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K. A. Miles

Functional CT imaging in oncology

K. A. Miles (✉)
Wesley Research Institute,
2nd Floor Day Care Centre,
The Wesley Hospital,
Brisbane, Australia
e-mail: k.a.miles@bsms.ac.uk

Present address:
K. A. Miles,
Brighton and Sussex Medical School,
University of Sussex,
Falmer, Brighton, BNI 9PX, UK

Abstract The two-compartment pharmacokinetics exhibited by iodinated contrast media makes these agents well suited to the study of tumour angiogenesis in which new vessels are not only produced in greater number but also are abnormally permeable to circulating molecules. The temporal changes in contrast enhancement of tumours on CT have been shown to correlate with histopathological assessments of angiogenesis with the intravascular and extravascular phases of contrast enhancement reflecting microvessel density and vascular permeability, respectively. By quantifying tumour contrast enhancement to capture physiological information about the vascular system, functional CT can provide a useful adjunct to the anatomical information afforded by MDCT in oncology, aiding with tumour diagnosis, risk stratification and therapy monitoring. By simultaneously assessing tumour vascularity and metabolic demand, the broader expansion of integrated MDCT/PET imaging will support highly sophisticated assessments of tumour biology within a single examination.

Keywords Functional CT imaging · Oncology · Contrast media

Introduction

The term "functional CT" can be used to describe new CT techniques that quantify contrast enhancement to capture physiological information about the vascular system. Although the possibility of using CT in this way was first proposed by Axel [1] within a decade of Hounsfield's description of CT, the advent of spiral and multi-detector CT systems (MDCT), along with release of commercial software, has enabled such techniques to become widely available. Furthermore, by creating a need for an in vivo method for assessment of tumour vascularity, the recent innovation of anti-cancer drugs that target the tumour vasculature has further stimulated the development of function CT [2]. The current anatomically based imaging criteria for assessing tumour response may not be suitable for monitoring these new agents which tend to stop tumour growth rather than produce tumour regression; however, as CT remains the mainstay for anatomical imaging of cancer, a CT based method for assessing tumour vascularity would enable relevant structural and functional in formation to be obtained in a single investigation.

This article describes the application of functional CT in oncology.

Tumour angiogenesis and contrast media

The pharmacokinetics of iodinated contrast media approximate to a two-compartment model with intravascular and extravascular compartments, a property that makes these agents well suited to the study of the vascular changes associated with tumour development. In order to grow beyond 1- to 2-mm, tumours must establish their own blood supply. In a complex process known as angiogenesis, tumours produce a range of growth factors resulting in the production of new blood vessels derived largely from the host vascular system. These new vessels are produced in greater numbers than found in normal

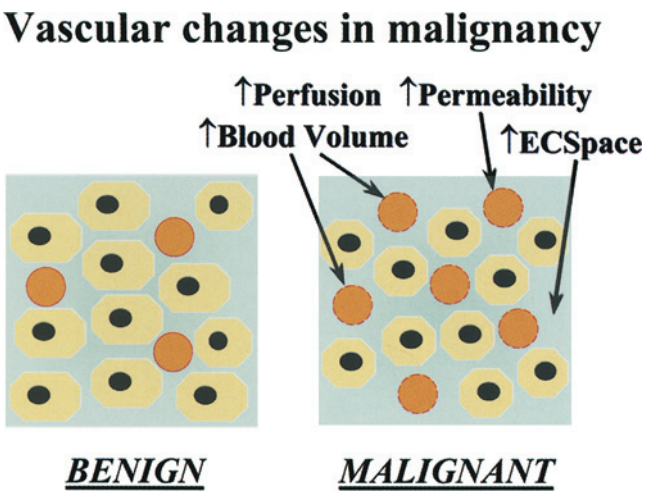

Fig. 1 Neovascularisation of tumour–tissue results in increased numbers of vessels with incomplete basement membranes. These pathological features translate to increased blood volume, perfusion, permeability and extracellular space measurements on functional CT

tissues [i.e. the microvessel density (MVD) is increased] and the tumour blood vessel walls demonstrate increased permeability to circulating molecules (Fig. 1); thus, the intravascular phase of contrast enhancement can provide a handle on microvessel density, whereas the extravascular phase can be used to evaluate vascular permeability [3]. Indeed, the peak enhancement of renal and lung cancers has been shown to correlate with MVD [4, 5, 6].

Methods

Functional CT assessments of tumour vascularity require a baseline non-contrast-enhanced image followed by repeated image acquisitions after a bolus of intravenous contrast medium. High-concentration contrast media are favoured on account their ability to produce increased tissue enhancement and favourable bolus geometry. To date, MDCT protocols have either used repeated short spiral acquisitions or a single-location sequence (i.e. no table movement) comprising either two adjacent 10-mm slices or four 5-mm slices (Table 1). The repeated spiral technique benefits from greater volume coverage but at the expense of potential measurement error from reduced temporal resolution; however, by focusing on peak enhancement measurements or the standardised perfusion value (SPV; see below), a combined technique is feasible in which a single-location timing sequence using a small test bolus of contrast medium is performed to determine the time of peak *tissue* enhancement (analogous to the timing sequences often used during CT angiography to determine the time of peak *vascular* enhancement). A larger bolus of contrast medium (given over the same time as the test bolus) is then used for a volume acquisition that has been programmed to occur at the moment of peak tissue enhancement.

Tumour enhancement patterns can be analysed semi-quantitatively (e.g. peak enhancement value, enhancement rate) or, with appropriate physiological modelling, used to quantify physiological parameters such as perfusion and vascular permeability [3]. Modelling approaches include compartmental analysis based on the Fick principle and those utilising deconvolutional analysis and are described in detail elsewhere [3, 7]. The physiological measurements obtained are reproducible and consistent irrespective of the observer or analysis methodology, and have been validated against a range of reference methods [7, 8, 9, 10, 11, 12, 13, 14, 15]. Commercial software packages are now available for calculating functional CT parameters with generation of colour-coded parametric maps.

In general, absolute physiological measurements, such as perfusion and permeability, are preferable to semi-quantitative parameters because perfusion and permeability values correct for variations that occur in the arterial input, both between patients and between studies in the same patient; however, perfusion values within a tumour are not only determined by the MVD but also by the cardiac output (Fig. 2). This dependence on cardiac output is particularly important when using functional CT to monitor the effects of anti-angiogenesis drugs or other agents that modify tumour vascularity, as some of these drugs are known to affect cardiovascular function; thus, a post-treatment reduction in tumour perfusion could merely reflect a drop in cardiac output with no change in tumour vascularity (Fig. 2a). More recently, a perfusion value that is normalised for cardiac output and body weight, the SPV, has been proposed and may be more appropriate for assessing angiogenesis [16]. The derivation of the SPV is analogous to the standardised uptake value widely used in positron emission to-

Table 1 Three example protocols for the application of perfusion CT in oncology

Acquisition type	Multiple spiral	Single location	Single location
Contrast medium Concentration	370 mg/ml	370 mg/ml	370 mg/ml
Volume	100 ml	40 ml	50 ml
Injection rate	4 ml/s	4–7 ml/s	7–10 ml/s
Slice thickness	20×3 mm	4×5 mm	2×10 mm
Image frequency	Every 20 s	Every 1 s	Every 3 s
No. of images	6	60	15
Tube current	100–250 mAs	50–100 mAs	100–250 mAs
Analysis method	Standardised Perfusion Value	Deconvolution for perfusion and blood volume	Compartmental analysis for perfusion and blood volume
Advantages	Large volume coverage; high spatial resolution	Good temporal resolution; high spatial resolution	Low image noise
Disadvantages	Poor temporal resolution	Image noise; limited volume coverage	Reduced temporal resolution; limited volume coverage

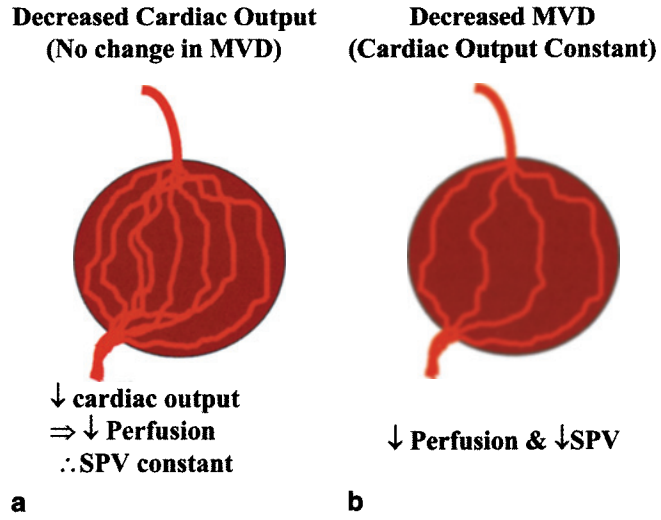

Fig. 2a, b The value of the standardised perfusion value (*SPV*) in reflecting tumour microvessel density (*MVD*). **a** Reduction in cardiac output with no change in MVD. Tumour perfusion will fall, but the SPV, which normalises perfusion to the cardiac output and weight, will remain constant. **b** Only a reduction in MVD will produce a fall in SPV

mography (PET) and early data suggests that a threshold SPV of 1.5 might be useful in discriminating benign and malignant tissues [16].

Applications

Histopathological studies have not only shown that the density of microvessels is greater in malignant tissues, but also that intensity of the angiogenic process is related to the ability of the tumour to metastasise so that highly vascularised are associated with a poor prognosis [17, 18]. These pathological features are reflected by the ability functional CT to assist both in tumour diagnosis and risk stratification. Furthermore, functional CT can be used to assess tumour response anti-angiogenesis and other chemotherapeutic agents and radiotherapy.

One of the more commonly used diagnostic applications of functional CT is the characterisation of pulmonary nodules that are indeterminate on conventional CT (Fig. 3). A number of techniques have been proposed for this purpose (Table 2) [5, 16, 19, 20, 21], but the simplest is to measure peak enhancement (following a bolus of contrast given on a dose/weight basis) where enhancement less than 15 HU (equivalent to an SPV of 1.5) is highly predictive for a benign lesion [19]. Nodules that enhance above this threshold may be either malignant or inflammatory and therefore require further investigation such as fine-needle biopsy or fluorodeoxyglucose (FDG) PET. Decision modelling techniques have shown that use of functional CT in this way can reduce health care expenditure by decreasing the numbers of patients requiring further more expensive investigations [22]. Functional CT can also reveal occult tumour sites undetected by conventional CT such as hepatic micrometastases or recurrent glioma [23, 24, 25, 26, 27].

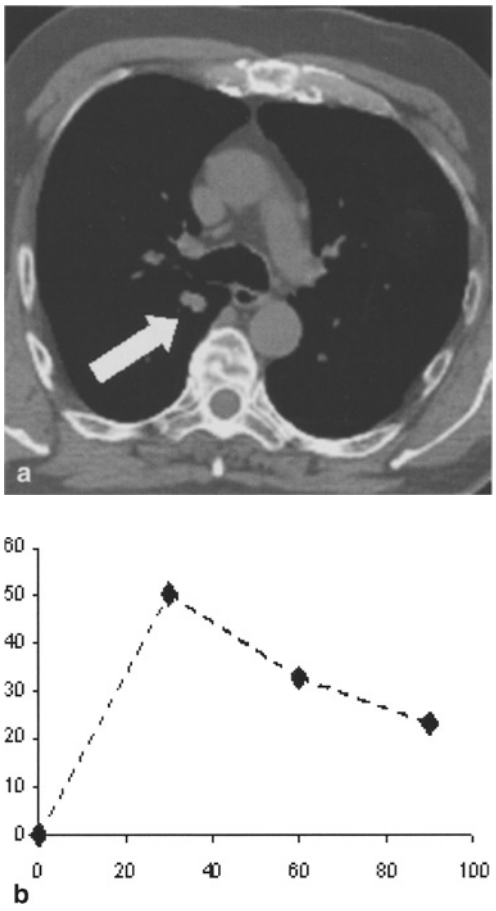

Fig. 3a, b **a** Contrast enhancement measurements from a pulmonary nodule of indeterminate nature on a conventional CT images (*arrow*). **b** The peak enhancement value is 50 HU, equivalent to an SPV of 5.1. As the nodule is highly perfused (peak enhancement >15 HU, SPV>1.6), it cannot be considered benign; however, tumours and inflammatory lesions, such as granulomata, may exhibit high perfusion values; thus, further investigation (e.g. fluorodeoxyglucose PET or fine-needle aspiration) is required

Risk stratification is an important issue for patients with cancer, as patients identified to have aggressive tumours may be suitable for additional treatment or invasive local treatments could be withheld when unlikely to be of benefit. Applications of functional CT in risk stratification include estimation of tumour grade in cerebral glioma where blood volume heterogeneity implies aggressive disease, and in lymphoma where high grade tumours tend to have perfusion values above 50 ml/min/ml [28, 29]. The in vivo grading of tumours in this way has the potential reduce the tissue sampling error by guiding biopsy to the tumour region most likely to exhibit the highest grade. Tumour grading with perfusion CT may

Table 2 Summary of reported functional CT techniques for the characterisation of pulmonary nodules

Reference	No. of patients	Technique	Contrast medium	Scan frequency	Slice width (mm)	Criteria	Sensitivity (%)	Specificity (%)
[19]	356	Multi-spiral	300 mg/ml, 420 mg/kg, 2 ml/s	1/min	3	>15 HU SPV=1.5	98, 1 min, 81	58, 1 min, 77
[21]	32	Multi-spiral	300 mg/ml, 100–150 ml, 2 ml/s	2/min	2	20–60 HU SPV≅2.1–6.2	88	36
[20]	65	Single location	300 mg/ml, 100 ml, 4 ml/s	1 in 2 s	5	>20 HU >0.2 ml/min (m) SPV≅2.1–2.3	95	85
[5]	35	Single location	300 mg/ml, 100 ml, 3 ml/s	1/s	2	≥16 HU SPV≅1.7	100	All, Ca
[16]	11	Single location	300 mg/ml, 50 ml, 7 ml/s	1 in 3 s	10	SPV≥1.6	100	50

also be of value when biopsy is difficult or when there is a propensity for tumour grade to change with time. Other examples of risk stratification include CT perfusion measurements in head and neck cancer which can predict the response to radiotherapy [30]. Furthermore, CT measurements of hepatic perfusion among patients with colon cancer appear to correlate with survival more closely than does the pathological Dukes' classification (M.R. Griffiths, pers. commun.).

Functional CT parameters can also measure the physiological response of tumours to drug treatment or radiotherapy. Changes in the permeability of cerebral glioma have been observed in response to steroid therapy and to the bradykinin analogue RMP-7 [31, 32] and reductions in tumour perfusion have been reported following successful lymphoma chemotherapy and during treatment of metastatic colon cancer with BW12C [29, 33]. Radiotherapy induced changes in tumour perfusion and permeability have been reported by Harvey et al. [34, 35].

The recent development of combined PET/CT imaging systems affords new opportunities for the simultaneous in vivo evaluation of tumour angiogenesis and glucose metabolism. Cellular biology has indicated a link between these processes in tumours, a fact reflected by an observed correlation between CT perfusion values and fluorodeoxyglucose (FDG) uptake on PET [16, 36]. However, the *relative* intensities of angiogenesis and glucose metabolism may more closely relate to tumour aggression than either process alone, with more advanced and more aggressive tumours demonstrating a relative excess of angiogenesis and perfusion [37]; thus, using integrated PET/CT systems to combine these two imaging parameters offers the potential for advanced characterisation of tumour behaviour.

Conclusion

Within cancer imaging, functional CT can provide a useful adjunct to the anatomical information afforded by MDCT, aiding with tumour diagnosis, risk stratification and therapy monitoring. Although the volume of tissue studied by current functional techniques is limited, novel techniques that combine SPV measurements with the rapid imaging feasible with 16-channel MDCT systems have the potential to image large tissue volumes with multi-planar reconstructions. By simultaneously assessing tumour vascularity and metabolic demand, the broader expansion integrated MDCT/PET imaging will support highly sophisticated assessments of tumour biology within a single examination.

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