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STATE-OF-THE-ART IMAGING FOR DETECTING CANCER IN THE CLINIC

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Introduction

Imaging is a key aspect of cancer diagnosis and staging, underpinning patient stratification, the selection of appropriate therapies and their subsequent management. Currently morphological imaging is the standard, with lesion diameter according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria [1] forming the mainstay of subsequent follow-up. However, mere measurement of lesion size is a poor indicator of the nature of the lesion, whether it represents viable or necrotic disease, whether it is rapidly proliferative or dormant, or of its metastatic potential, all of which determine outcome. Functional imaging approaches have the potential to more accurately characterise disease, and identify its extent, but there are a range of new techniques being developed that require validation for specific applications. Careful selection of the most appropriate state-of-the-art imaging techniques therefore is essential for cancer assessment in the clinic.
Evaluating the primary site

Morphological techniques such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the commonest diagnostic techniques used to stage cancer, detect enlarged lymph nodes, and lung or liver metastases. Functional imaging techniques such as Positron Emission Tomography (PET) with 2-[fluorine-1]fluoro-2-deoxy-D-glucose (FDG), also is used in staging some cancers e.g. lung and lymphoma [2,3]. In pelvic tumours however, MRI is superior to other imaging modalities for evaluating disease extent and is now an integral part of preoperative assessment in rectal, cervical and prostate tumours [4,6]. Although most MRI examinations are carried out using external coils, signal to noise ratio (SNR) of an MR signal can be dramatically improved by matching the coil size with that of the target by placing the coil as close as possible to the area of interest. Endorectal MRI is routinely used to assess prostate cancer. Preoperative assessment with endovaginal MRI allows detection of small ($\leq 1\text{cm}^3$) cervical tumours (sensitivity 87%, specificity 65%) and identifies the extent of parametrial spread (sensitivity 80%, specificity 91.3%) [7].

Application of diffusion sensitising gradients to the MR pulse sequence provides image contrast through measurement of the diffusion properties of water within tissues. In a highly cellular tissue, extracellular water would not be able to diffuse far during the MR observation period without being blocked by structural interfaces such as cell membranes; this would lead to a short diffusional path and a reduced apparent diffusion coefficient (ADC). Conversely, in cystic or necrotic portions of tumours with fewer structural barriers present, the diffusional path-length is associated with a high ADC value. ADC maps, derived from diffusion-weighted
imaging, can therefore provide a non-invasive measure of cellularity [8]. In the brain, diffusion-weighted MRI (DW-MRI) can separate tumour and peritumoural oedema with variable changes occurring within tumour tissue reflecting tumour heterogeneity. Diffusion tensor imaging adds information about directional dependence of molecular diffusion and helps in defining the relationship of the tumour to fibre tracts prior to surgical excision. In the breast, DW-MRI also has been used to detect cancer and identify extension [9,10]: ADC values for invasive ductal carcinoma are lower than for noninvasive ductal carcinoma. In the liver, a breath-hold technique allows relatively robust mapping of lesions in the right lobe although cardiac and abdominal wall motion reduce sensitivity in the left lobe. Early data is also showing that ADC may predict the response of hepatic metastases to treatment [11], as low pre-treatment ADCs correspond to a subsequent good therapeutic response. In the prostate, ADC values of malignant nodules appear significantly lower than in non-malignant prostate tissue [12]. This has particular implications for identifying the 30% of cancers that arise within the central gland. More recently, whole body DW-MRI using a free breathing approach with methods to incorporate multiple slice excitations is proving increasingly popular for assessing the total extent of disease/metastatic involvement.

In the absence of visible morphological lesions magnetic resonance spectroscopy (MRS) may be used to investigate the biochemical make up of tissue. MR visible nuclei (e.g. $^1$H) with different chemical bonds experience different local magnetic fields and give rise to signals at different resonant frequencies. Magnetic field strength, relaxation times, line broadening due to magnetic susceptibility effects, and radiofrequency coil efficiency all contribute to spectral quality. Acquiring MR signals from an array of voxels in single or multiple slices allows the metabolite distribution of each voxel to be represented as a map (Magnetic Resonance
Spectroscopic Imaging, MRSI). Three-dimensional MRSI has the advantage of covering an entire volume of interest and has been exploited clinically to evaluate/investigate metabolites in brain and prostate tumours [13,14].

For many cancers $^{18}$FDG PET-CT is emerging as a sensitive tool for the detection of primary, but particularly for detecting recurrent disease. The Health Technology Assessment of PET found evidence that $^{18}$FDG-PET improved diagnostic accuracy over alternatives in detection of colorectal and head and neck recurrence [31]. It is likely that evidence will grow for the role of $^{18}$FDG-PET and more disease specific PET tracers in detecting small volume recurrence before conventional imaging in many tumour types – as this happens the sensitivity may well surpass our understanding of the clinical implications of these findings and suitable strategies will have to be designed.

**Evaluating metastatic disease**

Surgical assessment of lymph nodes is still considered the gold standard but is costly, time consuming and can increase risks to the patient [16-18]. CT and MRI can be used to detect lymph node metastasis but cannot differentiate between benign and metastatic nodes. Ultra small particles of iron oxide (USPIOs) are lymph node specific contrast agents that can be administered intravenously to detect node metastases with MRI [19]. The particles are normally taken up by macrophages in the reticuloendothelial system of normal lymph nodes [20] which results in signal intensity loss in T$_2$-W and T$_2^*$-W images due to the susceptibility artefact from iron. Metastatic tumour within nodes does not take up USPIO and the nodes continue to
show high signal intensity. Unfortunately USPIOs have been administered solely within clinical trials settings and licensing for routine clinical use is pending.

For imaging bone metastases, Technetium disphophonate ($\text{Tc}^{99m}$MDP) scintigraphy has formed the mainstay, but is limited by lack of anatomical resolution, quantitation and the healing osteoblastic “flare” phenomenon following therapy. On conventional MRI, signal abnormalities persist despite tumour regression. Functional indices such as glucose uptake on $^{18}$FDG PET and water diffusivity on DW-MRI allow quantitative analysis [21] and can reasonably be applied as whole body protocols [22]. $^{18}$F-fluoride PET also may be used as an osteoblastic tracer although specificity problems are similar to those encountered with traditional MDP bone scintigraphy. However, the improved spatial resolution and the combination with CT clarifies exact anatomical location of a lesion [23,24]. Other PET tracers currently under evaluation include $^{11}$C methionine and $^{11}$C or $^{18}$F choline derivatives. The interest in choline has grown from evidence that malignant cells have elevated levels of choline and upregulation of choline kinase activity as a result of increased cell turnover. $^{18}$F choline PET-CT has shown potential both to upstage and downstage bone disease in prostate cancer compared to $\text{Tc}^{99m}$MDP bone scintigraphy [25,26].

Accurate mapping of hepatic metastases is crucial for treatment planning with gadolinium enhanced MRI the gold standard for small lesion detection [27-31]. Liver specific agents that either target hepatocytes and produce positive enhancement on T1W images (ie [Gd-EOB]-DTPA, Primovist® Bayer Schering Pharma Berlin; Mn-DPDP, Teslascan® Amersham Health, Oslo, Norway) or which target Kupffer cells causing signal loss on T2W images (ie. Ferumoxide,Endorem™) are also increasingly used. Choice of agent is often led by availability and operator preference. Hardware advances which allow 3D volume acquisitions have further improved lesion detection
DW-MRI is also very useful for lesion detection and assessment of response to treatment [33,34] and there is evidence to suggest that the combination of Mn-DPDP MR imaging and DW-MRI results in even higher diagnostic accuracy [35]. Ultrasound contrast agents can be used to characterise lesions but at the moment it cannot rival the 3D volume acquisitions of CT and MR [36]. Intraoperative contrast enhanced ultrasound however, has been shown to have a significant impact on surgical strategy compared to conventional intraoperative ultrasound [37].

**Prediction and early monitoring of treatment response**

In addition to conventional morphological and contrast enhanced studies, DWI-MRI is being widely used to assess treatment response [38-40] where changes due to cell swelling and apoptosis are measurable as changes in ADC at an earlier stage than subsequent conventional radiological response indicators. An increase in ADC values early after treatment initiation is associated with a subsequent reduction in tumour volume: a clear, substantial, and early increase in the ADC after successful therapy in drug sensitive breast tumors treated with Paclitaxel was potentially of great value in identifying response within a much shorter time scale than the associated changes in gross tumour volume [41]; in liver lesions <8cm³ in volume at presentation, DW-MRI predicted response by 4 or 11 days after commencement of therapy [42]. These observations are thought to be associated with an initial decrease in tumour cellularity in response to cell kill (and subsequent increase in extracellular space) reflected in an increase in tumour ADC value. Furthermore pre-treatment ADC values of primary and metastatic malignant brain lesions have been shown to predict response to radiotherapy: tumours with higher ADCs respond less favourably [43].
Similarly, in patients with locally advanced rectal cancer, low mean pre-treatment tumour ADC predicted for a larger percentage size change of tumours after chemotherapy [44]. These results are consistent with the hypothesis that a high ADC may be indicative of tumour necrosis and consequently greater resistance to treatment.

Future perspectives

As tumour hypoxia causes stress-induced cellular responses and reduces the effectiveness of many therapies, non-invasive hypoxia measurements are being explored to enable refinements in treatment planning, e.g. dose-boosting hypoxic areas of potential radiation resistance with intensity modulated radiotherapy (IMRT). Intrinsic susceptibility MRI (exploiting the paramagnetic properties of deoxyhaemoglobin) is being investigated as a biomarker of tumour hypoxia [45]. In addition, spectral absorption differences of oxy- and deoxyhaemoglobin assessed by optoacoustic (between 3 and 5cm depth) or optical reflectance (high resolution but only 1mm depth) imaging are being developed and possess the advantage of relatively low cost, portability and ease of translation. Increasingly, radiolabelled PET markers of hypoxia also will become available.

Proliferation is a feature of malignant disease and its measurement can provide a sensitive index of treatment response. The PET tracer 3-deoxy-3[^18F]-fluorothymidine ([^18F]-FLT) phosphorylated intracellularly by thymidine kinase 1 (TK1) accumulates in S phase cells where TK1 levels are increased [46]. ^18F-FLT accumulation correlates directly with immunohistochemical markers of proliferation, such as Ki67. Availability of this tracer will mean increased use of proliferation as a measure of tumour response to treatment.
Necrotic or apoptotic death, the aim of many therapeutic strategies, can be detected using MRS or radionuclide methods. Recently, we have shown an increase in unsaturated fatty acid chains with apoptosis and growth arrest using a diffusion weighted pulse sequence on MRS. $^{99}$mTc labelled Annexin V also can be used to image cell death utilising binding to exposed phosphatidylserine. A number of SPECT and PET based radio-pharmaceuticals exploiting this property are expected to become available as molecular probes within the next 5 years. In addition, ultrasound radiofrequency echo properties of tissue have been shown to change in association with apoptosis, providing potential for an early indicator of response.

As functional imaging methodology becomes available, is robustly reproducible and is validated, it will assume an increasing role in screening, staging and response assessment at all stages of the cancer patient’s pathway. The use of functional techniques also will be fundamental in assessing at an early stage not only whether a drug is therapeutically effective, but acting by its intended mechanism. The choice of appropriate functional technique for each application will remain critical and tailoring to each clinical question will be essential for an optimal outcome.
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