Perfusion CT: An Overview Of Technique And Clinical Applications

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Introduction
Perfusion CT is an exciting CT technology which allows functional evaluation of tissue vascularity. Due to rapid
technological advancements in the multi-detector CT systems and the availability of commercial software perfusion CT has
broadened its role in the routine imaging with wide ranging applications from initial assessment of acute stroke to
comprehensive evaluation of tumors. The greatest impact of the perfusion CT has been in the assessment of stroke patients,
where the rapid scan timing and fast post processing has cemented its role as a modality of choice for evaluation of the both
structural and functional status of cerebral vasculature [1]. Perfusion CT is also finding increasing utility in oncology with a
wide array of applications in tumor diagnosis, staging, prognostic evaluation and monitoring therapeutic response[2-9].
Though primarily still used as a research tool, perfusion CT is emerging as a preferred technique for assessment of tumor
response to the anti-angiogenic drugs[10, 11]. This article reviews the basic principles, technique and discusses the various
oncological and non-oncological clinical applications of perfusion CT in various oncological and non-oncological settings.

Why CT perfusion?
Though an array of other imaging techniques allow assessment of tissue perfusion, CT is particularly ideal for this purpose
due to several reasons[1, 12]. The principal reason being its widespread availability and better experience with this modality
which permits its use in day to day clinical practice[12]. This is particularly true in acute settings, like stroke evaluation where
the CT is accessible round the clock and allows image acquisition with ease[1]. Another key advantage is the linear
relationship between the iodine concentration and the density changes in the tissue which makes processing straightforward
and simpler compared to MRI where the contrast-signal relationship and the quantification are problematic[1]. Again, the
availability of commercial software makes multi-center assessment easily achievable as quality assurance becomes easier.
Furthermore, since MDCT is already established as an modality of choice for tumor diagnosis and response assessment,
inclusion of an additional study for perfusion analysis becomes less cumbersome[12]. PET perfusion studies suffer from the
drawback of the need for a cyclotron and are more prone for partial volume effects and artifacts and poor anatomic
resolution[1].

The major limitation of CT however is the risk of exposure to ionizing radiation which limits its routine use especially for
follow up studies. In evaluation of tumor perfusion, the reduced volume of tumor coverage also hampers evaluation of the
entire tumor. Furthermore, the readers should be aware that the choice of imaging modality for functional evaluation of
tumors is dictated by the desired perfusion parameter and the treatment being given.

CTp Technique
The basic principle of perfusion CT is based on the temporal changes in tissue density following intravenous administration
of iodinated contrast media. The chronological changes in tissue density are dependent on the iodine concentration and are
a reflection of the nature of tissue vascularity. By rapid sequential acquisition of images during the passage of contrast in the
tissues, perfusion CT allows quantification of the tissue vascularity.

i. Physiology of contrast enhancement
In the time following intravenous injection of the contrast media, the contrast distributes within the tissues resulting in
increasing tissue density on CT. The tissue enhancement seen following contrast administration can be divided into two
phases based on its distribution in the intra vascular or the extra vascular compartment[13]. In the initial phase following
contrast injection, the enhancement is mainly due to the contrast within the intravascular space[13]. Later in the second phase as contrast passes from the intravascular to the extra vascular compartment across the capillary basement membrane, enhancement results from contrast distribution in both intravascular and extravascular compartments[13]. Thus in the initial phase, the enhancement is determined to a great extent by the blood flow while in the second phase the enhancement depends on the blood volume and the permeability of capillaries to the contrast medium[13].

ii. Mathematical modeling techniques
By obtaining a series of image in quick succession in the region of a particular tissue it is possible to record the temporal changes in the tissue attenuation occurring after intravenous injection of contrast. Two basic functional CT paradigms are measured from the CT data: i.e. perfusion measurements and permeability studies[13]. The quantification of perfusion recorded by CT is done using mathematical modeling techniques which use data from the tissue and the vascular system. The two most commonly used analytical methods for quantifying various perfusion parameters from the dynamic CT data are: Compartmental analysis and De-convolution analysis[14, 15]. Both the analytical methods require obtaining time attenuation data from the arterial input for estimation of tissue vascularity and to correct for inter patient variations in bolus geometry[14, 15].

Compartmental analysis
This mathematical modeling technique is based on single compartment or two compartment model[14-16]. The single compartmental model is used to estimate the tissue perfusion and as the name suggests it considers the intravascular and extra-vascular spaces as a single compartment. This model which is based on Fick’s principle calculates tissue perfusion based on conservation of mass within the system[15, 16]. It estimates the perfusion either from the maximal slope or the peak height of the same tissue concentration curve normalized to the arterial input function[15-17]. The two compartmental model is used for the evaluation of capillary permeability and blood volume[15-17]. This model assumes the intravascular and extra vascular spaces as separate compartments and measures perfusion parameters using a technique called Patlak analysis. Patlak analysis is a nuclear medicine processing technique that is used to determine the rate constant of tissue uptake of a tracer from the vascular space by using the value of tracer concentration in tissue and blood[16]. Simply put, it quantifies the passage of contrast from intravascular space into the extra vascular space[13].

Deconvolution analysis
This is based on the use of arterial and tissue time-concentration curves to calculate the impulse residue function (IRF) for the tissue. Impulse residue function is a theoretical tissue curve that is obtained from the direct arterial input assuming that the concentration of contrast material in the tissue is linearly dependent on the input arterial concentration when the blood flow is constant[14-16]. After flow correction, the height of this curve gives the tissue perfusion and the area under the curve will decide the relative blood volume[15]. For the estimation of capillary permeability a distributed parameter model is used which consists of an extended de-convolution model[16].

c) Which one is better?
Preliminary results have shown that both the techniques are broadly equivalent [18]. However they differ in terms of their theoretical assumptions, susceptibility to noise and motion[15]. Compartmental analysis is based on the assumption that the bolus of contrast media has to be retained within the organ of interest at the time of measurement which may result in underestimation of perfusion values in organs with rapid vascular transit or with large bolus injection[15]. While deconvolution assumes that the shape of IRF is a plateau with a single exponential wash-out. Though this assumption works well for most of the organs, it might not be suitable for organs such as spleen and kidney which have complex microcirculations[15]. Hence, it is preferable to use compartmental analysis for organs with complex circulatory pathways. Deconvolution methods are appropriate for measuring lower levels of perfusion (< 20ml/min/100ml) as they are able to tolerate greater image noise due to inclusion of the complete time series of images in calculation[15]. This is particularly beneficial for accurate measurement of lower perfusion values which are typically seen in tumors following treatment response[15]. But then, the inclusion of all the acquired images for calculation introduces possibilities of image mis-registration due to motion of the patient. On the other hand, compartmental analysis effectively uses three images for perfusion measurement: the base line image and the image immediately before and after the time of maximal rate of contrast tissue enhancement and hence patient motion are rarely of significance.

iii. Validity and reproducibility
CT perfusion methods have been validated against various techniques including microsphere methods and stable xenon washout methods in animal and human studies[17, 19-24]. The perfusion CT measurements have been correlated in various clinical trials with histological markers of tissue vascularity in tumors of lung and rectal cancer[9, 10, 25]. Reproducibility of perfusion measurements have been done with good correlation for CT measurements and a variability of 13-35% in animal and human studies in normal brain tissue, colorectal carcinoma, lung cancer and hepatocellular carcinoma[8, 26-30]. Sahani et al reported excellent correlation (r = 0.9, p < 0.01) of CT perfusion parameters of HCC with repeat CT perfusion studies performed within 24 hours of each other[8]. The mean variability for the perfusion parameters was 4% with blood flow showing the least variability(1%) and permeability surface showing the maximum variability(13%)[8]. Goh et al compared the reproducibility of perfusion measurements of colorectal cancer and skeletal muscle obtained with MDCT and found that the quantitative perfusion measurements are reproducible with measurements being less variable for tumor than for skeletal muscle[30]. To ensure that changes observed in perfusion parameters after treatment indeed represent drug effects it is recommended to perform baseline reproducibility studies for clinical trials relying on functional techniques[28].
Goh et al and his colleagues found that though intraobserver agreement was better than interobserver agreement in measurement of perfusion values in colorectal carcinoma, the limits of agreement varied widely[28]. Goh et al and his colleagues advocate that the same reviewer perform the follow up measurements for individual patients to account for interobserver variability particularly when evaluating tumors where the expected changes in perfusion are small[28].

iv. Acquisition protocols
The typical perfusion protocol consists of a baseline image acquisition without contrast enhancement followed by a dynamic image acquisition performed sequentially after intravenous injection of contrast media[15]. The dynamic image acquisition includes a first pass study or a delayed study or both depending on the physiological parameter which is to be measured[15]. This is particularly relevant while evaluating the therapeutic response of various anti-angiogenic agents[15]. The first pass study comprises of the images which are acquired in the initial 45-60 sec and are used for assessing perfusion (blood flow) and blood volume. For the measurement of vascular permeability, it is necessary to include a delayed phase which can range from 2 to 10 min[15, 16].

The choice of technique also depends on the mathematical modeling method used. Deconvolution method being less sensitive to noise allows the use of a lower tube current and allows scanning with higher temporal resolution[15, 16]. The typical perfusion protocol for measurement of perfusion and blood volume is image acquisition for a total duration of 40-60sec with 1 sec images every 1 second after injection of 40-50ml of contrast at a rate of 4-7 ml/sec with a tube current of 50-100mAs [9, 15, 16]. For permeability measurements a two-phase study is suggested based on the distributed parameter model[15, 16]. The first or dynamic phase is as described above followed by a second phase which involves acquisition of 1 sec images acquired every 10 seconds for 2 minutes[15, 16].

For the compartmental model presence of image noise results in miscalculation of perfusion values hence a higher mAs value with lower image frequency is preferred[15]. The typical image acquisition sequence for compartmental analysis for measurement of perfusion and blood volume is for a total duration of 40-60sec with 1 sec images every 3-5 sec after injection of 40-50ml of contrast at a rate of 7-10 ml/sec with a tube current of 100-250mAs[15, 16]. For the permeability measurements, two compartmental model is used (Patlak analysis technique) which includes acquisition of images every 10-20 secs after injection of 100 ml of contrast at a rate of 4 ml/sec with a tube current of 100-250mAs[15, 16].

v. Other considerations

1. Contrast medium bolus
One of the important considerations for adequate assessment of perfusion of a tissue is the contrast medium bolus used for the intravenous injection[14, 15]. A short sharp bolus is essential for adequate perfusion assessment with compartmental method and hence a small bolus of 40-50 ml is administered with a higher injection rate between 5 to 7 ml/sec[14, 15]. Though deconvolution can tolerate lower injection rates but higher rates (upto 7 ml/sec) are still beneficial to maximize tissue enhancement and to improve signal to noise ratio[14, 15]. Due to linear relationship of iodine concentration and tissue enhancement a higher concentration of contrast media is preferred (370mg iodine/ml)[14, 15].

2. Patient factors
Motion is of considerable significance during image acquisition as it can lead to image misregistration and errors in calculation of perfusion values. Respiratory motion can be restricted to a certain extent by proper instruction to patients regarding breathing. For perfusion studies in the abdomen, straps over the abdomen to minimize abdominal wall motion have been used[28, 31-33]. Some authors recommend use of hyoscine butylbromide (Buscopan) to patients with perfusion scanning of the bowel to minimize the bowel peristalsis during CT study [28, 31-33]. It is important to select areas without metallic stents, prosthesis, surgical implant which can cause beam hardening artifacts and result in variation in the perfusion values[17]. In hollow viscera such as colorectum and stomach distension of the hollow viscus with saline and water is crucial for optimal evaluation[9].

3. Vendor specifications
The analytical methods used and the acquisitions protocols vary from scanners to scanner and between commercial vendors (Table 1 & 2). GE uses the deconvolution approach and allows calculation of parametric maps of blood flow, blood volume, MTT and permeability measurements[8, 9, 17] (Figure 1). The Philips CT perfusion package uses the slope method to calculate the perfusion maps and its gives the peak enhancement image, time to peak enhancement and MTT maps[8, 9, 17]. Siemens uses the slope method to calculate perfusion[15, 34]. Blood volume and time to peak enhancement parametric maps are also calculated[15, 34].

Clinical Applications
I. Non- oncological Neuro- Imaging
The maximum impact of perfusion CT in the patient management has been in its role as an adjunct in the initial evaluation of patients with acute stroke[35-37]. This topic will be dealt in detail in another article in the same issue. Perfusion CT has found increasing applications in non stroke settings as well. In head trauma patients, it allows identification of abnormalities of regional blood flow which could cause significant secondary brain damage and has been found to been more sensitive
than conventional CT in the detection of cerebral contusions [1, 38, 39]. Studies have proven that it can provide quantitative assessment of the cerebral vascular auto-regulation in head trauma patients and could be used as a guide for brain edema therapy as well as to monitor treatment efficiency [38, 39]. In patients with head trauma intracranial hypertension manifests with reduced BF and BV and increased MTT suggesting cerebral ischemia [39]. This finding has important implications in triaging patients with head injury and intracranial hypertension at risk of cerebral ischemia with aggressive and early treatment compared to those with preserved brain perfusion [39].

In patients with subarachnoid hemorrhage (SAH) vasospasm is a frequent cause of significant morbidity and perfusion CT has been used to monitor cerebral perfusion after SAH [40]. Nabi et al. reported that those patients with reduced mean CBF values are more likely to have delayed infarct due to vasospasm [41]. The mean blood flow and blood volumes were significantly lower in patients with moderate to severe vasospasm compared to those without vasospasm [41].

**Body Imaging**

a. Pancreatitis and pancreatic necrosis

Pancreatic necrosis which is a critical complication of acute pancreatitis is one of the prognostic indicators of acute pancreatitis. Pancreatic necrosis is more prone for infective complications which again substantially increase the mortality rate [42]. So prediction of pancreatic necrosis in a setting of acute pancreatitis has great clinical implications [42]. Early detection and identification of pancreatic necrosis will allow induction of intensive care for these patients with early initiation of prophylactic antibacterial treatment to prevent infective complications and improve the prognosis [42]. Tsuji et al. and his colleagues studied 30 patients with acute pancreatitis and perfusion CT was found to have a sensitivity and specificity of 100% and 95.3% respectively in detection of pancreatic ischemia [42]. BF and BV parameters were used to indicate the presence of pancreatic ischemia both of which showed reduction compared to normal pancreas [42]. All the patients who were predicted on perfusion CT to have pancreatic ischemia 3 days after the onset of symptoms went on to develop necrotizing pancreatitis [42]. Though further studies are necessary to allow its routine use in assessment of patients with acute pancreatitis, it has immense clinical implications to improve the prognosis of patients with severe acute pancreatitis.

II. Oncological applications

Perfusion CT is emerging with increasing applications in oncology with clinical evidence in several areas. These include (a) lesion characterization—to differentiate between benign and malignant lesions (b) depiction of occult malignancy (c) staging of cancers and providing prognostic information and (d) to monitoring therapeutic effects of the various treatment regimes like chemoradiation or antiangiogenic drugs [16]. A brief introduction of tumor angiogenesis followed by the discussion of its clinical applications is done below.

**Angiogenesis**

Angiogenesis is defined as the process of developing new capillary blood vessels resulting in the vascularisation of tissues [43]. This process which is integral to the growth and spread of tumors consists of several dynamic processes mediated by a host of growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor and platelet derived endothelial cell growth factor (PD-ECGF) [43, 44]. Metastases to distant sites is related to angiogenesis of tumors and tumors with higher vascularity have been associated with a poor outcome [14, 43, 45, 46]. Perfusion CT displays and allows quantification of the abnormal vasculature which characterizes tumors. While normal tissues have a well organized hierarchical branching pattern and network, in contrast the tumor vessels are dilated, tortuous and organized in a chaotic spatially heterogenous fashion (Figure 2) [47].

**Why Image angiogenesis?**

There has been an increasing focus on the field of tumor angiogenesis and several “anti-angiogenic” drugs are being developed accounting for an estimated cost of whopping $ 4 billion [14, 43, 45, 48]. This has necessitated the need for development of an in vivo biomarker which would help evaluate angiogenesis and monitor the therapeutic effects of these new breed of drugs [48, 49]. Especially so because being non-cytotoxic, these agents produce disease stabilization without significantly affecting the tumor size. This calls for the use of functional techniques like perfusion CT for evaluation of the therapeutic response. Moreover, these techniques allow evaluation of treatment effect much sooner than the currently used criteria which evaluate variation in tumor size [43]. This is because of the time lag that exists between the functional and morphological changes seen in tumors following treatment. Thus imaging angiogenesis allows better monitoring of treatment and also helps predict outcome. However, tumor size evaluation should also be considered in response evaluation of anti-angiogenic agents, as they do cause reduction in size [49].

**Imaging Biomarkers**

The biomarker which can be used to image the effects of the anti-angiogenic drugs can be either direct or indirect (surrogate) in nature [49]. A direct biomarker for checking antiangiogenic response would be the actual blood vessels in the tumor which form the actual target where the agents exert their effects [49]. An ideal direct biomarker is the measurement of microvessel density in the tissue sample which is considered the “gold standard” for quantification and monitoring of angiogenesis. Microvessel density is defined as the mean number of endothelial cells or endothelial cell clusters in a given number of microscopic fields, which are clearly separate from the adjacent tumor cells and connective tissue elements [50].

Microvessels are highlighted by staining the endothelial cells with anti-CD34 antibodies. As microvessel density has been
established as a prognostic indicator for many cancers, the most direct strategy to monitor anti-angiogenic therapy would be periodic biopsies. There are several limitations in its use for evaluation of tumor angiogenesis: (i) they require invasive tissue sampling such as biopsy, (ii) they need to be standardized, (iii) presence of random sampling errors and that (iv) they do not explore the entire tumor volume which can hamper evaluation due to the heterogeneity of malignant tumors[43].

Surrogate biomarkers or indirect biomarkers are hence used instead of the direct biomarkers for measuring angiogenesis response to treatment i.e decrease or increase in the number or type of blood vessels[49]. Dynamic contrast enhanced imaging studies like CT and MRI are emerging as the surrogate biomarkers for measuring angiogenesis response[49]. The advantages of these techniques are that they are non invasive, can be repeated frequently, and they dynamically reflect the microcirculatory function in living individual [6]. CT perfusion has been validated and has shown to be feasible technique to show changes of perfusion to anti-angiogenic therapy[51] (Figure 3).

**Clinical applications**

**A. Brain tumors**

Brain tumors and surrounding peri-tumoral areas have higher BF, BV and PS compared to the normal tissue in animal models[26]. In humans, however variable elevations in BF and BV and a conspicuous increase in PS have been observed in the tumor and not in the peri-tumoral areas[40, 52, 53]. Grading of gliomas is also possible with perfusion CT [2]. High grade gliomas show a higher mean BF, BV and lower MTT compared to low grade gliomas. Using a cut off BF of >1.92 ml/ 100g or a BF cutoff of >1.48 ml/min/100g and MTT of < 1.94 sec improved the sensitivity and specificity of detecting high grade gliomas[2]. The mean cerebral blood volume in high grade gliomas were higher than low grade gliomas[2].

In cerebral tumors after radiotherapy, CTp is valuable in the differentiating between recurrent tumor and radiation necrosis [54]. Jain et al found that tumor recurrence showed an increase in BF, BV and decrease in MTT compared to radiation necrosis, which showed reduced BF, BV and increased MTT [54]. Furthermore, the perfusion maps obtained help in targeting tumor foci in heterogeneous lesions (mixture of tumor and necrosis) for biopsy and radiation planning[54]. These foci of tumor show higher CBV and shorter MTT compared to the rest of the lesion and appear as “hot spots” on perfusion maps. These “hot spots” can undergo targeted biopsy or radio surgery thus improving treatment response [54].

**B. Head and neck tumors**

As treatment approaches are undergoing a sea change from surgery based approaches to organ preserving chemoradiation therapies, it becomes important to detect those patients who are equally responsive to chemotherpay [55]. The gold standard so far for detecting tumor response after chemotherapy involved direct laryngoscopy with biopsy under general anaesthesia[55, 56]. Perfusion CT is being increasingly used as an alternative to direct laryngoscopy for evaluating tumor response and has been found to be feasible technique and reproducible technique with no significant intra-reader or inter-reader variability [55-57]. Evaluation of head and neck tumors using de-convolution based techniques have shown increased BF, BV, PS and reduced MTT in squamous cell carcinoma of the head and neck compared with the adjacent normal structures[3]. The BF of squamous cell cancers of the head and neck has been found to be around 76-126 ml/100g/min, Blood volume (BV) 5.6 ml/100g, MTT was 3.2-3.9 sec and the PS measured 24.1-40.6 ml/100g/min[57]. Rumboldt et al and his colleagues studied 17 patients with head and neck cancers and were able to differentiate between benign and malignant processes based on the MTTs[57]. Benign processes showed lower blood flow and longer MTTs compared to malignant processes[57]. No malignant lesion had a MTT longer than 5.5 sec and all lesions with MTT of 3.5 -5.5 seconds differed from the non malignant lesions of having a permeability of less than 25ml/100g/min[57].

Herman et al investigated the value of CT perfusion as a predictive factor of local and regional failure and cause specific survival in head and neck cancer treated by radiotherapy[56]. Herman et al and colleagues found that the tumor perfusion rate was an independent predictor of the failure rate after radiotherapy and independent of tumor volume [56]. Their analysis found that patients with low perfusion value (<83.5 ml/min/100g) showed a statistically significantly higher local failure rate than those with high perfusion value[56].

**C. Lung cancer**

In non small cell lung carcinoma, it has been found that histopathological types of lung cancer correlated with the tumor angiogenesis as depicted on CT[5, 58]. The MVD of adenocarcinoma is found to be more intense that in squamous cell carcinoma[5, 58]. Increasing tumor size has been found to result in lower CT perfusion values[5, 58]. Necrotic tumors exhibited significantly lower perfusion, PEI and BV than those of non-necrotic tumors[5, 58]. Perfusion parameters have not found to be associated with lymph node metastasis. This stresses on the point that the mechanism of producing lymphatics might different from that of angiogenesis.

**Lymphoma**

CT is currently the imaging modality of choice for the diagnosis, staging and follow up of lymphoma. The data on the utility of the perfusion CT in evaluation of patients with lymphoma is limited [59]. The chief reason for this being that angiogenesis is not a predominant features of lymphoma. Dugdale et al performed perfusion CTs on 26 patients with lymphoma and observed that intermediate and high grade lymphoma had a higher perfusion (>0.5ml/min/ml) compared to low grade tumors[59]. Active lymphoma also showed an increase in perfusion compared to inactive lymphoma with serial evaluation showing an increase in perfusion with progression from inactive to active disease[59]. However the permeability measurements did not show much change between the two groups[59].
Liver tumors
Perfusion CT could be used for in vivo assessment of tumor angiogenesis and neo-vascularity in hepatocellular carcinoma (HCC) and has benefits in making the differential diagnosis, evaluating tumor aggressiveness, monitoring therapeutic effects and determining the final outcome of HCC patients[60]. CT perfusion has been found to be a feasible and reproducible technique for quantifying tumor vascularity and angiogenesis in advanced HCC[8]. Ippolito et al. showed that the perfusion parameters of HCC are significantly different compared to the surrounding liver[61]. HCC demonstrates higher BF, BV, PS and lower MTT compared with background liver. Sahani et al. in his study of 22 patients with locally advanced HCC demonstrated significant differences between CTP values of well differentiated tumors and those of moderately and poorly differentiated tumors[8]. Well differentiated HCC demonstrated relatively higher tumor BF, BV and PS and lower MT than did moderately and poorly differentiated HCC[8]. Sahani et al. also did not find significant difference in the perfusion parameters of HCC in cirrhotic and non cirrhotic patients and those with and without portal vein thrombosis confirming that HCC are preferentially supplied by hepatic arteries[8]. Ippolito et al. did not find any difference between the perfusion parameters of cirrhotic liver parenchyma in patients with HCC compared to those without HCC[61]. The perfusion values of HCC metastases have been found to be similar to the primary lesions in the liver [8]. Kan et al. has proved that functional CT allows accurate quantification of changes in liver tumor perfusion during and after an embolization procedure, thus helping optimise the therapeutic outcomes[62]. Kan et al. also reported that perfusion CT was able to assess changes in liver tumor perfusion in response to antiangiogenic treatment[4].

Patients with known metastatic disease of the liver have increased arterial perfusion compared to the those without metastases[63-65]. A clinical application of this is the ability to use this concept for characterization of focal hepatic lesions[63-65]. Meijerink et al. reported that total liver volume perfusion improved the detection of colorectal liver metastases, although the authors did face difficulty in differentiating between benign and malignant focal perfusion alterations[66].

Rectal cancer
Microvessel density in colorectal carcinoma (CRC) is significantly increased as compared to the adenomas and normal colonic mucosa[6]. Findings have suggested that superficially invasive carcinomas are capable of eliciting neo-vascularization of similar to those with distant metastases[6]. Li et al CT perfusion imaging is more suited for assessing tumorigensis in CRC than the histological MVD technique[6].

Rectal cancer shows high blood flow and shorter mean transit time compared to normal rectum[9] (Figure 2). After treatment with chemoradiation rectal cancers have been found to show a consistent decrease in blood flow and increase in mean transit time after chemotherapy and radiation therapy[9]. Rectal cancers with high blood flow and low mean transit time indicating high rate of angiogenesis and microvessel density within the tumor were found to have poor prognosis[9]. High perfusion values in association with a poor response to chemotherapy and radiation therapy can be explained by large numbers of intratumoral arteriovenous shunts with a high perfusion rate and low exchange of oxygen[9].

Another area where perfusion CT may be useful is in the differentiation of colorectal carcinoma and diverticulitis [67]. Goh et al. found that functional perfusion CT measurements enable differentiation and better discrimination, in comparison with morphologic criteria, between cancer and diverticulitis [67]. He found that patients with cancer had the highest blood volume, blood flow, and permeability and faster transit time compared to inactive diverticular disease which had lower blood volume, blood flow and permeability.

Pancreatic carcinoma
Pancreatic perfusion CT has been validated to show excellent agreement on tumor blood flow measurement with Xenon CT[24]. The normal human pancreas has been found to have a perfusion value of 1.25-1.66 mL/min/mL [68]. There is an age-dependent physiological decline in pancreatic perfusion values [69]. Miles et al. found that the pancreatic perfusion values were higher in patients with Wilson’s disease and pancreatic perfusion was reduced in patients with diabetes and in failing pancreatic transplants [68]. Pancreatic tumors such as islet cell tumors show increased perfusion values due to hypervascular nature of the tumor[69]. Xue et al. reported increased blood flow and blood volume in insulinoma compared to background pancreatic parenchyma in their study of 12 patients with pathologically proven insulinoma [69]. Perfusion CT has been found to be a useful predictor of effect of pancreatic tumor treatment with anticancer drugs[24].

Prostate carcinoma
The mean prostatic blood flow of 0.14 +/- 0.03 ml/min/g and a mean blood volume of 0.13+/-0.02 ml/g have been found on perfusion CT evaluation[70]. Tumor angiogenesis has been considered to be an important factor in the progression of prostate cancer and the microvessel density, a marker of angiogenesis has been correlated with prostate cancer stage, metastatic potential, disease specific survival and progression after therapy[71-74]. Differences in the vascular permeability and architecture between tumor and normal tissues contribute to corresponding differences in oxygenation and gene expression and impact adversely on response to radiation therapy and overall patient outcome[70]. Decreased perfusion may also restrict the effectiveness of chemotherapy agents that are dependent on the blood supply for transport into the tumor [70].
Tumor microvasculature is a key element of tumor physiology that influences the aggressiveness of cancer and their response to treatment[70].

**Future directions**

Perfusion CT has achieved great strides as a functional technique since its inception and its scope in the clinical and research setting is escalating. Development of newer MDCT scanners with increased detector arrays and advanced features may soon allow perfusion analysis of greater volumes of tissue. Greater anatomical coverage would not only permit a comprehensive evaluation of the tumor vascularity, but also enable perfusion evaluation of multiple organs concurrently. This would facilitate simultaneous functional evaluation of primary tumor and their metastases. Low dose MDCT techniques with improved reconstruction algorithms generating high resolution images may allow reduction in radiation exposure which would benefit patients undergoing multiple perfusion examinations. One of the impediments in accurate quantification of tissue perfusion is the degradation of CT data which occurs due to motion particularly secondary to respiratory mis-registration. Respiratory gating could minimize misregistration artifacts and sophisticated softwares like "motion tracking algorithms" may allow more precise functional estimation[17]. Integrated PET/CT systems with prospects of combining perfusion measurements with PET data is an exciting new innovation which has wide ranging implications in investigation of ischemic tissue and tumors[17].

**References**

Table I. CT perfusion analytical methods and parameters evaluated with different vendors.

<table>
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<th>CT Perfusion (GE)</th>
<th>Functional CT (Siemens)</th>
<th>Brilliance (Philips)</th>
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<tbody>
<tr>
<td>Mathematic model</td>
<td>Deconvolution method</td>
<td>Two-compartment model</td>
<td>Slope method</td>
</tr>
<tr>
<td>Principle of the model</td>
<td>Impulse residue function (IRF) which is time enhancement curve of tissue due to idealized instantaneous injection of one unit of contrast</td>
<td>One way transfer of CM from intra to extra-vascular space proportionate to blood clearance constant, Perfusion is ratio of max slope of tissue enhancement curve to max arterial enhancement</td>
<td></td>
</tr>
<tr>
<td>Parameters measured</td>
<td>BF, BV, MTT, PS</td>
<td>BV and permeability</td>
<td>MTT, time to peak enhancement</td>
</tr>
<tr>
<td>Advantages</td>
<td>BF, BV, MTT and PS can be calculated using a single CT study</td>
<td>1. Simple analysis 2. Efficient in calculation of rate constant K value</td>
<td>1. Short scan duration 2. “No venous outflow” is true 3. No recirculation</td>
</tr>
<tr>
<td>Limitations</td>
<td>Partial volume averaging correction required</td>
<td>Assumes that back flux of CM from EVS to IVS is negligible for first 1-2 min</td>
<td>Sensitive to image noise</td>
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BF=Blood flow, BV=Blood volume, MTT= Mean Transit Time, PS= Permeability surface area product, EVS= Extravascular space, IVS= Intravascular space, CM= Contrast media.

Table II. Glossary of terms commonly used in CT perfusion

<table>
<thead>
<tr>
<th>Perfusion parameter</th>
<th>Definition</th>
<th>Marker (In Oncology)</th>
<th>Units</th>
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<tbody>
<tr>
<td>BF (Blood Flow)</td>
<td>Flow rate through vasculature in tissue region</td>
<td>Tumor vascularity</td>
<td>mL/100 g/min</td>
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<td></td>
<td></td>
<td>Tumor grade</td>
<td></td>
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<tr>
<td>BV (Blood volume)</td>
<td>Volume of flowing blood within a vasculature in tissue region</td>
<td>Mitotic activity and vascularity</td>
<td>mL/100 g</td>
</tr>
<tr>
<td>MTT (Mean transit time)</td>
<td>Average time taken to travel from artery to vein</td>
<td>Perfusion pressure</td>
<td>seconds</td>
</tr>
<tr>
<td>PS (Permeability Surface)</td>
<td>Total flux from plasma to interstitial space</td>
<td>Immature leaky vessels</td>
<td>mL/100 g/min</td>
</tr>
<tr>
<td>TTP (Time to peak)</td>
<td>Time from the arrival of the contrast in major arterial vessels to the peak enhancement</td>
<td>-</td>
<td>seconds</td>
</tr>
<tr>
<td>Perfusion</td>
<td>Flow rate through vasculature in tissue region</td>
<td>Tumor vascularity</td>
<td>ml/min/ml</td>
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<td>Tumor grade</td>
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Fig 1: Perfusion CT scans of the rectal cancer. A) Axial contrast enhanced CT image of the pelvis show irregular enhancing mass in the rectum causing wall thickening. Functional CT perfusion color maps of (B) blood flow (mean, 96.7ml/100g/min) (C) blood volume (mean, 6.9 ml/100g) (D) mean transit time (9.2 seconds) and (d) permeability-surface area product (mean, 15 ml/100g/min) show the perfusion changes in rectal cancer.
Figure 2. Color schematic diagram highlighting the vascular pattern in normal tissues and tumors. A) The well organized hierarchical vascular pattern of normal tissues is seen with proper branching of the vessels. Also note the ordered variation in the size of the vessels. The vessels demarcated in red demonstrate arteries and the vessels in blue represent veins with intervening capillaries. B. The chaotic tumor vasculature shows dilatation, tortuousity and spatial heterogeneity of the vessels.

Figure 3. Pre and post antiangiogenic CTp images in a 65 yr old male with malignant fibrous histiocystoma of the thigh. (A)Colored perfusion map of blood flow at baseline before antiangiogenic treatment shows increase tumor blood flow (110ml/100g/min). (B) Colored perfusion map after treatment shows significant reduction in tumor blood flow (60ml/100g/min).