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ABSTRACTS OF PAPERS

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SAMENVATTINGEN VAN DE UITEENZETTINGEN

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RESUMES DES COMMUNICATIONS

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The specificity of oncological imaging

M. Lemort[1]

It has now become common sense to say that treatment paradigms in oncology are changing. From large range, toxic, deleterious treatments that had only a very small margin of benefit we are now going to targeted, more specific, more effective therapies. This change challenges research mechanisms, treatment habits and health economics. Even if cancer is a widespread disease and a major cause of chronic illness and mortality, costs of large-scale research and development of a competitive business model begin hampering innovation.

Diagnostic imaging being a tool of primary importance to assess the progress of disease and to give objective data on efficacy of a given treatment, it unavoidably has to take into account this paradigmatic change in therapy. Till now, radiology has had as first objective to detect and diagnose lesions based on morphological images and clinical data in the organ or area of concern. Primary lesions were first sighted, and then if it was going wrong, individual metastases. Then, if a classical treatment was applied, response criteria were disappearance of the lesion(s), or a (large) reduction in size (often coarsely measured).

It is evident that clinicians and researchers on one side, industry on the other side are now demanding that we adapt our methods to design new imaging biomarkers that could be surrogate markers for therapy monitoring, giving earlier indications of treatment success and outcome. This implies not to rely only on anatomy and size measurements, but on other characteristics of the tumour such as metabolism or microenvironment. Physiological imaging or metabolic imaging (using or not specific tracers) is to be implemented. In-depth knowledge of both the common characteristics of cancer cells or tumours and the tools to explore these are then required.

In addition, since cancer is by nature not a disease limited to an organ but has to be considered from the start as a potentially generalized disease, oncological radiology does not comply very well with the organ-oriented subspecialisation which is very common in our profession. There is a so-called transversal component complementary to the vertical, organ-oriented, subspecialisation that forces oncological radiologists (which are not a legion) to have a more holistic approach of the patient. The same is true for the multidisciplinary interaction in the oncology centre. Even for such an – apparently – simple problem as size measurement of lesions, mastering of response criteria such as RECIST 1.0 or 1.1 that could imply measurements of multiple lesions in multiple organs is no easy task. Physiological and metabolic imaging often overshoots the limits of an organ or system and may require a whole-body approach. Development of novel imaging biomarkers imply a global careful thought from imaging specialists on standardisation and quality assurance, before large clinical trials can validate the approach. This is what we will try to do notably in the Imaging Group of the EORTC.

This is why I think oncological imaging has a specificity which has to go beyond the traditional subspecialties of diagnostic radiology and also beyond the anachronistic distinction between radiology and nuclear medicine which is for me more and more nonsense.

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New trends in cancer therapy, new needs for imaging markers

M.J. Piccart-Gebhart, K. Saini[1]

This is an exciting time in oncology. The past decade has seen a vast expansion in our knowledge about the basic biology of cancer. This has been made possible by advances on several fronts, including sequencing of the whole genome, the use of microarray technology, development of gene signatures, unravelling the signal transduction pathways, modulation of apoptosis and angiogenesis, gene silencing using RNAi, laser capture microdissection, use of targeted therapy, advanced bioinformatic algorithms, the use of nanotechnology in drug delivery, and advanced imaging techniques.

Imaging technology has made remarkable progress in the recent past, and multi-slice spiral CT, high Tesla MRI, digital mammography, and PET are everyday tools in many cancer hospitals. Multimodality imaging, especially the combination of PET and CT has matured into a valuable tool, and FDG-PET-CT has been widely adopted for diagnosis, initial staging, and response assessment in various malignant tumors with high diagnostic accuracy. While the development of integrated PET/MRI is technologically more challenging, advanced prototypes are already available. Monoclonal antibodies labelled with positron-, gamma-emitting molecules, optical dyes, or paramagnetic contrast agents are used for PET, SPECT, optical, and magnetic resonance imaging, respectively. Non-FDG tracers under development for oncology applications include markers of hypoxia, tumor proliferation; and amino acid metabolism. In addition, new tracers that bind to specific intra- or extra-cellular targets (eg. HER2 receptor) are being developed.

Overexpression of the HER2 protein is seen in about 20% of invasive breast cancers. Such cancers are associated with high recurrence rate, shorter disease free interval, a propensity for cerebral metastases and decreased survival. Molecular imaging of HER2 can therefore facilitate a tailored approach based on specific tumor characteristics of individual patients. Because of the inherent heterogeneity of breast cancer and possible discordance in HER2 status between primary tumors and distant metastases, a non-invasive method like molecular imaging is needed to assess HER2 expression.

Molecular PET imaging using radionuclide-labelled trastuzumab is currently undergoing human trials, and is expected to help select patients for appropriate anti-HER2 therapy. More importantly, serial molecular imaging will help differentiate between responders and non-responders. This early readout of drug efficacy will thus modulate future treatment and help deliver truly "personalized medicine".

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How to scan a patient in a clinical trial?

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In order to accelerate validation of new drugs in oncology and reduce costs,

clinical trials endpoints are often based on response rate (observable and measurable tumor shrinkage directly linked to drug effect) or time to progression as surrogate of overall survival, meaning that radiology is a cornerstone in clinical trial evaluation.

Imaging plays 3 roles in clinical trials: detection, characterization and quantitative assessment. The first 2 receive most attention in radiologists training, the latter less.

Quantitative assessment is nevertheless of utmost importance as a decrease in variability of measurements permits to reduce cohort to be investigated to study drug effect.

CT is the most routinely used technique in oncological trials evaluating effects of tested new drugs as it can explore quickly all body, as it is an easily reproducible examination, widely available and not too expensive to use.

Parameters of acquisition of the CT system as slice thickness, reconstruction intervals, KV and mAs, field of view, IV injection of contrast protocols, iodine contrast load, use of oral contrast, coverage of body to be scanned must be clearly defined to insure reproducibility of examinations and should be applied throughout the study for each enrolled patient.

In case of contra-indication of iodine contrast media, abdomen and pelvis can be studied by MRI. Sequences must be clearly specified. Examination will be completed by a plain chest CT to screen and follow lung metastasis.

At this point in time tumor evaluation remains mostly based on anatomical measurements as functional imaging is still neither sufficiently standardized nor widely available, with the exception of FDG-PET in specific situations.

To document objective response to treatment, radiological examinations are assessed utilizing specific criteria fitted to the tumor studied. The oldest and less codified is WHO bidimensional measurement. RECIST 1.0 and now new version 1.1 are tools to follow solid tumors. Cheson criteria are adapted to follow lymphoma. More specific criteria are needed as some new medications do not provoke tumor shrinkage: Choi's criteria for the follow-up of GIST are not only based on tumor dimension but also on internal density modifications due to treatment. New criteria are needed to assess effect of non cytotoxic drugs.

Specific training must be organized for each study to reduce variability between readers, as this is a FDA requirement.

Most clinical trials are multicenter and for phases 2, 3 and 4 enroll a large number of patients. Care must be taken to assure a constant imaging quality through accreditation of medical devices. Most studies impose the follow-up of patient on same equipment.

For new drug approval by regulatory agencies like FDA or EMEA, centralized review is organized in addition to local radiologist work, with interpretation performed by 2 independent reviewers and an adjudicator in case of disagreement.

Transmission of anonymized data to imaging core lab is now facilitates by PACS electronic archiving with DICOM standard. When coping with clinical trials examinations, care must be taken not to compress data to be compliant with FDA rules.

In conclusion, it may be said that radiologists play a key role in oncologic clinical trials as tumor response is actually mostly based on anatomic measurements.

Reproducibility in the data acquisition parameters, lesion measurements and assessment in accordance with specific criteria adopted in clinical trials are of utmost importance.

In the future new imaging techniques based on physiologic effects of drug showing earlier changes than tumor size regression will be utilized but they are at this time considered not widely enough accessible or not sufficiently reproducible for multicenter large scale clinical trials and they must still be validated by regulatory agencies.

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Automated diagnosis from brain cancer metabolism

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Magnetic resonance spectroscopy methods can be employed to study medical problems both *ex vivo* and *in vivo*. NMR spectroscopy *ex vivo* by classical, vertical-bore instruments is often used to obtain metabolic profiles of cancer cells and tissues. Solid biopsies can be studied by HR-MAS NMR or by perchloric acid extraction. A typical problem would be comparison of a tumour cell line with a single gene knocked out (or over-expressed) against the normal or "wild-type" cells in which that gene was functional. The data obtained a set of concentrations of tissue metabolites, is a subset of the metabolome – the totality of small-molecule metabolites in an organism, cell or disease state – and is termed a "metabolic profile (Griffiths & Stubbs, 2005).

Data analysis methods such as principle component analysis (Raamsdonk et al., 2003), and pattern recognition (Tate et al., 2006) are often necessary to visualise these complex datasets. I will show the use of use of a relatively new method: metabolite-metabolite correlation analysis (Kose et al, 2001). These correlations maps are helpful in understanding the perturbed metabolic pathways in the cells due to gene modifications, enzymatic modulations (inhibition/over-expression), toxic and/or drug effects and nutrient supply. However, although NMR of the metabolome is proving to be a very useful scientific technique it seems unlikely that studies of patient biopsies by this method will have a routine clinical role as there are many established methods for studying biopsies *ex vivo*.

A routine clinical use for MRS is more likely to be found *in vivo,* although attempts to develop one have been fraught with difficulties. The history of MRS (i.e. NMR spectroscopy *in vivo*) is almost as long as that of MRI. The first rat muscle spectra were produced in 1974 (Hoult et al., 1974), the year after Lauterbur and Mansfield independently demonstrated MRI. At first it was by no means clear that MRI would be clinically useful, and the unique ability of MRS to detect and quantify metabolites non-invasively in living tissue seemed at least as promising as the low-resolution soft tissue images from the early MRI instruments. However, during the 1980s and early 1990s MRI rapidly became an enormously important clinical imaging method, revolutionising the diagnosis and management of many diseases. In contrast, MRS is still looking for a routine clinical role more than 30 years after it was introduced, even though it has become well-established in many areas of medical research.

The number of metabolites detected by MRS *in vivo* is much smaller than with the *ex vivo* methods. By ^{1}H MRS of tumours *in vivo* it is usually possible to detect lactate, lipids, a "total choline" peak, creatine, myo-inositol and N-acetyl aspartate. Despite this limitation many studies have shown that ^{1}H MRS can give useful information about brain cancer (Howe et al. 2003), and it would be easy to integrate it into a conventional radiological MRI examination (it adds around 20 minutes to a session). Also, the current diagnostic procedures leave much to be desired. Although MRI gives exquisitely detailed images and the radiologist can often give a fairly confident diagnosis, the definitive diagnosis and the grading of malignancy are still made by the histopathologist from a biopsy of the living brain, a very unpleasant procedure with significant risks of haemorrhage causing stroke-like paralysis, and even death. However, even though the existing method is unsatisfactory and even though addition of ^{1}H MRS to routine radiological examinations, can substantially improve diagnosis and grading without requiring a brain biopsy, there has been no widespread clinical adoption of MRS for brain tumour diagnosis. One possible reason is that few radiologists are skilled at MRS interpretation, a method that is very different from the subjective image analysis in which they are trained. To try and eliminate that bottleneck, two multi-centre EU programmes (INTERPRET and eTUMOUR) have developed an automated pattern recognition method that requires no biochemical knowledge (Tate et al., 2006), and combined it with a large database of spectra obtained from brain tumour cases with validated diagnoses. An anticipated problem that was overcome by this method was the subtle differences between spectra produced by different manufacturers' instruments or different pulse sequences (e.g. STEAM and PRESS): the program was successfully trained to ignore them.

The pattern recognition computer programs developed by INTERPRET and eTumour use the "raw" spectrum (i.e. without any manual quantification of the peaks). The INTERPRET prototype presents the results in a Decision Support System (DSS) that allows the radiologist (or other clinician) to integrate the new information into a conventional clinical diagnostic procedure. This procedure is designed to give the physician useful help in situations in which there are inadequate numbers of spectra of a rare type of cancer in the database, or even none at all. The eTumour method (CADS) is more automated, and the results are presented with a numerical probability for each alternative diagnosis.

Conventional radiology classifies tumours with a specificity of 85-100%, though sensitivity is much more variable and some tumour types (high-grade meningiomas and low-grade oligodendrogliomas, for instance) are poorly diagnosed at present (Julià-Sapé et al, 2006). An unpublished blinded trial on the use of the INTERPRET DSS on 50 consecutive brain tumour patients (Margarida Julià-Sapé, Carles Arús and colleagues) has shown that diagnosis of gliomas by radiologists is significantly improved when they are given the results from the DSS. A trial of the eTumour method (Monleon et al., 2010) gave roughly similar results. There is clearly scope for improving radiological diagnoses of brain tumours by the use of these decision support systems and MRS databases, but optimisation of the way they are used by radiologists is still required. Large trials will be necessary to demonstrate improved diagnosis of individual tumour types.

If the these decision support systems go into regular clinical use we will have to find ways to constantly update the database of spectra on which they depend, as MRS technology will continue to change and histopathological classification will doubtless improve. In the long term it is not impossible that a non-invasive radiological method utilising MRS data could give a better prediction of disease outcome than conventional histopathology, but we will need to acquire extensive long-term response data to test that idea.

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From tissue to the cellular level: diffusion-weighted MRI and MR spectroscopy

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At the time of diagnosis of malignancy, determination of locoregional disease extent and detection of potential distant metastases is important for treatment planning and assessment of patient prognosis. In the post-treatment phase, accurate and, preferably, timely assessment of the patients response to treatment is necessary in order to detect tumour recurrence at an early stage and thus enable salvage treatment with curative intent. Additionally, non-surgical treatment such as RT, chemotherapy and the novel generation of targeted cytotoxic and antivascular agents do not necessarily lead to a decrease of tumour volume as a result to treatment, especially in the early treatment phase requiring. As such, specific imaging biomarkers are required.

The reliance of morphological and size-related criteria confront conventional MRI to a certain extent with similar limitations as computed tomography (CT) for lesion characterization, and differentiation of tumoral recurrence as treatment induced inflammation and fibrosis.

Similarly, in the non-surgical treatment of malignancy the response evaluation criteria in solid tumours (RECIST) may fall short to accurately separate responders from non-responders.

Early detection of treatment effects and thus the early separation or responding from non-responding lesions may help to guide treatment escalation or change of treatment strategy in case of non-favourable response, while toxic side-effects may be avoided in non-effective treatment. In this setting, diagnostic imaging modalities that probe the tumoral microstructure or metabolism may be useful as they do not depend on lesion morphology, size or volumetric changes for lesion characterization.

Mainly due to the technical challenges, the clinical application of magnetic resonance spectroscopy (MRS) remains limited to a number of anatomical subregions and strict clinical indications. Development of MRS has been focussed on applications in brain tumours, prostate cancer and breast tumours. MRS in combination with anatomical sequences may provide more detailed information about a tumour's location and extent of its infiltration in the surrounding tissues. Furthermore, MRS may be useful for treatment monitoring and to guide biopsy procedures. Although the technique has already been researched for nodal staging in breast cancer and the head and neck, further technique optimization and especially improvement of spatial resolution is required in order to show additional value for characterization of subcentimetric lymph nodes.

Diffusion-weighted magnetic resonance imaging (DWI) is a non-invasive imaging technique that measures differences in water mobility between different tissue microstructures. The water mobility is influenced by cell size, density and cellular membrane integrity, and is quantified by means of the apparent diffusion coefficient (ADC). The ability to measure small differences in tissue microstructure enables DWI to differentiate tumoral tissue from normal tissue and inflammatory or necrotic tissue. Currently, DWI is often used for imaging of body-regions (for instance: liver, head and neck, pelvis,....) as a problem solving technique complementary to CT or fluorodeoxyglucose positron-emission tomography (FDG-PET); for instance in the detection of small liver metastases. In addition, DWI shows value for tumour differentiation and primary tumour detection, locoregional staging (primary tumour and regional lymph nodes), characterization of metastases and early assessment of treatment effects. One of the major advantages of DWI in the recent past years has been the rapid technological development which makes the technique suitable for whole-body imaging. This may be of use for tumour screening and staging and may show value in the treatment follow-up or prediction of patients with systemic cancer spread like, for example, lymphoma or metastatic solid tumours like neuroendocrine tumours, breast cancer and colorectal cancer, where the treatment with antivascular and targeted cytotoxic compounds may lead to heterogeneous tumour response.

In the presentation, advantages and disadvantages in the application of MRI and DWI will be outlined as well as their potential complementary value to anatomical and metabolical imaging modalities. In addition development for clinical applications will be discussed.

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Chemical Shift MR imaging in pre-operative evaluation of prostate cancer: ready? validated? challenging?

T. Scheenen[1]

In order to improve the non-invasive detection of cancer in the prostate, its location, grade and stage, several MR techniques have been and are being explored. Before prostatectomy, it is of great importance to know the location and extent of the tumour to assess the risk of positive resection margins and to assess the possibilities of a nerve-sparing operation. Among the different MR techniques, chemical shift MR imaging (CSI) has shown promising results. With the CSI technique MR signals of molecules other than water and fat are studied. From every voxel of an imaginary three-dimensional box around the prostate (Figure 1), spectra are constructed with signals from protons from metabolites at characteristic positions (the so-called 'chemical shift'). Multiple studies have shown significant differences in the metabolic state of different tissue types as depicted by CSI. Prostate cancer tissue is characterized by reduced levels of citrate (Ci) and increased levels of choline-containing compounds (Cho), which both are detectable *in vivo* with CSI together with signals from creatine (Cre) and polyamines. In the multi-centre IMAPS (International Multi-Centre Assessment of Prostate MR Spectroscopy) study at 1.5T, CSI was validated for prostate cancer localization throughout the gland, and its reproducibility was assessed. At 1.5T, CSI of the prostate is usually performed with an endorectal coil for reception of the MR signal. With the steady increase in availability of 3T MR systems, CSI has also proven its value at this high-

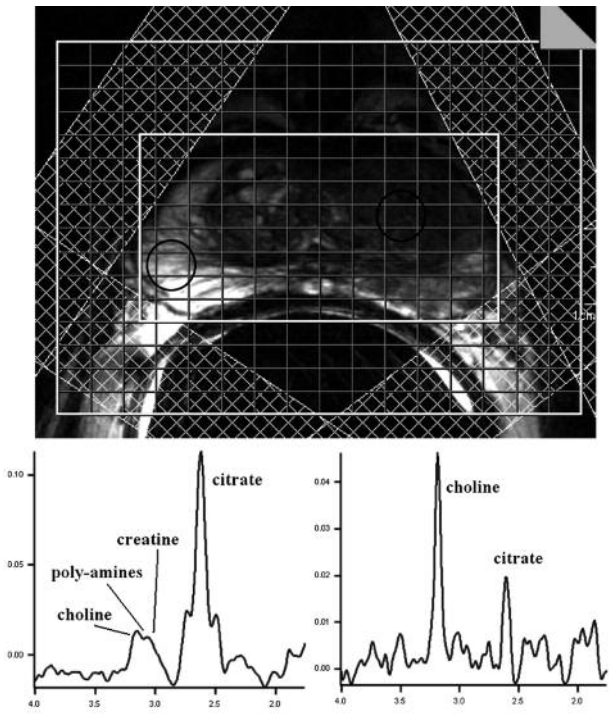

Fig. 1. — Axial T2-weighted MR image of the prostate of a patient with prostate cancer at 3 Tesla. From two voxels, indicated with a sphere, the spectra are shown: one in healthy peripheral zone (left) and one in a cancer focus (right).

er magnetic field strength in single institution studies, and possibilities for measurements without endorectal coils have been investigated. Recently, new possibilities at 7T were explored for CSI of the prostate at unprecedented spatial resolution.

Within the IMAPS study, 99 untreated patients with proven prostate cancer from 8 different institutions underwent T2-weighted MR imaging and 3D CSI with an endorectal coil at 1.5T. After the MR exam, patients were treated with a prostatectomy, and the histopathological analysis of the resected prostates was the gold standard for the presence and location of cancer. Ten other subjects underwent the MR examination twice, to assess the reproducibility of the technique. Based on the gold standard, blinded from the CSI spectra, a selection of voxels was assigned to peripheral zone (PZ), central gland (CG), peri-urethral area (U), and cancer (PCa) tissue. After fitting the spectra and visual quality control values for the (Cho+Cr)/Ci ratio (CC/C) were evaluated as a marker for tumor tissue. Mean values of this metabolic ratio for PZ, CG and PCa were significantly different. Within non-cancer tissues, but between patients of different institutions, no statistically significant differences were found, and the within subject differences of the reproducibility study showed smaller standard deviations within a subject than across subjects. The area under the ROC curve, discriminating between cancer and non-cancer tissue was 0.88 for PZ and 0.76 for the combined CG & U. In a different, prospective multi-center study in the United States no clear additional benefit of CSI over T2-weighted MRI alone was found in the localization of cancer within the prostate. As this study was undertaken without validation of the at that point relatively immature measurement technique, without a clear definition of tumor sizes to be detected, and with – still existing – matching difficulties between histopathology and MRI, its results were disappointing. In both trials, a visual quality control after semi-automatic fitting of all data is still a necessity, as this process has not been automated in a robust and trustworthy way, which is the current hurdle to overcome before easy introduction of the technique into clinical routine.

At 3 Tesla it has been shown that in a validation setting the CSI technique with only an array of external coils can produce almost equal results to CSI with an endorectal coil at 1.5 Tesla. Currently, more efforts are underway in a broader setting to not only validate this technique in a combination with other MRI techniques, but also to assess its diagnostic value in the localization and grading of prostate cancer. The current greatest technical challenge can be found at the ultra-high field strength of 7 Tesla, at which the first volunteers have been measured with CSI techniques of not only protons, but also of phosphorus nuclei, offering potential for a more fundamental insight in the disease.

In short, it can be stated that CSI of the prostate in the localization of prostate cancer is validated: it is a robust and quantitative technique producing similar results across different institutions. Once post-processing is fully automated and reliable (currently a shared challenge among vendors and clinical institutions), the technique is ready for introduction into clinical routine. The greatest challenges of the CSI acquisition technique can currently be found in ultra-high magnetic field strengths.

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Whole-body MRI: achievements and expectations

F.E. Lecouvet, P. Omoumi, J. Malghem, B. Tombal, B. Vande Berg[1]

Whole body-MRI (WB-MRI) has emerged for several years as a new imaging technique. It enables the study of the complete skeleton, but extends its indications to the study of almost all organs of the body.

The development of the sequences and coils, as well as the major input of diffusion-weighted imaging, contribute to establish WB-MRI as one of the leading imaging approaches of cancer, challenging and outperforming other techniques and current multimodality diagnostic algorithms used to stage cancer.

The technical bases of image acquisition and reconstruction, recommendations for image reading and interpretation, limits and pitfalls of WB-MRI can be illustrated by practical examples.

The challenges for the radiologists include adequate protocol design, highly dependent on the targeted cancer, disease-oriented whole organ screening, huge information management, and knowledge of limits and some confusing findings at WB-MRI.

The next challenges are the use of WB-MRI surveys to quantify metastatic disease and evaluate the response of this disease to treatment.

The fundamental clinical and therapeutic issues and the role of WB-MRI in the modern management of cancer patients will be illustrated.

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Working together: data integration of CT and MR with PET and SPECT

P. Flamen

Medical imaging has undergone a tremendous development over the last three decades. Diagnostic information provided by the structural imaging modalities, essentially based on alterations of morphology, structure and anatomy, was complemented by functional (ultrasound, dynamic CT, diffusion and perfusion MRI) and metabolic or molecular information provided by nuclear imaging techniques (PET and SPECT). The success of PET is based upon the high avidity of most malignant

tumors for FDG, a surogate marker of glycolysis, its whole body field of view, and, most importantly, on its integration with CT scan, leading to the currently standard PET-CT technology. Integrated PET-CT resulted in a significantly higher diagnostic confidence of both modalities through continuous cross checking of structural and metabolic aspects of diagnosis. This proofed invaluable for restaging disease after surgery or ablatif techniques, or after chemo or radiotherapy, because in these conditions accurate diagnosis of residual or recurrent tumor activity, utmost important from a prognostic point of view, was often difficult using stand alone radiological techniques because of the treatment induced non-specific structural changes. The lecture will deal with the future developments of multimodality imaging (PET-SPECT-CT-MRI) and how further image integration will impact on the personalized cancer patient care of tomorrow.

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ABSTRACTS OF PAPERS FOR FULL MEMBERSHIP

RESUMES DES TRAVAUX DE TITULARIAT

SAMENVATTING VAN DE TITULARIAATSWERKEN

CHEST

18F-FDG PET-CT and Fever of unknown origin

B. Arys[1]

Fever of unknown origin (FUO) is frequently a challenging diagnostic problem.

The present retrospective study evaluates the role of PET-CT using 18F-FDG in the investigation of FUO.

Methods: A total of 97 patients (42 men, 55 women, age range 13-84 years) underwent a 18F-FDG PET-CT scan for the clinical problem of 'febris e causa ignota' over a time period of 5 years.

The performance of PET-CT in identifying the etiology of the FUO was assessed.

Final diagnosis was based on histopathology, microbiology, clinical follow-up and imaging follow-up.

*Results:*PET-CT detected suggestive foci of increased 18F-FDG uptake in 50 patients (51.5%). In 82% of these patients a final diagnosis was made. We found an infectious or inflammatory pathology in 35 patients, a responsible benign neoplastic cause in 2 patients and a malignancy in 4 patients. In 14% of the patients with a suggestive focus on PET-CT the result was false positive, as confirmed by other diagnostic means. 2 patients in this group were lost for follow up.

18-FDG PET-CT was negative in 47 patients (48.4%). 42 patients in this group were true negative and no cause for the FUO was found in follow up (follow-up period 12-48 months). In 5 patients a final diagnosis was reached by other means of investigation. 3 of these patients had a systemic infection, 1 patient had an erysipelas and 1 patient had a poorly differentiated gastric carcinoid tumor.

*Conclusion:*In an overall patient population with FUO an infectious or inflammatory cause is found in 41%, in 5.3% malignancy is found, in 2.1% a benign neoplastic cause and in 51.6% no cause is found.

18F-FDG PET-CT identified the underlying infectious of inflammatory pathology in 89.7% in the current study population. Underlying neoplastic processes were identified in 85.7%. The overall usefulness of PET-CT for diagnosis or exclusion of pathology was in this study 87% with a negative predictive value of 89% rising to near 100% for diagnosis or exclusion of focal pathology.

Thanks to the high sensitivity, high specificity and the high negative predictive value PET-CT is a very useful diagnostic modality for assessment of FUO. It should however find its place as a second line diagnostic approach after a previous accurate workup. Further prospective studies are needed to confirm these findings.

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