Eur J Cancer Clin Oncol, Vol. 25, No. 10, pp. 1399–1402, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Commentary

Nuclear Magnetic Resonance: a Diagnostic Aid in Oncology

J. DAGNELIE,* M. LEMORT* and M.C. SEGEBARTH†

**Institut J. Bordet, Radiology Department, 1 Rue Héger-Bordet, B-1000 Bruxelles, Belgium and †Hôpital Erasme, 808 Route de Lennik, 1070 Bruxelles, Belgium*

(A COMMENT ON: Silingardi V, Davolio-Marani S, Federico M *et al.* Bone marrow infiltration in hairy cell leukemia after interferon therapy detected by magnetic resonance imaging. *Eur J Cancer Clin Oncol* 1989, **25**, 209–213.)

THE PAPER of Silingardi *et al.*, published in this journal, provides a nice illustration of the use of magnetic resonance imaging (MRI) for the evaluation of tumor extension, taking advantage of some important characteristics of the technique: the high sensitivity for the detection of subtle tissue changes, the specific appearance of fat, and the ability to analyze a large region of interest in a single slice. The paper also illustrates some limitations of this method: the difficulties of quantifying objectively the MR signal intensities, and the limited tissue specificity.

Nuclear magnetic resonance (NMR) has gained considerable importance within the spectrum of diagnostic modalities. Currently, diagnostic applications of NMR provide mainly morphological information: tomographic images of the human body are obtained with the high spatial resolution (of the order of 1 mm), and with exquisite contrasts between soft tissues.

Magnetic resonance imaging (MRI) relies upon the measurement of nuclear signals generated by the hydrogen (^{1}H) nuclei (protons) in response to radio frequency (RF) pulses. The carrier frequency of these pulses is tuned at the Larmor frequency of the protons, in order to induce an efficient ('resonant') interaction between RF excitation and the protons.

Optimization of the signal-to-noise ratio and, concomitantly, of the spatial resolution, is the main requirement underlying the choice of the proton to focus upon with MRI. With ^{1}H MRI, one detects in particular the protons of the water molecules, the latter constituting the major component of biological tissues. Hence, the water protons generate by far the most intense NMR signals. Despite a much lower tissue concentration of the sodium (^{23}Na) ions, it has been shown also that ^{23}Na MRI has clinical potential, particularly for the examination of cerebral strokes [1]. The number of groups putting some effort into the development of this type of MRI is limited, however.

The MRI intensities in the ^{1}H images are mainly determined by the 'relaxation' of the water protons toward equilibrium, following excitation by the RF pulses. This relaxation behavior is a function of the macromolecular environment of the water molecules, and consequently may vary between soft tissues.

Hence, the MRI contrasts between different soft tissues are of intrinsic nature. They can be modulated by varying the timing within the RF pulse trains applied. Usually, one enhances the effect of either of the two relaxation phenomena taking place ('T2' or 'transverse' relaxation and 'T1' or 'longitudinal' relaxation), so that the MR images are either T2 or T1 weighted.

Usually, the MRI contrasts between soft tissues are considerable, provided appropriate timing of the RF pulse trains is being applied. Unfortunately, the NMR signal lacks specificity, and it happens that no contrast can be generated between tissues of different nature. As an example, it is difficult in the case of brain tumours to make a clear distinction between the tumor region and the surrounding

Accepted 20 June 1989.

edema. Contrast agents have been developed, the uptake of which is ruled by mechanisms very similar to the ones encountered with iodine contrast agents used in regular radiological practice. The mechanism of contrast formation is very different, however. The uptake of MRI contrast agents (for example the paramagnetic chelate Gd-DTPA) is observed indirectly rather than directly as is the case with iodine. The unpaired electrons of the Gd ion affect the relaxation behavior of the water protons located in the vicinity of the paramagnetic chelate. Hence, the MRI intensities are modified, for example in the case of brain tumors, in regions where a disruption of the blood–brain barrier has led to an uptake of the paramagnetic contrast agent. At present, no significant side-effects of the paramagnetic contrast media are known.

Bone tumors and bone metastases are particularly well analyzed by MRI [2]. In the evaluation of primary bone tumors, a clear assessment of the intraosseous extension is provided [3]. Replacement of the medullar fat by tumor tissue as well as skip metastases are demonstrated more confidently than with CT. Also the extraosseous extension is well assessed, relationships with vital structures such as blood vessels can be analyzed without the use of contrast agents, and extension into muscular or articular compartments is well demonstrated making use of the multiplanar possibilities of the technique. Subtle bone metastatic deposits can be detected early. This is particularly important for the diffuse form, for which high resolution CT is less reliable. Here also, the replacement of the normal medullary fat by tumoral tissue is observed.

The presence of *primary brain tumors* is usually better demonstrated by MRI than by CT [4]. Low grade astrocytomas may be demonstrated by MRI only. In general, tumor extension is better depicted, particularly when paramagnetic contrast agents are used. These increase the specificity of the method, permitting, in favorable cases, differentiation between tumor tissue and adjacent edema. However, the lack of specificity of the MRI intensities has caused some disappointment relative to the early expectations. Notwithstanding this limitation, MRI is currently a mandatory step in the pretherapeutic evaluation and in the posttherapeutic follow-up of primary brain tumors.

The detection of *brain metastases* may also benefit from MRI [5]. Without gadolinium, brain metastases are difficult to delineate. Edema, if present, is well seen, but the tumor nodule is less well demonstrated. With paramagnetic contrast enhancement, MRI proves more sensitive than contrast-enhanced CT for the detection of small metastatic deposits. Hemorrhagic metastases may be well demonstrated without the use of contrast agents. MRI is considered to become the method of choice for the detection of brain metastases in the initial staging of cancer patients.

Spinal cord tumors are better demonstrated by MRI than by any other diagnostic method. For the first time, the radiologist can see directly the cord parenchyma and evaluate its internal abnormalities. Tissue analysis of the spinal cord is, in contrast, rarely possible with CT, due to the bony environment of the spinal canal. Myelography or CT-myelography give information which is limited to the shape of the spinal cord. Here also, the use of paramagnetic contrast agents is useful [6], particularly in defining and outlining intra- and extramedullary spinal neoplasms, and in differentiating solid tumor components from syrinx, from cyst, or from pseudotumor areas of cord expansion. Contrast agents improve the sensitivity and specificity of the examination.

Extramedullary spinal tumors are equally well examined by MRI. Of particular interest for the oncologist is the ability to detect *spinal epidural metastases* [7], and to assess their association with bone lesions and repercussion on the cord. This is possible without intrathecal administration of any contrast agent, and avoids the application of the traumatic myelographic procedure. The search for epidural metastases is frequently an emergency procedure. MRI is the correct solution if an emergency access to the instrument can be guaranteed. Due to the limited number of installations, this is currently rarely the case.

For *head and neck tumors* [8], MRI is superior to CT, for the detection of tumor tissue as well as for the definition of the tumor limits. This is particularly true for lesions in a muscular environment, where contrast-enhanced CT may fail to demonstrate tumor tissue. The anatomical relationships of the tumor are better assessed with MRI than with CT, and the arbitrary orientation of the image plane facilitates the analysis of this complex anatomical region. Dental amalgams, which generate important artifacts on CT, generally do not harm the interpretation of MR images of the pharynx and buccal cavity. MRI, however, requires optimal cooperation of the patient, the examination time being rather long. Patients' movements often lead to degradation of the image quality, although they rarely preclude image interpretation. Also for this pathology, the MR image lacks specificity. There is some hope however, that differentiation between tumor and post-therapeutic fibrosis will become possible.

For the evaluation of the pathology of the *lungs, hili and mediastinum* [9], MRI is not useful, given the excellent results obtained with CT. It is, however, of great utility in accurately assessing the tumoral invasion of blood vessels and pericard. For this indication, multiple slice acquisition in sagittal or coronal directions is particularly important. MRI

is also beneficial for the evaluation of pleural or apical lesions, particularly in delineating soft tissue involvement. In addition, it has been said that MRI is more valuable than CT in the diagnosis of local recurrence of a tumor when pulmonary fibrosis has been induced by radiotherapy [10].

For *retroperitoneal* tumors [11], MRI is more efficient than CT in detecting lymphadenopathies, but it can not assess the tumoral involvement in a non-enlarged lymph node. Given the limited access to NMR facilities, MRI is applied only when the CT findings are doubtful. Tumors of the retroperitoneum (particularly tumors of the kidneys), are perfectly studied by MRI, given the natural contrast between tumoral tissue and perirenal fat, and given the absence of motion artifacts.

MRI has a particularly low sensitivity and specificity for the diagnosis of *primary pelvic tumors* and therefore has no role as a screening test in their detection. MRI provides a better picture of tumor invasion within adjacent organs, and a more accurate diagnosis of recurrence. MRI could be useful in studying the effect of a therapeutic irradiation.

Clinical indications for MRI in *senology* [12] are limited given the excellent results obtained by the combination of other diagnostic techniques. However, MRI can provide additional information in case of diagnostic difficulties. In particular, it can be helpful in deciding whether a radical mastectomy or a simple lumpectomy should be performed. MRI shares the same morphological signs with mammography with the exception of the microcalcifications, invisible with MRI. It has also its own semiology: disappearance of fatty lobules, internal structure of the lesions. In addition, MRI has the advantage of being a tomographic technique. MRI is not an appropriate screening method.

As to the *liver* [13], MRI provides a detection sensitivity of hepatic metastases and hepatomas which is very similar to that of other diagnostic methods. The specificity of the MRI examination exceeds that of the other techniques, however. In contrast, CT and ultrasonography are more accurate for the evaluation of pancreatic tumors.

Magnetic resonance imaging does not usually take advantage of the possibility offered by the MR technique to distinguish the MR signals generated by nuclei embedded in different chemical environments (MR spectroscopy or MRS). It is, for instance, possible to generate separate water and fat images, exploiting the faint differences between the Larmor frequencies of water and CH_2 protons [14]. Whereas this particular type of *in vivo* spectroscopic examination still mainly provides morphological data, usually the information content of the MRS measurement is of a metabolic nature [15]. Depending on the nucleus one focuses on, different metabolites can indeed be detected. For instance, in the case of ^{31}P MRS, the detected signals stem from a number of metabolites which play a key role in the energy metabolism of the cells, such as ATP, PCr, inorganic phosphate, and some phosphomono- and phosphodiesters. In addition to providing information about the relative concentrations of these metabolites, the ^{31}P MR spectra also provide a non-invasive way of measuring the tissue pH. In the case of ^{1}H MR spectroscopy, for instance of the brain, signals can be detected from *N*-acetylaspartate, alanine, creatine and choline compounds, and lactic acid. A large number of experiments performed on cells, on perfused organs, or *in vivo* on animals have demonstrated the potential of MRS in providing clinically useful information about tumors. Preliminary human studies on brain tumours have been reported recently [16, 17]. While these studies have confirmed the clinical potential of the technique, they also have demonstrated a number of difficulties which remain to be overcome in order for the technique to be applicable routinely in the clinical context.

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