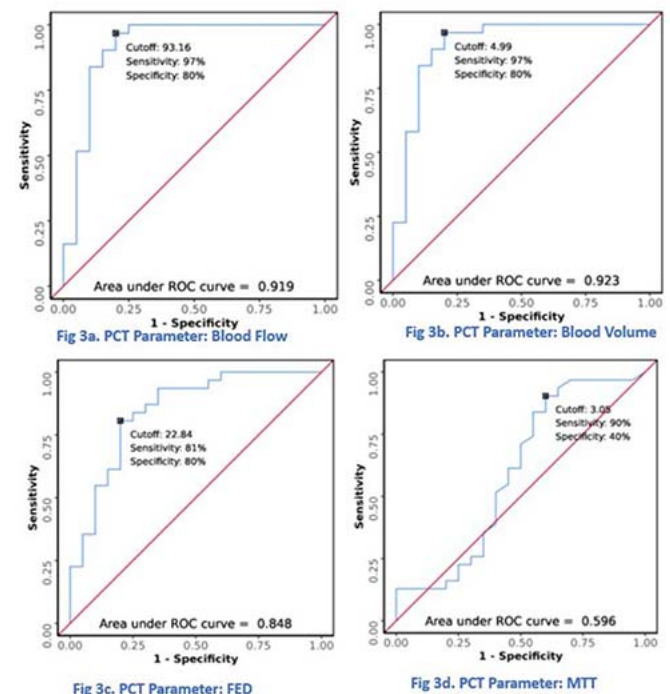


Figure 3: ROC Curve analysis showing diagnostic performance of PCT parameters in predicting histopathology of ovarian tumors (malignant vs benign)

The AUROC for BV was 0.923 (95% CI: 0.835-1, $p<0.001$). A cut-off of $BV \geq 4.986$, predicted malignancy with a sensitivity of 97% and specificity of 80%. (Figure 3b) The odds ratio (95% CI) for predicting malignancy when $BV \geq 4.986$ was 58 (9.55-352.21) and the relative risk (95% CI) was 7.91 (2.65-28.46).

FED also showed good diagnostic performance. The AUROC for FED in the prediction of malignancy was 0.848 (95% CI: 0.734-0.963) ($p<0.001$) (Figure 3c). A cut-off of $FED \geq 22.836$ had a sensitivity of 81% and specificity of 80% in predicting malignancy. The odds ratio (95% CI) was 13.71 (3.44-54.61) and the relative risk (95% CI) was 2.82 (1.62-5.57).

Mean transit time (MTT), however, did not show significant results ($p=0.255$). The AUROC for MTT was 0.596 (95% CI: 0.419-0.772). A cut-off of $MTT \geq 3.048$, predicted malig-

nancy with a sensitivity of 90% and specificity of 40% (Figure 3d). The odds ratio (95% CI) was 4.5 (1.13-17.88) and relative risk (95% CI) was 2.08 (1.07-5.11). Similarly, T max did not show significant results ($p=0.787$). The AUROC for T max was 0.523 (95% CI: 0.338-0.708) and at a cut-off of ≥ 2.416 , sensitivity of 94%, and specificity of 35% were established. The odds ratio was 5.03 (1.12-22.61) relative risk (95% CI) was 2.28 (1.07-6.44).

The association between HPE (benign/malignant) and other parameters is shown in Table I. Age and PCT parameters BF, BV, and FED showed significant association ($p<0.05$) with HPE. PCT parameters BF and BV were the most accurate parameters (90.2% diagnostic accuracy) with equal sensitivity, specificity, PPV, and NPV. The second-best accurate parameter was FED (80.4% accuracy) with sensitivity equal to BV and BF (Table II). The mean CT perfusion parameters of the control group were BF: 31.44 mL/100gm/min, BV: 3.39

ml/100gm, FED: 16.97 mL/100gm/min, MTT: 6.61 sec and T max: 9.28 sec.

Furthermore, coming to the histopathological grading of the 21 malignant ovarian tumors, 11 were low grade, and 11 were high grade (50% each). Analyzing the role of PCT parameters in predicting the aggressiveness/grade of malignant ovarian tumors, BF and BV were not statistically significant ($p=0.844$ and 0.694 , respectively). The AUROC for FED in predicting high grade was 0.727 (95% CI: 0.51 - 0.945), thus demonstrating fair diagnostic performance, however not statistically significant ($p=0.076$). In contrast, MTT showed significant results ($p=0.033$) in the prediction of high-grade malignancy (Table III). The association of T max was again not significant ($p=0.511$). Thus, no significant role of PCT parameters in the prediction of aggressiveness of malignancy could be established.

Table I: Association between HPE impression and parameters

Parameters	HPE Impression		p
	Benign (n=20)	Malignant (n=31)	
Age (Years)***	32.60 ± 8.67	42.52 ± 13.11	0.002¹
Age***			0.004²
18-30 Years	11 (55.0%)	6 (19.4%)	
31-40 Years	4 (20.0%)	10 (32.3%)	
41-50 Years	5 (25.0%)	4 (12.9%)	
51-60 Years	0 (0.0%)	10 (32.3%)	
61-70 Years	0 (0.0%)	1 (3.2%)	
Histopathology***			<0.001²
Epithelial: Serous Cystadenocarcinoma	0 (0.0%)	16 (51.6%)	
Epithelial: Mucinous Cystadenocarcinoma	0 (0.0%)	3 (9.7%)	
Epithelial: Endometrioid Carcinoma	0 (0.0%)	5 (16.1%)	
Epithelial: Serous Cystadenoma	6 (30.0%)	0 (0.0%)	
Epithelial: Mucinous Cystadenoma	2 (10.0%)	0 (0.0%)	
GCT: Mature Teratoma	10 (50.0%)	0 (0.0%)	
GCT: Dysgerminoma	0 (0.0%)	1 (3.2%)	
Krukenberg	0 (0.0%)	6 (19.4%)	
Epithelial: Endometrioid Cyst	2 (10.0%)	0 (0.0%)	
CT Perfusion: BF***	81.70 ± 60.36	218.08 ± 107.75	<0.001⁴
CT Perfusion: BV***	4.62 ± 3.79	13.31 ± 6.97	<0.001⁴
CT Perfusion: MTT	3.48 ± 0.63	3.78 ± 1.44	0.255 ⁴
CT Perfusion: T max	4.30 ± 2.13	4.36 ± 2.14	0.787 ⁴
CT Perfusion: FED***	18.38 ± 17.87	53.91 ± 44.69	<0.001⁴

***Significant at $p<0.05$, 1: t-test, 2: Fisher's Exact Test, 3: Chi-Squared Test, 4: Wilcoxon-Mann-Whitney U Test

Table II: Performance of PCT parameters for predicting HPE impression: Benign vs. malignant

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
BF (Cut off: 93.16 by ROC)	96.8% (83-100)	80.0% (56-94)	88.2% (73-97)	94.1% (71-100)	90.2% (79-97)
BV (Cut off: 4.986 by ROC)	96.8% (83-100)	80.0% (56-94)	88.2% (73-97)	94.1% (71-100)	90.2% (79-97)
MTT (Cut off: 3.048 by ROC)	90.3% (74-98)	40.0% (19-64)	70.0% (53-83)	72.7% (39-94)	70.6% (56-83)
T max (Cut off: 2.416 by ROC)	93.5% (79-99)	35.0% (15-59)	69.0% (53-82)	77.8% (40-97)	70.6% (56-83)
FED (Cut off: 22.836 by ROC)	80.6% (63-93)	80.0% (56-94)	86.2% (68-96)	72.7% (50-89)	80.4% (67-90)

Table III: Performance of PCT parameters for predicting grades of malignancy: High grade vs. low grade

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
BF (Cut off: 185.79 by ROC)	63.6% (31-89)	63.6% (31-89)	63.6% (31-89)	63.6% (31-89)	63.6% (41-83)
BV (Cut off: 8.242 by ROC)	72.7% (39-94)	54.5% (23-83)	61.5% (32-86)	66.7% (30-93)	63.6% (41-83)
MTT (Cut off: 3.184 by ROC)	81.8% (48-98)	72.7% (39-94)	75.0% (43-95)	80.0% (44-97)	77.3% (55-92)
T max (Cut off: 3.736 by ROC)	63.6% (31-89)	63.6% (31-89)	63.6% (31-89)	63.6% (31-89)	63.6% (41-83)
FED (Cut off: 20.266 by ROC)	100.0% (72-100)	36.4% (11-69)	61.1% (36-83)	100.0% (40-100)	68.2% (45-86)

Discussion

Summary of main results: This study included 51 complex ovarian masses and PCT parameters- BF, BV, FED, MTT, and T max were studied. BF and BV had equal sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 96.8%, 80%, 88.2%, 94.1%, and 90.2%, respectively ($p < 0.001$). FED was the second most diagnostically accurate parameter. MTT and T max were not significant. None of the PCT parameters helped differentiate low and high-grade malignant tumors.

Results in the context of published literature: The current survival rate of ovarian cancer is 30-50%; thus, making a prompt diagnosis is of paramount importance (2). Ultrasound is often the first imaging modality; however, patients are often referred for a CT scan which provides a detailed picture of loco-regional staging and metastasis. In addition to ultrasound, the role of Risk of Malignancy Index-1 (RMI-1) has also been evaluated in post-menopausal adnexal masses. RMI-1 scores are calculated through the formula: $[RMI = \text{Ultrasound Score} \times \text{Menopause Score} \times \text{Serum Ca-125 Level}]$. Durmus et al. found that at a score of ≥ 200 , RMI would predict malignant adnexal masses with a sensitivity of 75%, specificity of 93%, PPV of 88%, and NPV of 85% (10).

Various CT features help in differentiating malignant tumors like thick irregular septations, cyst walls, solid enhancing area, and invasion into adjacent viscera with distant metastasis (11). Bhimani et al., found sensitivity, specificity, and PPV of 97.8%, 92.1%, and 93.7% respectively for diagnosing malignant ovarian tumors on CT scans (12). In the present study, CT had a very high sensitivity of 100%, specificity of 80%, and diagnostic accuracy of 92% with $p < 0.001$ for detecting malignancy.

Malignant tumors have increased angiogenesis which can be assessed using various perfusion techniques, such as CEUS, perfusion CT (PCT), and perfusion MRI (6,13,14). It is easier to perform PCT in India as CT scanners are widely available and relatively less expensive. Adding dynamic PCT provides functional assessment with a very minimal increase in scan time. MRI is expensive with a longer scan time and is prone to susceptibility artifacts.

The present study comprised 51 ovarian tumors (31 malignant and 20 benign) with a mean patient age of 38.6 years. Benign tumors were more common in patients aged 18-30

years, whereas malignant tumors showed a bimodal distribution in the 31-40 and 51-60-year age groups. Mondal et al. reported a median age of 35 years.; most benign tumors occurred in the 20-40-year range, while malignant tumors were observed in the 41-50-year range, in contrast to the present study, which exhibited a bimodal distribution (15). They also found benign tumors to be more common than malignant ones, which is consistent with our results.

Mondal et al., found serous cystadenomas to be the most common benign tumor in contrast to mature teratomas in the present study. Among malignancies, serous cystadenocarcinomas were the most common in their study as well (15). A population cohort study by Dilley et al., also found abdominal pain and distension to be the most common symptoms (39% each) similar to the present study (16).

In the present study, all the patients underwent CECT along with PCT. To decrease the radiation, low-dose scans were acquired; tube current 120 mAs, voltage 80 kV, and 10 cm 4D FOV with an effective dose of 7 mSv. The average total effective dose was 13-14 mSv whereas, in routine, the median effective dose of a single NCCT abdomen is 15 mSv (17).

Singla et al., (2018) conducted a study on 40 patients, analyzing the role of PCT parameters in adnexal masses, and found BF, BV, and PS to be statistically significant in differentiating benign and malignant masses (18).

On extensive research, a similar study was found in Chinese literature by Jiang et al., on 12 ovarian tumors correlating perfusion imaging with micro-vessel density. They studied time density curves and found that benign tumors have a slowly rising curve reaching a peak at 40-sec as compared to 25-sec in malignant tumors. They studied perfusion, TTP, BV, and peak enhancement images correlating them with immunohistochemical staining of the vessels and found a significant difference between perfusion parameters of benign and malignant ovarian tumors ($p < 0.05$) (19). Because this study had a very small sample size, the study by Singla et al. is the only study published in the literature with a good sample size (18).

In the present study, a cut-off value of $BF \geq 93.15$ ml/min/100 gm was statistically significant ($p < 0.001$) in differentiating benign and malignant ovarian tumors, fairly in comparison to Singla et al., (cut-off value of ≥ 83.15 mL/min/100 gm) with a sensitivity and specificity of 95%

(18). A cut-off of 80.43 mL/min/100gm in the current study would yield a sensitivity of 96.8% and specificity of 75%.

The present study got a cut-off value of $BV \geq 4.986$ ml/100 gm ($p < 0.001$) with a sensitivity of 97% and a specificity of 80% in contrast to Singla et al., who established a cut-off of ≥ 14.25 mL/100 gm being 95% sensitive and 90% specific (18). A cut-off of 14.37 mL/100gm in our study would yield a sensitivity of only 41.9% and a specificity of 95%.

FED in the current study had a cut-off value of ≥ 22.836 ml/100 gm/min ($p < 0.001$) with 80.6% sensitivity and 80% specificity in comparison to Singla et al., (cut-off of ≥ 14.5 mL/100 gm/min; 85% sensitive and 85% specific) (18). A cut-off of 15.61 mL/100gm/min in our study would yield 93.5% sensitivity and 65% specificity. MTT and T max were not found to be significant presently, on the contrary, Singla et al., found T max to be statistically significant with a cut-off of 5.6 sec to be 90% sensitive and 85% specific (18).

In the present study, three mature cystic teratomas (> 10 cm) revealed thick, enhancing nodular walls which led to a suspicion of malignancy. Moreover, they also displayed high BF, BV, and FED values. However, histopathological examination revealed no evidence of malignancy. It was found that high vascularity is not a reliable factor, as there may be focal areas of struma ovarii or carcinoid which may appear hyper-enhancing. Instead, the presence of enhancing soft tissue components with obtuse margins relative to the cyst wall, along with adjacent infiltration and metastasis, appears to be more reliable features of malignant transformation (20). Moreover, we found tortuous comma-shaped vessels in two cases which turned out to be low-grade mucinous and high-grade bilateral serous cystadenocarcinoma, hence this abnormal morphology of vessels can be used as a predictor of malignancy.

The present study also aimed to ascertain if PCT parameters can help predict the aggressiveness of malignant tumors in terms of their histopathological grading. It was hypothesized by Singla et al., that PCT parameters may help in differentiating between high and low-grade malignant tumors (17). However, in the present study, none of the PCT parameters was helpful in the same. This could be due to a relatively small sample size. Apart from differentiating ovarian tumors, PCT can also provide a baseline scan for assessment of tumor prognosis and response to chemotherapy in malignant cases (21).

Limitations and Strengths: A few limitations were that decreasing the radiation dose also decreased the SNR of images in obese patients. High contrast pressure injection is required, which is difficult in frail/obese patients. Contrast cannot be injected in patients with deranged renal function, alternatively, a scan can be planned just before hemodialysis in such patients. Despite these limitations, PCT helps in assessing tumor vascularity and can serve as an additional tool in indeterminate cases. Hence, it becomes important to establish the cut-

off values of PCT parameters due to the paucity of studies on this subject.

Implications for Clinical Practice and Future Research: For women with ovarian masses, a diagnostic difficulty still exists in differentiating benign and malignant tumors. Perfusion-based imaging techniques help to evaluate the neovascularity of tumors objectively. The results of the present study regarding the role of low-dose perfusion computed tomography in differentiating benign and malignant ovarian tumors are substantial, hence, it can be an advantageous technique in indeterminate ovarian tumors.

Conclusion

Despite the availability of various imaging techniques, a diagnostic dilemma persists in differentiating benign and malignant ovarian tumors. Perfusion-based imaging helps objectively evaluate an ovarian tumor's neovascularity and obtain anatomical and functional information. Hence, PCT can be a useful tool for differentiating benign and malignant ovarian tumors, with no added radiation dose to the patient.

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the institutional ethical committee of VMMC & Safdarjung Hospital, New Delhi, India (S No. IEC/VMMC/SJH/ Thesis/ October/ 2020-11/CC-278 dt. 10.12.2020). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: NB, the corresponding author, designed and revised the work, interpreted the data and submitted the case. NB has approved the submitted version for publication. AG has drafted the work and approved the submitted version for publication. RM has revised the manuscript and approved the submitted version for publication. No disclosure. SS provided the subjects for the study. All authors read and approved the final manuscript.

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