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The reliability of the computed tomography perfusion parameters as a predictor of colorectal cancer grade: influence of tumor region of interest position

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Abstract

Background: The aim of this study is to prospectively determine whether the computed tomography perfusion (CTP) can predict the tumor grade in colorectal cancer (CRC), and investigation of the best position of the tumor region of interest (ROI) could improve the tumor grade differentiation.

Results: The mean blood flow (mBF) at the tumor edge was significantly different among different tumor grades with the highest value noted in moderately differentiated and the lowest value in poorly differentiated CRC (111.67 ± 38.91 vs. 52.25 ± 21.97 ml/min/100 g, respectively, $P = 0.03$). At the tumor center, the BF and blood volume (BV) showed highest value in moderately differentiated and the lowest value in poorly differentiated CRC ($P < 0.001$, 0.02 respectively). The ROC curve revealed that the BF at the tumor edge showed its best results as regard its sensitivity 73.9% and specificity 82.1% in the characterization of moderately differentiated CRC from the other subtypes at > 92.2 ml/100 g/min cut off point and their AUC and P value were (0.82 and < 0.001 respectively), while the AUC of the BF at the tumor center was 0.81 and its P value was 0.03. In the characterization of poorly differentiated CRC from the other subtypes, BF cut off value at < 67.32 ml/100 g/min at the tumor edge showed the best performance of its sensitivity 88% and specificity 88% with 0.92 AUC and P value was < 0.001 , while the AUC of the BF at the tumor center was 0.89. BF was higher at the edge than at the center of the tumor (88.53 ± 22.45 vs. 78.79 ± 28.98 ml/min/100 g; $P < 0.001$ respectively).

Conclusions: PCT could help in prediction of the poorly and the moderately differentiated CRC and the mBF was the most reliable parameter in prediction of the grade. The variation in ROI position has no substantial difference in the prediction of the tumor grade; however, this variation has a significant impact on the measurements of the PCT parameters especially the BF.

Keywords: Colorectal cancer grades, Multidetector computed tomography, Perfusion

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Background

Colorectal cancer (CRC) is the third most common cause of cancer deaths worldwide [1]. It was found that grading of CRC has a strong prognostic impact [2], and also has a great impact on the treatment strategy, especially in selecting an adjuvant treatment for high risk stage II CRC patients with poorly differentiated tumor [3]. That is because the poorly differentiated CRC has a high risk for recurrence and unfavorable prognosis [4]. Also, it was found that its 5-year survival rate is significantly lower (29%) compared to that of the well and moderately differentiated CRC (59%) [5].

Preoperative specimens from endoscopic colorectal biopsies are often used but are mostly failed to grade tumors because of the lack of sufficient tissue [6]. Perfusion computed tomography (PCT) can quantify the tumor grade noninvasively by measuring the perfusion vascular parameters, including tissue blood flow (BF), blood volume (BV), and permeability surface area product (PS) using the mathematical model [7]. It was reported that the mean blood flow (mBF) is significantly higher in moderately differentiated compared to the well and poorly differentiated CRC [8]. Another study reported that the mBF value was highest in the well-differentiated and lowest in poorly differentiated CRC [9]. Indeed, debate continues regarding the correlation between CRC perfusion parameters and tumor grade, demonstrating the need for further studies in this area. Another point of debate needing more research is position of the tumor region of interest (ROI), that influence the ultimate values and it is unclear which portion of the tumor should be analyzed in computed tomography (CT) perfusion to reflect the tumor grades.

Thus, the purpose of the current study was to prospectively determine whether the CT perfusion parameters can predict the tumor grade in CRC, and investigate the best position of the tumor ROI used to improve tumor grade differentiation. We try to promote these vascular parameters obtained through imaging as a promising alternative for endoscopic colorectal biopsy in patients who are unfit for endoscopy at the time of diagnosis.

Methods

Patient's selection

This prospective study was approved by our institutional review board (IRB no. 17100795). Written informed consent was obtained from each patient after receiving information about the details of the study. Between February 2018 till December 2018, 51 patients with CRC that was proved preoperatively by endoscopy were eligible for this study (26 (51%) males, 25 (49%) females; mean age, 53.87 ± 16.13 years; range, 19–86 years). The examined tumors were located in rectum ($n = 21$), sigmoid colon ($n = 14$), hepatic flexure ($n = 5$), descending colon ($n = 4$), transverse colon ($n = 2$), ascending colon

($n = 4$), and splenic flexure ($n = 1$), that is based on CT findings and confirmed by endoscopy. Patients were excluded if they had (1) severe renal disease ($n = 2$), (2) pre-operative radiation therapy or chemotherapy ($n = 4$), (3) no surgical intervention after CT ($n = 0$), (4) contraindication to contrast media ($n = 2$), (5) no pathological reports ($n = 3$), (6) pathologically benign colorectal mass ($n = 10$), and (7) tumor depth less than 2 cm based on CT ($n = 5$).

CT technique

Pre-operative PCT scans were performed on all patients by using a 16 detector CT scanner (Bright Speed, GE Healthcare Technologies). After 4 h of fasting, 1000 ml of water was ingested 30 min prior to scanning to opacify the small bowel according to normal practice in our institution. Twenty milligrams of spasmolytic agent hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Ingelheim am Rhein, Germany) was administered intravenously to all patients immediately prior to data acquisition to minimize bowel peristalsis during the CT. Opacification of large intestine with saline was done for all the patients prior to the CT examination, using balloon enema nozzle connected with a tube to an enema bag containing 1.5 l of saline.

An abdominopelvic CT was performed initially to localize the colorectal tumor without IV contrast for cine imaging in perfusion examination using the following parameters (120 kV; 140 mA; 5 mm slice thickness; 1.5 s speed; 36 cm FOV). Identification of the tumor margin was done by two radiologists with consensus (ME and LMRK with experience 15 and 10 years respectively in abdominal CT imaging). Then plan of the perfusion study after coordination of the scan was performed.

For the perfusion study, a pump injector was used to inject 100 ml of iopromide 370 mg of iodine per milliliter intravenously (Ultravist 370; Bayer) at a rate of 5 ml/s, using the following parameters: 120 kV; 100 mA; 5 mm slice thickness; 4i/rot speed rotation; FOV 36 cm. Four contiguous sections were obtained, each collimated to 5 mm (tumor coverage was 2 cm). Dynamic PCT scans began 7 s after the start of IV injection and continued for 65 s. All patients underwent surgery and histopathological study after perfusion PCT was performed.

Image analysis

Image analysis was performed using commercial software based on deconvolution analysis (Body protocol Perfusion; GE Healthcare Technologies). The radiologists reviewed the images and selected one image that has the best-visualized and the mostly enhanced tumor with consensus.

An arterial input was selected by using the mouse to place a circular ROI $1 = 20 \text{ mm}^2$ in the area of the best-visualized artery (aorta, iliac, or femoral artery) (Figs. 1a

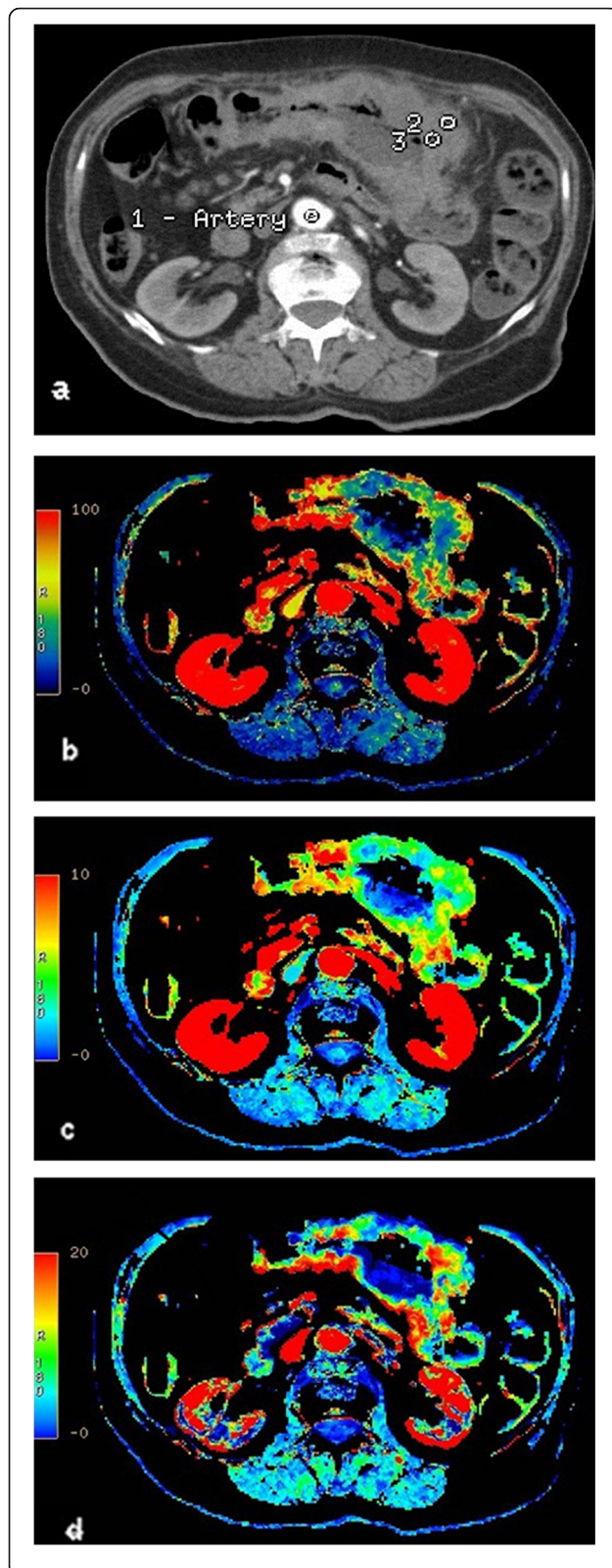


Fig. 1 A 42-year-old man with poorly differentiated cancer of the transverse colon. **a** Morphologic CT image, demonstrated the position of each ROI, ROI 1 = 20 mm² in the artery, ROI 2 = 30 mm² at the tumor edge, ROI 3 = 30 mm² at the tumor center. Corresponding parametric color maps (**b–d**); blood flow (**b**), blood volume (**c**), and permeability surface area (**d**)s

and 2a). By using the software, the arterial time enhancement curve was done automatically then a parametric map was produced. The mean values of BF, BV, and PS were recorded, also their three perfusion maps (Figs. 1b–d and 2b–d) were generated for two ROIs, that is similar in size and different in position; (a) ovoid or circular ROI 2 = 30 mm² were manually selected at the most enhanced area at tumor edge (Figs. 1a and 2a), (b) another circular or ovoid ROI 3 = 30 mm² were manually selected that placed at the most enhance area at the tumor center (Figs. 1a and 2a). Care was taken to exclude peri-rectal or peri-colonic fat and intraluminal gas when present, by viewing a cine loop of the perfusion CT images. A time attenuation curve for the selected tumor tissue and the mean values for BF, BV, and PS for each ROI were then derived automatically.

Tumor grades

The surgical specimens were fixed with 10% formaldehyde and embedded in paraffin. The differentiation of the grades was assessed by an experienced gastrointestinal pathologists and was divided into three subgroups: well, moderately, and poorly differentiated CRC.

Statistical analysis

Data was collected and analyzed those using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in the form of mean \pm SD or median (range) while nominal data were expressed in the form of frequency (percentage). A Student *t* test was used to compare different perfusion parameters with the two positions of the ROIs while the ANOVA was used to compare different perfusion parameters based on grades of CRC. Level of confidence was kept at 95%; *P* value < 0.05 was considered significant. Sensitivity, specificity, and accuracy for each significant perfusion parameter in the prediction of tumor grade were calculated using cut off values chosen on the basis of receiver operating characteristic (ROC) curves.

Results

Fifty-one patients underwent surgery after PCT scans; there were 11 (21.6%), 17 (33.3%), and 23 (45.1%) well-differentiated, poorly, and moderately differentiated CRCs respectively. The difference in the perfusion parameters among different tumor grades at the edge of the tumor was summarized in Table 1, and demonstrated that the mBF was

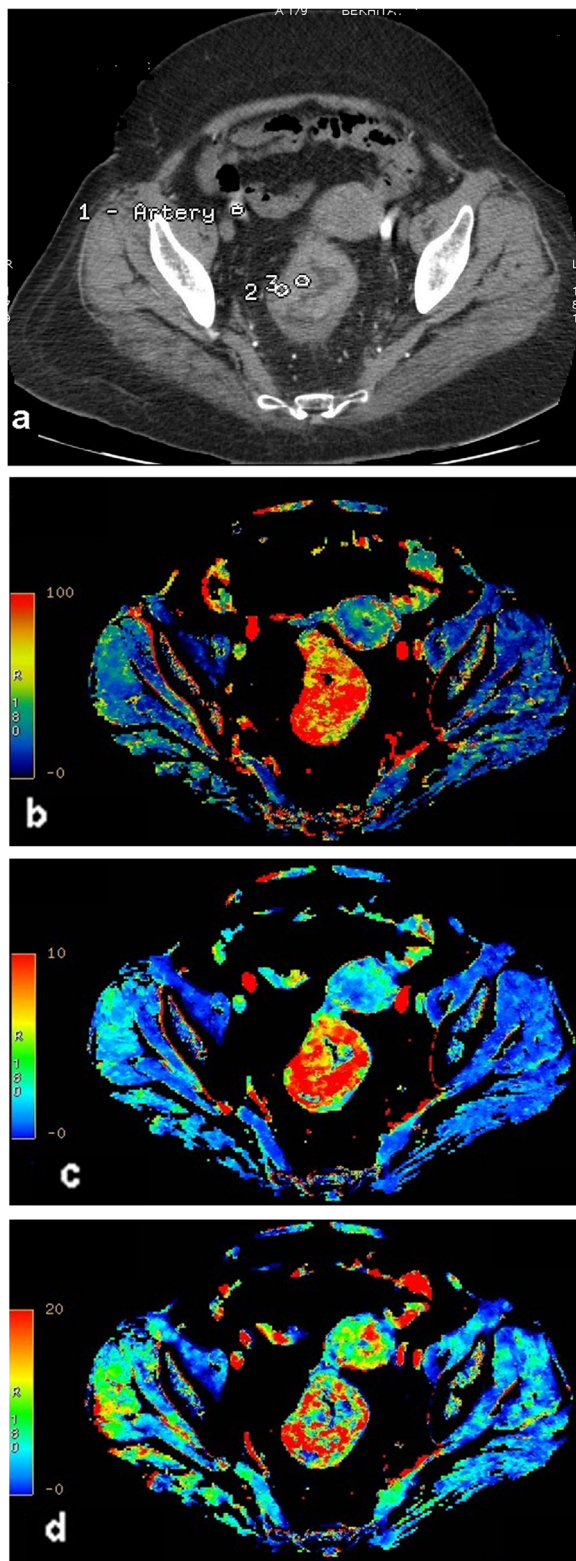


Fig. 2 A 53-year-old woman with moderately differentiated cancer of the sigmoid colon. **a** CT image shows the location of the ROIs; ROI 1 = 20 mm² in the artery, ROI 2 = 30 mm² at the edge of the tumor, ROI 3 = 30 mm² at the center of the tumor. Corresponding parametric color maps (**b-d**); **b** blood flow, **c** blood volume, and permeability surface area **d**

significantly different among different tumor grades with the highest value of the BF noted in a moderately differentiated CRC and the lowest value noted in the poorly differentiated CRC. The highest BF and BV was noted in moderately differentiated CRC at the tumor center with significant difference ($P < 0.001$, 0.02 respectively), followed by well-differentiated CRC and the lowest value was noted in the poorly differentiated CRC as summarized in (Table 2).

Because there was a statistically significant difference among different grades in BF at the tumor edge and also in BF and BV at the tumor center, so their diagnostic accuracy was assessed using ROC curves. The ROC curve revealed that the BF value at the tumor edge showed its best results as regard its sensitivity (73.9%) and specificity (82.1%) in the characterization of moderately differentiated CRC from the other subtypes at >92.2 ml/100 g/min cut off point and their area under the curve (AUC) and P value were (0.82 and <0.001 respectively), while the AUC of the BF at the tumor center was 0.81 and its P value was 0.03 (Fig. 3). The confidence interval of the BF at the edge and the center of the tumor were (0.701–0.938, 0.684–0.934 respectively).

In the characterization of poorly differentiated CRC from the other subtypes, BF cut off value at <67.32 ml/100 g/min at the tumor edge showed the best performance of its sensitivity (88%) and specificity (88%) with 0.92 AUC and P value was <0.001, while the AUC of the BF at the tumor center was 0.89 (Fig. 4). The confidence interval of the BF at the edge and the center of the tumor were (0.000–0.171, 0.003–0.208 respectively).

The AUC and the specificity of the BF at the edge and the center of the tumor in diagnosis of well-differentiated CRC were low (0.58 and 0.64 respectively) and (47.5%, 50% respectively), but its sensitivity at the edge and center was high (90.9%, 90% respectively).

The AUC of the BV at the edge and center of the tumor in the diagnosis of the moderately, poorly, and well-differentiated CRC were low (0.63 and 0.65–0.75 and 0.77–0.56 and 0.46 respectively).

Perfusion parameters of colorectal cancer at the tumor edge and tumor center using 30 mm² ROI are summarized in (Table 3) and demonstrated that the mBF was significantly higher at the tumor edge than at the center ($P < 0.001$).

Discussion

Quantitative PCT measurements are increasingly being used to assess the hemodynamic behavior of the tumor

Table 1 Correlation of the CT perfusion parameters to the grade of colorectal cancer at the tumor edge using 30 mm² ROI

	Well differentiated	Moderate differentiated	Poorly differentiated	P value
Blood flow (ml/100 g/min)	96.19 ± 21.20	111.67 ± 38.91	52.25 ± 21.97	0.03
Blood volume (ml/100 g)	7.44 ± 3.01	7.56 ± 3.81	5.07 ± 3.88	0.09
Permeability area (ml/100 g/min)	9.90 ± 6.47	10.80 ± 7.57	11.15 ± 6.30	0.89

Data were expressed in the form of a mean (SD). *P* value was significant if < 0.05

that could reflect its patho-physiological nature, which may affect the therapeutic decision and patient prognosis. As the treatment strategy should consider not only the stage but also the grade of the tumor, it is worthwhile to try to stratify the tumor grade with a non invasive method like the PCT.

Regarding the grade differentiation of the CRC, we found that measuring the BV at the edge and center of the tumor was an unreliable predictor of any grade of the CRC as a result of its low values of the AUC and the specificity in the diagnosis of the three grades of the CRC. There were some differences in the mBF at the edge and center of different CRC grades that could be relied upon in differentiating various subtypes of CRC. The mBF was significantly higher in moderately differentiated than in a well-differentiated CRC and the lowest value was noted in poorly differentiated CRC. There was no statistical significant difference in BV or PS in different tumor grades at the tumor edge. However, at the tumor center, the BV in addition to the BF were significantly higher in moderately than in well differentiated CRC and the lowest values were also noted at the poorly differentiated CRC. Kim et al. [8] also reported that the mBF was significantly increased in moderately differentiated compared to well-differentiated CRC and decreased in poorly differentiated CRC compared to moderately and well-differentiated CRC. They described the lowest value of the mBF of the poorly differentiated CRC by two hypotheses that supported their results. The first one is that the interstitial pressure in poorly differentiated CRC increase and compresses the small capillaries more than in well and moderately differentiated CRC. The second is that the growth rate of the poorly differentiated CRC is too rapid to develop angiogenesis of mature vessels. However, there are some conflicting results between Sun et al. [9] and our results. They reported that the mBF was significantly higher in well-differentiated CRC than that in moderately and poorly differentiated CRC, explaining that by the hypothesis of the better the tumor differentiation, the greater the BF value. There are two reasons that might have

led to the difference between Sun et al.'s [9] results and our results. First, Sun et al. [9] used the single ROI that was drawn with freehand method around the peripheral visible boundary of the tumor, but we measured the perfusion parameters at one level of the tumor with definite size of the two ROI. Second, the difference in the software of CT perfusion applications and number of CT detectors as they used CT with 256 detectors and the software depends on the slope method, that leads to generate a great difference in the quantitative perfusion results [10].

From our study and the previously described studies [8, 9], it is obvious that the poorly differentiated CRC could be identified by its hypoperfusion nature, at the edge and the center of the tumor. Our results showed that the sensitivity, specificity, and AUC of the mBF at the edge and the center of the tumor were 88%, 94–88%, 85%, and 0.92, 0.89 at < 67.32 and < 68.45 ml/100 g/min cutoff point respectively. This is the golden result, as we could detect the poorly differentiated CRC that might need adjuvant chemotherapy, and has a poor prognosis. This is so valuable in generally ill and unfit patient, especially with frequent failure of preoperative specimens from endoscopic colorectal biopsies to grade tumors because of the lack of sufficient tissue [6].

The moderately differentiating CRC could be identified by its hyperperfusion nature with 73.9%, 73.9% sensitivity, 82.1%, 85.7% specificity, and 0.82, 0.81 AUC of their mBF value respectively at the edge and center of the tumor, at specific cut off point > 92.2, > 85.2 ml/100 g/min. It was difficult to identify the well-differentiated CRC at > 67.5 and 68.5 ml/100 g/min cut off point at the edge and the center of the tumor respectively, because of the low specificity and AUC values.

Integral to the quantitative assessment of the PCT parameters and the CRC grade in our study, we also assessed the variation in position of the tumor ROI and its relation to the quantitative CT perfusion parameters. We demonstrated that the difference in the position of

Table 2 Correlation of the CT Perfusion parameters to the grade of colorectal cancer at the tumor center using 30 mm² ROI

	Well differentiated	Moderate differentiated	Poorly differentiated	P value
Blood flow (ml/100 g/min)	83.77 ± 17.29	98.80 ± 34.07	48.50 ± 22.29	< 0.001
Blood volume (ml/100 g)	7.20 ± 2.32	7.44 ± 3.73	4.62 ± 3.03	0.02
Permeability area (ml/100 g/min)	12.15 ± 7.26	11.10 ± 6.13	11.13 ± 4.17	0.87

Data were expressed in the form of a mean (SD). *P* value was significant if < 0.05

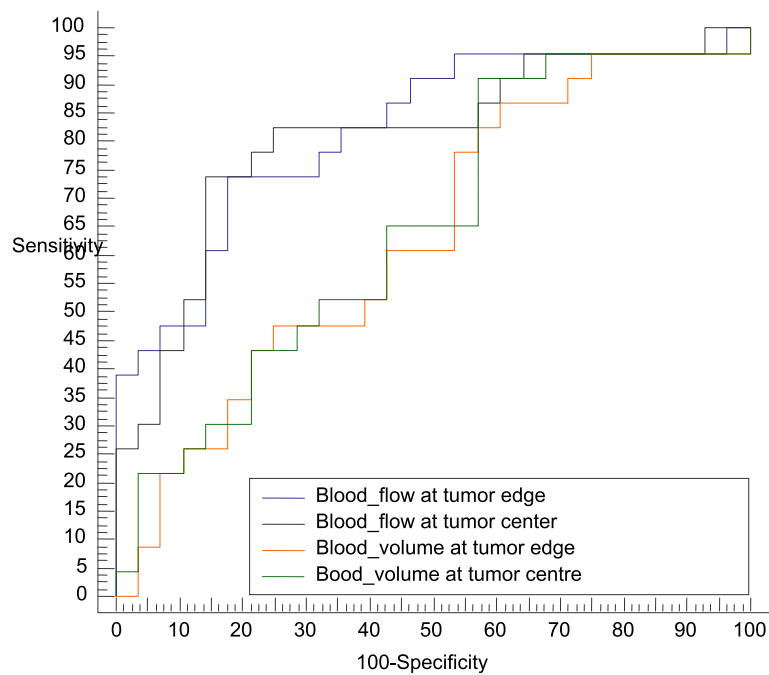


Fig. 3 Diagnostic performance of blood flow and volume in diagnosing moderately differentiated colorectal cancer

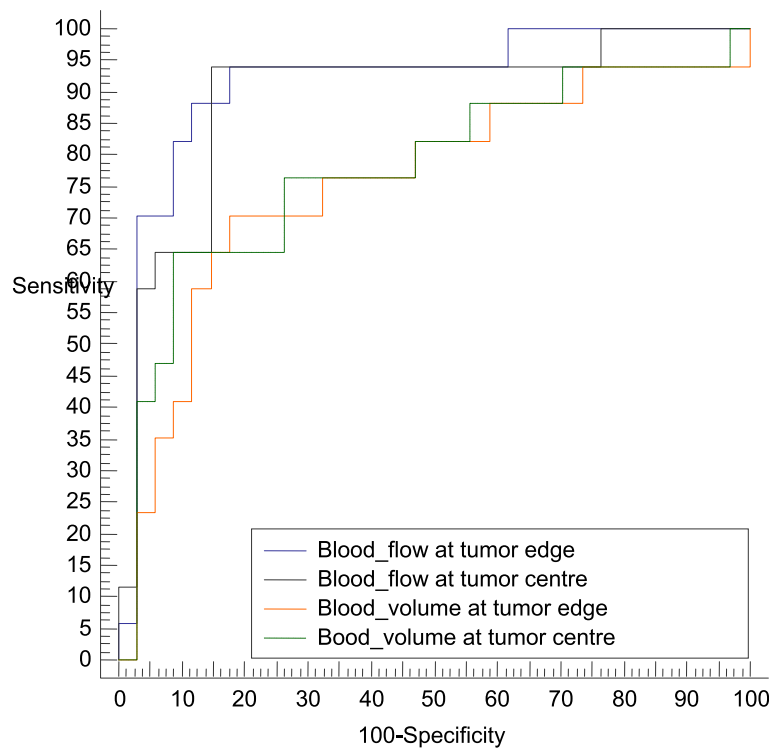


Fig. 4 Diagnostic performance of blood flow and volume in diagnosing poorly differentiated adenocarcinoma

Table 3 Perfusion parameters of colorectal cancer at the tumor edge and at the tumor center using 30 mm² ROI

	30 mm ² ROI at tumor edge	30 mm ² ROI at tumor center	P value
Blood flow (ml/100 g/min)	88.53 ± 22.45	78.79 ± 28.98	< 0.001
Blood volume (ml/100 g)	6.70 ± 3.79	6.45 ± 3.44	0.14
Permeability-surface area (ml/100 g/min)	10.72 ± 6.82	11.34 ± 5.73	0.17

Data were expressed in the form of a mean (SD). P value was significant if < 0.05

the tumor ROI significantly affect the quantitative measurement of the tumor perfusion parameters specifically the blood flow, as the mBF value was significantly higher at the edge than at the center of the tumor. This finding is concordant with two previous studies [11, 12], who reported that the perfusion parameter values of the same ROI size were highest at the tumor edge and lowest at the tumor center. This was explained by the presence of vascular dilatation at the periphery of the tumor compared with that in the center that appeared compressed and elongated [12]. The difference in tumor perfusion between the rim and the center has been noted also in another study that has been done on the rabbits with VX2 liver tumors and reported that the hepatic blood flow and volume were significantly higher at the periphery than at the center of the tumor [13].

We studied the impact of the ROI position in predicting the tumor grade, and we found no substantial difference in the ROI position either at the edge or the center of the tumor in prediction of the tumor grade, as the confidence interval of the BF and BV at the edge and the center of the tumor were overlapped.

There were several limitations to our study. First, the study sample size was small with a few numbers of well-differentiated CRC cases. Accordingly, a study with a larger number of patients is needed. Second, the CT scans were performed using 16 rows CT scanner, so perfusion scan was performed on just 2 cm thickness of the tumor, not whole-tumor perfusion. Third, we measured the perfusion parameters at one level of the tumor with definite size of the ROI and considered this measurement as a reflection of the perfusion of the whole tumor. Lastly, radiation hazards still remain a limitation in perfusion CT.

Conclusions

The PCT could help in prediction of the CRC grade, especially the poor and the moderately differentiated CRC. The mBF is the most reliable PCT parameter that could be relied upon in this issue. The variation in ROI position has a great impact on quantitative measurements of the perfusion parameters, specifically the BF which is higher at the edge than at the center of the tumor. However, this variation has no substantial difference in the prediction of the tumor grade.

Abbreviation

PCT: Perfusion computed tomography; CT: Computed tomography; CRC: Colorectal cancer; ROI: Region of interest; BF: Blood flow; mBF: Mean blood flow; BV: Blood volume; PS: Permeability surface area; SPSS: Statistical Package for the Social Science; ROC: Receiver operating characteristic; AUC: Area under the curve

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Ethical approval and consent to participate

This prospective study was approved by the Research Ethics Committee of the Faculty of Medicine at Assiut University in Egypt in (IRB no. 17100795). Written informed consent was obtained from each patient after receiving information about the details of the study.

Authors' contributions

LMRK: Dr. Lamiaa was responsible for study design, revision and interpretation of the perfusion images for all the patients who enrolled in this study, analysis and interpretation of the data, statistical analysis, editing, drafting, and submission of the manuscript. Guarantor of integrity of the entire study. PEM: Dr. Peter was responsible for data acquisition, statistical analysis, and performance of all the perfusion study and clinical studies. ME: Dr. Mostafa was responsible for study concept, revision, and interpretation of the perfusion images for all the patients who enrolled in this study. AAE: Dr. Afaf was responsible for final approval and revision of the manuscript before its submission. MMS: Dr. Mona was responsible for data acquisition and analysis, accuracy of the references, examination, and referral of all the patients to the radiodiagnosis department. MTH: Dr. Marwa was responsible for quality control of the data, revision all the pathological specimen after surgery, and writing the pathological part of the manuscript. HAE: Dr. Hanan was responsible for data acquisition. All authors have approved and read the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors whose names are listed on the title page and shared in the Manuscript entitled : "The Reliability of the Computed Tomography Perfusion Parameters as a Predictor of Colorectal Cancer Grade: Influence of tumor Region of Interest position," certified that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers, membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

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