REVIEW

Perfusion computed tomography in colorectal cancer: Protocols, clinical applications and emerging trends

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Abstract

Perfusion computed tomography (CT) has emerged as a novel functional imaging technique with gradually increasing importance in the management of colorectal cancer (CRC). By providing the functional tumor microvasculature, it also helps the assessment of therapeutic response of anti-angiogenic drugs as it may reflect tumor angiogenesis. Perfusion CT has been applied in clinical practice to delineate inflammatory or neoplastic lymph nodes irrespective of their size, identify micro-metastases and to predict metastases in advance of their development. It is of increasing significance for preoperative adjuvant therapies and avoidance of unnecessary interventions. Despite controversies regarding the techniques employed, its validity and reproducibility, it can be advantageous in the management of CRCs in which the prognosis is dependent on preoperative staging. With recent advances in the perfusion CT techniques, and incorporation to other modalities like positron emission tomography, perfusion CT will be a novel tool in the overall management of CRCs. This article aims at reviewing the existing clinical applications and recent advances of perfusion CT with a reference to future development in the management of CRCs.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer mortality in the developed countries with increasing prevalence in developing countries due to the changing life style and eating habits[1]. More than 940 000 new cases of CRC and nearly 500 000 related deaths are reported each year worldwide.

CRCs are almost primary adenocarcinomas. Neovascularization is considered as an initial triggering event in colorectal tumor growth and dissemination[2]. The main mechanisms inciting neovascularization are angiogenesis, the growth of new blood vessels by budding or sprouting from the existing vasculature and vasculogenesis which is the de novo vascular formation from precursor endothelial cells known as angioblasts. Neovascularization arises early in the adenoma-carcinoma sequence *via* upregulation of various angiogenic factors including vascular endothelial growth factor[3]. Thus, the *in vivo* imaging techniques that assess the microvascularity play an immense role in the management of patients with CRC.

Functional imaging techniques including perfusion computed tomography (CT) have emerged as new dimensional tools in the evaluation of blood supply and kinetics in the oncological as well as non oncological aspect of medical fields. A definite radiological preoperative staging is mandatory for adequate management because the treatment protocols need to be standardized based on tumor invasion depth, status of the regional lymph nodes, and distant metastases. Although perfusion CT has been used for a while in the arena of neurological science, it has gained momentum recently in cancer management. In the field of oncology, perfusion CT is emerging as a novel technique applied in the diagnosis, staging, grading, prognostic evaluation based on tumor vascularity, and therapeutic response monitoring. Although many other promising imaging techniques allow for tissue perfusion measurement, CT is particularly ideal for various reasons such as its

widespread availability, affordability, prevalence of better experience, routine availability of commercial software and readily incorporation of perfusion software for vascular measurements into existing CT protocols[4,5].

PERFUSION CT PRINCIPLES AND PROTOCOLS IN CRCS

The basic principle governing perfusion CT is the temporal changes in the tissue enhancement following intravenous administration of iodinated contrast media[6,7]. Compartmental and deconvolution analyses are the two commonly used analytical methods to quantify vascular physiology from the data acquired from the dynamic CT. In the compartmental modeling technique, analysis can be done by one compartment method which assumes the intravascular and extravascular compartment as a single compartment and allows measurement of tissue perfusion based on Fick's principle during the first pass of contrast, and by double compartment method which assumes the intravascular spaces as two compartments and estimates capillary permeability and blood volume (BV) by Patlak analysis which denotes the passage of contrast into the extravascular space from the intravascular space[6]. The deconvolution model on the other hand is based on determining the impulse reside function for the targeted tissue which applies to the arterial and tissue concentration-time curves.

A general perfusion CT technique typically requires a baseline unenhanced image acquisition, followed by a series of images acquired over a time period after an intravenous bolus injection of iodinated contrast media[8,9]. The unenhanced CT acquisition primarily provides a wide coverage to the targeted organ, thus serving as a localizer to select the appropriate tissue area to be covered in the following dynamic CT acquisition range. A large coverage area of about 8-16 cm in the dynamic acquisition scan providing increased sample volume has become possible with the recent advances in the scanner technology, although a 2-cm or 4-cm coverage area is still in practice in majority of the institutions. For perfusion measurement, the first pass study includes the images acquired during the initial phase for a total of approximately 40-60 s. By the compartment method, the acquisition of images is done every 3-5 s whereas by deconvolution method, images are acquired every 1 s[8,9]. For permeability measurement, second-phase images are acquired, ranging 2-10 min after the first pass study. By compartmental method, the images are obtained every 10-20 s whereas by deconvolution method every 10 s for 2 min after the first pass study[9,10].

Special considerations have to be taken while performing the perfusion studies in CRC. Patients are usually kept on 4-6 h of fasting before water soluble contrast material is given for ingestion to assist in opacifying the small intestine. Image misregistration and errors in estimation of perfusion values due to the respiratory as well as abdominal motions during image acquisition must be avoided. Although respiratory gating may not be so practicable, it is worthwhile instructing patients for minimal respiratory efforts. Abdominal gating is useful for proper assessment of the tumor physiology. Use of abdominal straps to curtail anterior abdominal wall excursion has been routinely performed. To overcome the bowel peristalsis during perfusion examination of colorectal region, spasmolytic drugs such as hyoscine butyl bromide or glucagon are recommended[11-14]. Besides, the use of water or saline to distend the lumen of colorectal region is advantageous for the optimal delineation of the tumor and accurate assessment of the bowel wall thickness[15]. Various fallacies do exist while selecting the region of interest, thus mandating careful judgment to avoid attenuation artifacts from various prosthesis as well as misregistration in areas prone to motion. Besides, the proper selection of arterial input is necessary to avoid errors in perfusion value measurement[7].

APPLICATIONS OF PERFUSION CT IN CRC

Perfusion CT has been applied increasingly in the diagnosis, differentiation, staging, grading and prognosis of CRC and for identification of occult malignancies and local or regional metastases and relapse, and prediction of tumor activity and monitor of treatment response to antiangiogenic drugs and chemoradiotherapy as well.

Henderson *et al*[16] noted that perfusion CT enables characterization of the tumor status based on extrapolating the physiological vascular parameters, thus allowing *in vivo* quantification of the microvasculature of the tumor. It has been considered that the gross morphological changes in tumor pathology occur at a later time period than the associated functional vascular profile alteration, precluding accurate and early quantification. Perfusion CT has therefore of a substantial value in assessing the tumor physiology, which is superior to other earlier performed methods[17-19].

Validation and correlation with microvessel density (MVD) in CRC

Perfusion CT exploits the enhancement characteristics of the tissue following contrast which heralds the vascular physiologic changes. Thus, perfusion CT which reflects the tumor physiology can be regarded as an indirect imaging biomarker for the *in vivo* evaluation of angiogenesis. MVD on the other hand represents the number of tumor blood vessels, varied in different tumor types, which may not reflect the angiogenic activity or angiogenic dependence of the tumor.

Dynamic contrast enhanced CT has been regarded as an appropriate non-invasive technique for assessment of angiogenesis, and positive correlations between CT parameters and immunohistologic measures, such as MVD, have also been noted[20]. Although Li *et al*[21] in their study revealed that there was no significant correlation in perfusion parameters between CRC and MVD, later observations by Goh *et al*[22,23] suggested

that BV and permeability surface area product (PS) measurement reflects angiogenesis and that perfusion CT is an appropriate technique for assessing tumor vasculature. CT perfusion imaging may be considered more valid for assessing tumorigenesis in CRC compared with the histological MVD[21].

Value in diagnosis of CRC

White et al[24] reported that MVD progressively increases from normal colonic mucosa through adenomas to CRC. However, MVD was not related to the Dukes' stage and appeared to decrease slightly with increasing Dukes' stage or tumor differentiation[21]. Bossi et al[25] reported that angiogenesis is an initial prerequisite in colorectal tumorigenesis. Goh et al[22] observed that CRC has high blood flow (BF), BV, PS and low mean transit time (MTT) values as compared with diverticular disease, which helps differentiate cancer from colonic thickness due to diverticulitis. Li et al[21] found that superficial invasive carcinomas are capable of eliciting neovascularization comparable to those with distant metastases. Rectal cancer demonstrated higher BF and shorter MTT than normal rectum. In their initial study, Bellomi et al[26] also found that BF, BV and PS are significantly higher in rectal cancer than in the normal rectal wall. Sahani et al[15] observed a significant difference in BF and MTT between rectal tumor and normal rectum. However, there was no significant difference in the BV and PS. Perfusion CT has not been found to be correlated with the tumor stages, depth of invasion, and lymph node metastasis in various studies in CRC. However, Li et al[21] observed that perfusion measurement had a negative correlation with increasing Duke's stage.

Value in prognosis of CRC

Besides a diagnostic value in CRC, perfusion CT has also been employed to assess various treatment modalities and predict the tumor response to those therapies[15,20]. Controversies exist while taking MVD as prognostic indicator because of incoherent results and various practical limitations. Bossi et al[25] indicated that MVD did not provide significant prognostic information in CRC. Pietra et al[27] observed that MVD in CRC without lymph nodes involvement has no correlation with conventional prognostic factors and provides no significant prognostic information. Sahani et al[15] observed that poor prognosis was more likely in tumors with high BF and low MTT possibly due to the increased angiogenic activity of the tumor cells. Bellomi et al[26], however, found that rectal cancers with high baseline BF and BV showed good response to chemoradiotherapy.

Value in metastases and treatment monitoring in CRC

Leggett et al[28] observed that increased arterial perfusion appeared to be an indicator of liver metastases in patients with CRC. It was also noted that progressive disease may be indicated by a reduction in the portal perfusion. Irrespective of the presence of focal liver lesions, there are alterations in the microvasculature and perfusion values

in CRC, it is not ideal to employ the same enhancement protocols in patients with liver metastases[27].

Perfusion CT has played an increasing role in monitoring therapeutic response to antiangiogenic drugs and chemoradiation as it may reflect tumor angiogenesis and provide insight of the functional tumor microvasculature[15,20,26]. However, there have been few studies to predict subsequent relapse in CRC. Goh et al[29] prospectively studied the vascular measurements in patients with rectal cancer to determine if it can predict subsequent metastatic relapse. It was observed that there was a significant difference in the vascularity of the tumors in patients who will subsequently develop metastases despite of curative surgery. Vascular parameter such as MTT was significantly high whereas tumor BF and permeability surface area product were low in patients who developed metastases. It was also noted that PS measurements were significantly higher in patients who already had evidence of metastatic disease compared with patients who subsequently developed metastatic disease[29].

Perfusion CT definitely has an implied role in the monitoring and prediction of treatment response to chemotherapy and radiation therapy in rectal cancers[26]. Sahani et al[15] observed that after completion of chemoradiotherapy, rectal cancer showed a consistent decrease of BF and an increase of MTT. Bellomi et al[26] observed similar results with decrease in BF, BV and PS after chemoradiation in rectal cancer. In a clinical trial of patients with rectal cancer treated with antiangiogenic therapy (bevacizumab), Willett et al[20] observed that CT perfusion helped monitor antiangiogenic changes within 2 wk of treatment and its characteristics are correlated with tumor MVD, which presented with decrease in MVD and other surrogate markers of angiogenesis.

CONCLUSION

Perfusion CT is strengthening its role as a preferred functional imaging technique in the management of CRC. Despite various limitations, perfusion CT has substantially influenced the imaging and treatment aspect in the management of CRC patients, particularly as a biomarker for monitoring the response of various treatment modalities, which may have further clinical usefulness in the staging of the disease and prognostic value as well. With the advancement in perfusion software and the development of new generation of scanners having a wider cine acquisition, it has allowed single or even multiple organ perfusions with the advantage of decreased radiation exposure and motion artifacts. Moreover, the integration of positron emission tomography (PET)-CT systems with FDG-PET data represents an exciting new innovative technology that has a wide range of clinical application as a single examination while minimizing the image misregistration. Development of new contrast agents which retain longer in intravascular compartment may also overcome some of the complexities of physiological modeling

required for conventional contrast agents that exhibit two-compartment pharmacokinetics. Perfusion CT which was primarily introduced as a research tool has now emerged as a definitive functional technique in the management of CRC.

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