

# Quantitative Tumor Perfusion Assessment with Multidetector CT: Are Measurements from Two Commercial Software Packages Interchangeable?<sup>1</sup>

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## Purpose:

To prospectively determine the level of agreement between tumor blood volume and permeability measurements obtained with two commercially available perfusion computed tomographic (CT) software packages.

## Materials and Methods:

This study was performed with institutional review board approval; informed consent was obtained from all participants. A total of 44 patients (24 men, 20 women; mean age, 68 years; range, 28–87 years) with proved colorectal cancer were examined prospectively with multi-detector row CT. A 65-second tumor perfusion study was performed after intravenous bolus injection of contrast material. Tumor blood volume and permeability were determined with two methods: adiabatic approximation of distributed parameter analysis and Patlak analysis. Agreement between the results was determined by using Bland-Altman statistics. Within-patient variation was determined by using analysis of variance.

## Results:

The mean values for permeability and blood volume, respectively, were  $13.9 \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1} \pm 3.7$  (standard deviation) and  $6.1 \text{ mL}/100 \text{ mL} \pm 1.5$ , as calculated with distributed parameter analysis, and  $17.4 \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1} \pm 7.3$  and  $10.1 \text{ mL}/100 \text{ mL} \pm 4.2$ , as calculated with Patlak analysis. The mean difference and 95% limits of agreement, respectively, were  $-3.6 \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1}$  and  $-18.4$  to  $11.2 \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1}$  for permeability and  $-3.9 \text{ mL}/100 \text{ mL}$  and  $-10.9$  to  $3.0 \text{ mL}/100 \text{ mL}$  for blood volume. The coefficient of variation was 37.4% for permeability and 46.5% for blood volume.

## Conclusion:

There was disagreement between the methods used to estimate tumor vascularity, which indicated the measurement techniques were not directly interchangeable.

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Perfusion imaging has been increasingly promoted for use in the assessment of tumor vascularity. The impetus for this has been the development of drugs that target angiogenesis, as the effects of these drugs may be better assessed by observing functional changes in vascular perfusion than by observing changes in tumor volume (1–4). The availability of computed tomography (CT) coupled with commercial perfusion software has made this method of assessment widely accessible to clinicians. Furthermore, reproducibility of the CT technique (4,5–11) gives CT an advantage over other imaging modalities that enable similar vascular assessments, such as dynamic contrast material-enhanced magnetic resonance (MR) imaging (12,13).

To date, however, measurement standardization has not been implemented, and commercial software used to obtain quantitative measurements does so with different approaches (4,14,15). For example, distributed parameter analysis (16) and Patlak analysis (17) involve the use of different mathematic algorithms to arrive at indexes of tissue permeability and blood volume. We believe that until now, with the exception of cranial circulation, there has been no assessment of the interchangeability of perfusion measurements obtained with different methods of analysis. Good agreement between results obtained with different assessment platforms is essential (*a*) if perfusion imaging is to be used in day-to-day clinical practice, (*b*) for comparison across different research studies, and (*c*) when different CT platforms are used within the context of the same multicenter trial. Thus, the aim of our study

was to prospectively determine the level of agreement between tumor blood volume and permeability measurements obtained with two commercially available perfusion CT software packages.

### Materials and Methods

GE Healthcare Technologies (Waukesha, Wis) and Siemens Medical Solutions (Forchheim, Germany) provided the software used for analysis. All authors retained control of all data collected and information submitted for publication.

### Participants

Institutional review board approval was obtained for this prospective study, and written informed consent was obtained from each participant. Each participant received an information sheet that detailed the study, including information on radiation exposure, and the study was explained to each participant. A total of 44 consecutive adult patients (24 men, 20 women; mean age, 68 years; range, 28–87 years) who were scheduled to undergo pretreatment staging of biopsy-proved colorectal cancer and had agreed to participate in the study were recruited. Nine patients had a T2 tumor, 25 had a T3 tumor, and 10 had a T4 tumor (defined by using CT criteria, as not all patients underwent subsequent surgical resection). Tumors were located in the cecum ( $n = 8$ ), ascending colon ( $n = 3$ ), transverse colon ( $n = 1$ ), descending colon ( $n = 2$ ), sigmoid colon ( $n = 13$ ), and rectum ( $n = 17$ ). These tumors had a mean longitudinal extent of 5.8 cm (range, 1.0–13.3 cm).

### CT Technique

After the patient had fasted for 4 hours, 1000 mL of water-soluble contrast material with a 2%–4% concentration of meglumine and sodium diatrizoate (Gastrografin; Bracco, Milan, Italy) was ingested 30 minutes prior to CT scanning to opacify the small bowel, as per usual practice in our institution. Unless contraindicated, 20 mg of the spasmolytic hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Ingelheim am Rhein, Ger-

many) was administered intravenously with an 18-gauge cannula situated in the antecubital fossa. All patients were scanned with a four-detector row CT scanner (LightSpeed Plus; GE Healthcare Technologies). An abdominal-pelvic study was performed initially without administration of intravenous contrast material to identify the CT spatial coordinates of the known colorectal tumor with the following parameters: 10-mm section thickness, 5-mm section interval, 30 mm/sec table speed, 120 kV, 180 mA, 0.6-second rotation speed, 50-cm scan field of view, and  $512 \times 512$ -mm matrix. The supervising radiologist (V.G., 8 years of experience with abdominal and pelvic CT and 5 years of experience with perfusion CT) identified the tumor margins; the spatial coordinates were noted and used to plan the subsequent dynamic study.

In the dynamic study, a pump injector (Percupump Touchscreen; E-Z-Em, Westbury, NY) was used to inject 100 mL of iopamidol 340 (Niopam 340; Bracco) at a rate of 5 mL per second. Four contiguous sections, each with a 5-mm collimation, were obtained at 1-second intervals through the midpoint of the tumor by using a cine-mode acquisition technique (120 kV, 60 mA, 50-cm scan field of view,  $512 \times 512$ -mm matrix, and 10-mSv effective dose). Image acquisition commenced 5 seconds after the start of intravenous contrast material injection to allow acquisition of baseline unenhanced images and continued for 65 seconds.

The dynamic CT study was followed by a diagnostic portal venous phase abdominal-pelvic study that started 75

### Advance in Knowledge

- There is disagreement between measurements of the same perfusion parameter that have been obtained with two different software platforms (distributed parameter analysis and Patlak analysis); this is likely due to empirical differences between analysis methods.

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### Author contributions:

Guarantor of integrity of entire study, S.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, V.G.; clinical studies, V.G.; statistical analysis, V.G.; and manuscript editing, all authors

See Materials and Methods for pertinent disclosures.

seconds after the commencement of intravenous contrast material injection and used the following parameters: 5-mm section thickness, 2.5-mm section interval, 22.5 mm/sec table speed, 120 kV, 280 mA, 0.6-second rotation speed, 50-cm scan field of view, and  $512 \times 512$ -mm matrix. This diagnostic study was used to determine both the local and the distant stage of the tumor. A radiologic report was issued after interpretation of these images, as per usual clinical practice.

### Image Analysis

All CT data were transferred to two commercially available stand-alone workstations (Advantage Windows 4.2, GE Healthcare Technologies and Leonardo, Siemens Medical Solutions). One radiologist (V.G.) viewed and analyzed all images.

### Distributed Parameter Analysis

Analysis of all images was performed initially with commercial perfusion software that was based on an adiabatic approximation of distributed parameter analysis (body protocol setting, Perfusion 3.0; GE Healthcare Technologies). A processing threshold of  $-50$  to  $150$  HU was chosen to optimize soft-tissue visualization. Arterial input was defined by using a mouse to place a circular region of interest (mean size,  $10 \text{ mm}^2$ ) within the best-visualized artery (the aorta or the iliac or femoral arteries) on the selected image. The arterial time-enhancement curve was derived automatically with the software, and resulting parametric maps were produced, with each pixel representing a parameter value. Mean permeability and blood volume measurements were obtained by using a mouse and electronic cursor to trace a freehand region of interest around tumor margins on the permeability and blood volume maps that best showed these tumors. Care was taken (a) to exclude surrounding pericolic or perirectal fat and (b) when intraluminal gas was present. Mean values for permeability (measured in milliliters per 100 g of tissue per minute) and blood volume (measured in milliliters per 100 g of tissue) were then recorded for

each tumor. To allow comparison of measurements, these values were subsequently converted to values per unit volume by using a tissue density measurement of  $1.05 \text{ g/mL}$ , which was the default value used by the software manufacturer; the resulting units of measure were milliliters per 100 mL per minute for permeability and milliliters per 100 mL for blood volume.

### Patlak Analysis

All CT data were subsequently reanalyzed by using commercial software based on Patlak analysis (syngo Body Perfusion CT, syngo 2006G; Siemens Medical Solutions). A rectangular box that indicated the tissue to be analyzed was placed with an electronic cursor and mouse on the same image that was analyzed previously; thus, a clear margin was left around the tumor. The same processing threshold ( $-50$  to  $150$  HU) was selected, as described previously. Arterial input was defined by selecting a circular region of interest with the mouse. We ensured that this region of interest was similar in size to one defined previously with the other software package. The region of interest was then placed within the same artery analyzed previously to generate the arterial time-enhancement curve. Mean permeability and blood volume measurements were obtained from the parametric maps generated automatically by the software package by similarly drawing a freehand region of interest around the tumor margins and by using the same image level used for the initial analysis. As before, mean permeability (measured in milliliters per 100 mL per minute) and blood volume (measured in milliliters per 100 mL) values were recorded for each patient.

### Statistical Analysis

Mean values and standard deviations were determined for permeability and blood volume, as measured with both methods. Agreement between corresponding measurements obtained with the different software platforms was assessed with the Bland-Altman test (18): The mean difference, standard deviation of the difference, and 95% limits of agreement were calculated for permeability and blood volume. The within-patient coefficient of variation was also calculated by using analysis of variance (19). All statistical analyses were performed with a software package (Stata 7.0; Stata, College Station, Tex).

### Results

The mean permeability and blood volume values, respectively, were  $13.9 \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1} \pm 3.7$  (standard deviation) and  $6.1 \text{ mL}/100 \text{ mL} \pm 1.5$ , as calculated with distributed parameter analysis, and  $17.4 \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1} \pm 7.3$  and  $10.1 \text{ mL}/100 \text{ mL} \pm 4.2$ , as calculated with Patlak analysis (Table). The mean difference and 95% limits of agreement indicated only moderate agreement between the sets of measurements (Table). The coefficient of variation was 37.4% for permeability and 46.5% for blood volume. Agreement between measurements was worse for blood volume than for permeability. Inspection of the plotted data showed a clear trend for measurements obtained with Patlak analysis to be higher than those obtained with distributed parameter analysis (Figs 1, 2). Overall, perfusion measurements obtained with Patlak analysis were higher than those obtained with distributed parameter analysis. For instance, permeability measure-

#### Perfusion Measurements

Perfusion Measurement	Distributed Parameter Analysis*	Patlak Analysis*	Mean Difference	95% Limits of Agreement
Permeability ( $\text{mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1}$ )	$13.9 \pm 3.7$	$17.4 \pm 7.3$	$-3.6$	$-18.4$ to $11.2$
Blood volume ( $\text{mL}/100 \text{ mL}$ )	$6.1 \pm 1.5$	$10.1 \pm 4.2$	$-3.9$	$-10.9$ to $3.0$

Note.—Mean measurements were higher for Patlak analysis. There was only moderate agreement between methods.

\* Data are means  $\pm$  standard deviations.

ments obtained with Patlak analysis were, on average, 1.34 times higher  $\pm$  0.74 than those obtained with distributed parameter analysis, while blood volume measurements obtained with Patlak analysis were, on average, 1.65 times higher  $\pm$  0.55 than those obtained with distributed parameter analysis.

## Discussion

To date, there has been a paucity of data regarding the interchangeability of perfusion CT measurements obtained with different analysis methods. Miles and Griffiths suggested that the two analysis methods may be broadly equiv-

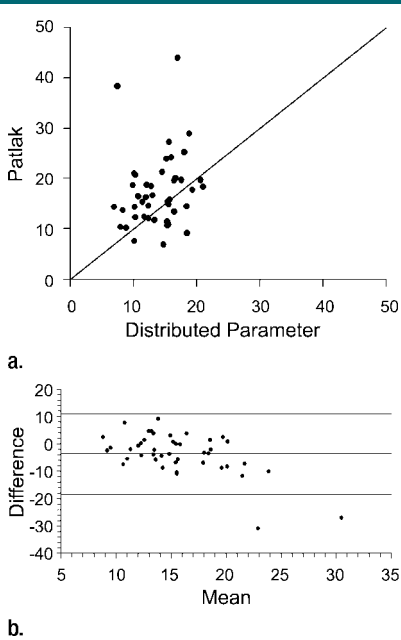
alent (4): In their article, they cited comparative work by Griffiths in which blood flow was analyzed with both deconvolution and compartmental analysis in the lung ( $n = 16$ ), spleen ( $n = 20$ ), and brain ( $n = 6$ ); correlation coefficients of 0.86, 0.90, and 0.79, respectively, were reported (4). However, the limitations associated with the use of correlation coefficients to assess agreement have been highlighted repeatedly (20). Correlation analysis involves examination of the linear association between two variables, not the level of agreement between them. Correlation may be high in the face of considerable disagreement. For example, if one test consistently produced a result that was exactly two times greater than that pro-

duced with another test, there would be perfect linear correlation despite disagreement of 100% (21). Although intraclass correlation overcomes some of these deficiencies, it is ultimately a poor test of agreement because systematic bias between sets of corresponding measurements is ignored (22).

To our knowledge, at the time of this writing there were no studies in which the level of agreement between perfusion measurements obtained with different algorithms for tissues outside the extracranial circulation was investigated. We chose to assess the interchangeability of blood volume and permeability measurements for the following reasons: These measurements provide a good representation of vascular density and vessel leakiness, which are important features of tumor angiogenesis. The technical parameters were most suitable for comparing these measurements. Blood volume reflects the volume of blood flowing within all vessels within the tissue of interest (ie, the volume of functioning vasculature), while permeability represents one-way diffusional transfer across the capillary endothelium from the intravascular compartment to the extracellular extravascular compartment. Blood flow and transit time were not compared for the following reasons: The acquisition parameters were suboptimal for the analysis method used to evaluate blood flow with one software platform, which prevented a fair comparison. Transit time was not assessed with one of the software platforms; therefore, transit times could not be compared.

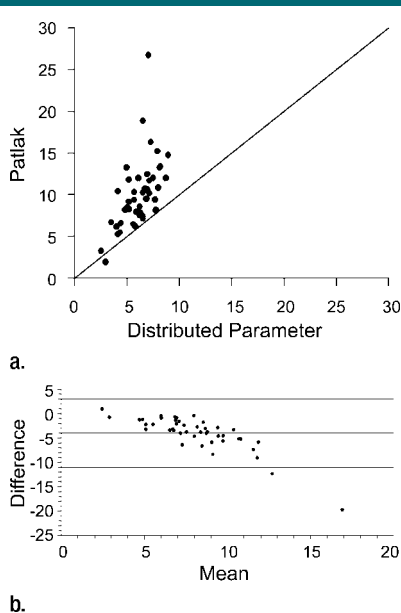
Agreement between the two commercially available and commonly used methods that were used in our study was less than optimal. This suboptimal agreement may be the result of various factors. First, different modeling techniques were used. The adiabatic approximation of the distributed parameter model used by one platform (body protocol setting, Perfusion 3.0) takes into account the varying intravascular concentration gradient from the arterial inlet to the venous outlet within the capillaries. The use of an analytic solution in the time domain, similar to the de-

**Figure 1**



**Figure 1:** (a) Scatterplot shows the distribution of permeability measurements obtained with adiabatic approximation of distributed parameter and Patlak analyses. The line of perfect agreement is indicated. The closer the data points lie to the line of perfect agreement, the better the agreement. In this case, agreement is moderate, with a slight tendency for measurements obtained with Patlak analysis to be larger than those obtained with distributed parameter analysis. (b) Corresponding agreement plot of the difference between measurements against mean values shows the distribution of values. The middle line indicates the mean difference. The outer lines indicate 95% limits of agreement.

**Figure 2**



**Figure 2:** (a) Scatterplot shows the distribution of blood volume measurements obtained with adiabatic approximation of distributed parameter and Patlak analyses. The line of perfect agreement is indicated. There is a clear bias for data points to lie above the line of agreement, thus revealing a trend for measurements obtained with Patlak analysis to be larger than those obtained with distributed parameter analysis. (b) Corresponding agreement plot of the difference between measurements against mean values shows the distribution of values around the mean difference (middle line). The outer lines indicate the 95% limits of agreement.

convolution method, allows blood flow, blood volume, mean transit time, and permeability to be determined simultaneously (16). While this approach has been validated for measurement of blood flow both in animals and in humans (5–7) and has been found to show acceptable reproducibility within and outside the cranial circulation (5–8,23), permeability measurements obtained with this technique have yet to be validated. Since permeability measurements are specific to the type of tracer molecule used, CT tracers will yield results that differ from those yielded by MR or positron emission tomographic tracers; thus, comparison with dynamic contrast-enhanced MR imaging is not helpful.

Patlak analysis is a two-compartment model that describes the one-way transfer of freely diffusible contrast material from the intravascular compartment to the extravascular extracellular compartment and permits blood volume and permeability to be determined. This method is a more straightforward approach to quantification than is the distributed parameter model. It also has an advantage over the distributed parameter model in that a high-temporal-resolution acquisition protocol is not necessary. Thus, greater tissue volume coverage can be assessed, permitting whole tumor or organ analysis to be performed with current technology (24,25). However, certain assumptions are made with Patlak analysis: It is assumed that the compartments are well mixed and that the amount of contrast material returning to the intravascular compartment from the extravascular extracellular compartment is negligible (ie, there is no backflux) (17). Whether this assumption is valid in tumor imaging has been questioned (15). Nevertheless, this approach has been used to assess tumor permeability outside the cranial circulation, including permeability of prostate, cervix, breast, and pulmonary tumors (26), as well as lymphoma (27). Therefore, although both techniques enable the determination of blood volume and permeability, there are conceptual and mathematic differences between them that may contribute to disagreement.

Second, there are differences in the susceptibility of these techniques to noise and motion, and, as a result, technical factors may contribute to disagreement. In our study, the same perfusion examinations were evaluated with each method, and factors such as contrast material administration rates and acquisition parameters remained constant. This might be expected to lessen measurement variability; however, previously recommended optimal acquisition parameters for each of the techniques have differed, thus reflecting the different modeling approaches used (14). For example, a higher-temporal-frequency acquisition is typically necessary for commercial software based on distributed parameter analysis, with a frequency of one acquisition per second for at least the first 45–65 seconds; however, lower frequencies (up to one acquisition every 5 seconds) can be tolerated after this time. On the contrary, a lower-temporal-frequency acquisition is suggested for commercial software based on Patlak analysis, with a frequency of up to one acquisition every 20 seconds.

Acquisition times of 2–10 minutes have been suggested for use in the assessment of permeability (14). However, tumor vessels are typically permeable, and it is possible that substantial reflux of contrast material into the intravascular compartment may occur within 2 minutes of administration. Indeed, in breast tumors, dynamic contrast-enhanced MR imaging has shown that up to 40% of the contrast agent bolus leaks into the extravascular space within the first pass (28); thus, whether such a long acquisition time is necessary for imaging of tumors is questionable (29). A high-temporal-frequency acquisition of more than 65 seconds was used in this study and enabled evaluation with the distributed parameter model. The temporal frequency was unlikely to have prejudiced evaluation with Patlak analysis. While there is preliminary evidence that acquisition times of more than 65 seconds do not yield permeability measurements that are substantially different from the distributed parameter model measurements (29), it is possible

that the 65-second acquisition time may have been suboptimal for Patlak analysis and contributed to the moderate level of agreement for permeability.

The level of agreement between measurements was also affected by observer variability and the intrinsic variability of automated software. One reader analyzed CT images to minimize observer variability, since it is known that intraobserver agreement is superior to interobserver agreement for detection of colorectal cancer (11); nevertheless, a degree of variability is inevitable. The different software analysis programs used rely on individual definitions of arterial and tissue input, from which both the arterial and the tissue time-enhancement curves are plotted and analyzed and parametric maps are produced. Inevitably, some variability was introduced in region of interest analysis, even though care was taken to ensure that regions of interest were similar in size and position.

The disagreement between measurements obtained with the two techniques indicates that measurements may not be directly interchangeable, and cross-study comparison will be problematic if this variation is not taken into account. We found that both permeability and blood volume measurements obtained with Patlak analysis were generally higher than those obtained with distributed parameter analysis. In reality, we do not know which measurements are correct. This is a limitation of our study. Patlak analysis may result in overestimation of permeability and blood volume; conversely, distributed parameter analysis may result in underestimation. The standard deviation indicates the potential for wide variation in corresponding values obtained with each technique. It may be possible to account for this by using a conversion factor that corrects for the bias we observed. Further work, perhaps in a multicenter trial, will be needed if comparison of measurements obtained with these software platforms is ultimately necessary.

In summary, we found that tumor vascularity measurements obtained with distributed parameter analysis and those obtained with Patlak analysis are not

directly interchangeable. It is likely that functional imaging will be used increasingly to assess tumor response to treatment for a number of reasons, not the least of which is the general availability of CT and appropriate perfusion software. However, our findings suggest that cross-study comparison will be problematic if variation between techniques is not taken into account. Standardization of analysis methods and software implementation is necessary, and a cautious approach to data interpretation is advocated until standardization can be achieved.

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