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Review

Novel imaging techniques as response biomarkers in cervical cancer

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ABSTRACT

The use of novel imaging techniques that have the ability to evaluate tumour biology and function shows a great deal of promise in providing early surrogate biomarkers of response to therapy which may allow for individualised or patient-specific regimes. This would have considerable clinical benefit in allowing for a treatment regimen tailored accordingly to meet the expected response, thereby reducing morbidity. Several of these imaging modalities such as dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DW-MRI), MR spectroscopy (MRS) and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) are now being introduced into the field of gynaecological oncology, with the majority of work being performed on cervical tumours. This review examines the use of these functional imaging techniques as response biomarkers in cervical cancer.

Contents

The management of advanced cervical cancer remains a significant challenge as many women fail to respond to recommended therapy [1], resulting in disease progression and ultimately patient death. Due to patient as well as tumour heterogeneity, it is rare for all cancers of a particular type to respond to a specific therapy, and as a result, many women continue to receive therapy from which they will derive little or no benefit. This undoubtedly leads to increased toxicity and morbidity, as well as undue costs. In addition, once therapy failure is detected months or years following completion of primary treatment, salvage options are poor.

There is now a trend toward cancer research directed at providing individualised therapy, and paramount to this is the development of biomarkers of response that have the ability to predict or detect early response to treatment. A predictive marker would be clearly beneficial in allowing the administration of a tailored regime for each patient while reducing toxicity and cost. Current prognostic markers such as tumour stage and grade are obviously deficient in providing an individual assessment of heterogeneity and therefore individual

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response, while chemosensitivity assays and DNA array technology are as yet difficult to translate into routine clinical practice.

It is now clear that significant potential lies with the advent of functional imaging techniques that are able to characterise biological tissues at the cellular level and provide molecular and metabolic information. This ability to non-invasively integrate physical and metabolic information has ensured that novel imaging techniques are one of the frontrunners in research aimed at discovering biomarkers of early tumour response to therapy.

This includes techniques such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), diffusion weighted MRI (DW-MRI), magnetic resonance spectroscopy (MRS) and F-18-fluorodeoxyglucose positron emission tomography (FDG-PET). As response biomarkers, these techniques have not yet been fully explored in gynaecological malignancies, although preliminary reports highlight their potential. In women with advanced cervical cancer, a rapid response predictor would provide a window of opportunity to alter therapy regimes. For example, this may include intensification of radiation dose, changes in concurrent chemotherapy, as well as the use of novel, experimental clinical therapies. It is the aim of this paper to introduce the use of these functional imaging techniques in cervical tumours, summarise the basic principles and provide insight on their proposed clinical utility for the future.

DCE-MRI

Basic principles

DCE-MRI has the ability to non-invasively characterise tissue vasculature including the anti-angiogenic response of tumour tissue during therapeutic intervention. By providing additional insight into tumour perfusion and capillary permeability, this technique allows evaluation of treatment response more readily than delayed assessments of tumour size.

Dynamic MRI involves the acquisition of sequential images during the passage of a contrast agent through a particular tissue of interest. Gadolinium-based contrast agents, such as gadopentetate dimeglumine, have a sufficiently small molecular weight to allow visualisation of lesion vasculature and are commonly used to assess vascular permeability. Following intravenous administration, the contrast agent travels through the vascular system, immediately leaks from the tumour vasculature, accumulates in the tumour and then rediffuses back into the vascular system, eventually being eliminated via the urinary system [2].

Dynamic imaging can depict the distribution of this agent by measuring variations in vessel and tissue enhancement over time. Moreover, the intensity of the enhancement has been shown to be related to the vascular density within tissue, while the rate and washout of enhancement is related to angiogenic factors such as microvessel density (MVD) and vascular endothelial growth factor (VEGF) [3-5]. Variations in contrast enhancement are associated with specific histopathological features of the tumour [6], with more aggressive tumours commonly exhibiting a more rapid and intense enhancement and washout, representing a higher vascular density and strong expression of VEGF. Response to therapy leads to a reduction in vascular permeability of the neoangiogenic vessels known to the present in tumours, and this is reflected by a decrease in the rate of enhancement.

Dynamic T1-weighted imaging is used to observe the extravasation of contrast from the vascular space into the interstitial space, supplying information on blood volume and microvascular permeability. T2* or susceptibility-weighted MRI can also be used to observe the transient first-pass effect of contrast, providing information about perfusion. Analysis of dynamic contrast-enhanced images and placement of a region of interest allows the generation of signal intensity versus time graphs which enable measurement of maximum enhancement, peak enhancement and rate of peak enhancement, as well as enhancement gradient or signal enhancement ratio (SER).

Relevant pharmacokinetic modeling parameters can also be determined for a defined region of interest on the image of choice, further allowing integration of function and form [7,8]. These quantitative perfusion parameters include the volume transfer constant, Ktrans, and the rate transfer constant, Kep, (Fig. 1). Also encouraging, is the ability of DCE-MRI to visualise the heterogeneity in angiogenic properties within an individual tumour. This is crucial in assessing early therapy response and individualising treatment regimes as it may allow for identification of a small subpopulation of tumour cells that remain resistant to treatment.

DCE-MRI in cervical cancer

DCE-MRI has been investigated in various studies as an early indicator of tumour response to therapy. The majority of this work

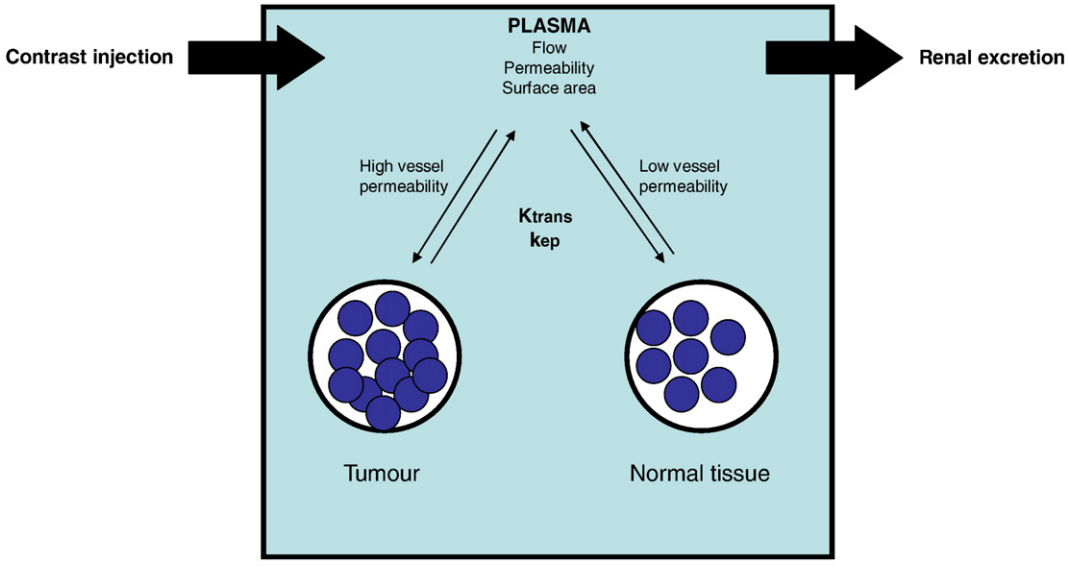

Fig. 1. Factors involved in contrast enhancement: ktrans, volume transfer constant; kep, rate transfer constant.