EARLY DIAGNOSIS AND SPACE OCCUPYING DISEASE AN EVER INCREASING COMPLEX PROBLEM

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SUMMARY

Several non invasive imaging procedures are discussed. Clinical strategies are introduced as a concept for their future utilization. Notions of sensitivity, specificity, predictive value and accuracy are defined and named as the basic tools for the implementation of such strategies.

Doctors are concerned about diagnosing space occupying disease at an early stage. It is hoped that the early recognition of pathology will allow for appropriate staging of the disease. Planning of the most adequate form of treatment will eventually lead to an improvement in the patient's management and follow-up. In order to achieve this aim, clinicians have helped themselves with a variety of investigations, of which imaging techniques have always played an important role. By tradition, conventional radiology and the utilization of X-rays have been dominant. In recent years, however, a number of different imaging methods have established themselves in clinical medicine and have matured into individual areas of application. These include imaging techniques based on the radioactive tracer method, imaging techniques based on ultrasound waves and imaging techniques based on the use of gamma rays and X-rays and the simultaneous utilization of a computer for image reconstruction of a cross section of an organ (emission and transmission computerized tomography, respectively). In this article, we review some of the concepts, areas of application and difficulties which arise with the utilization of these techniques in medicine and an attempt is made to place them within the general diagnostic problem of space occupying disease detection. Thermography, xeroradiography, mammography, ionography, Freznel zone plate imaging and electron magnetic resonance imaging represent techniques which are only mentioned in order to exclude them from the scope of this paper.

The Concept of Non-invasive Imaging

One of the most attractive characteristics which these techniques have in common is the degree of safety with which they can be applied to the investigations of patients. From this point of view, they have indeed revolutionized clinical investigation of large

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numbers of individuals. The absence of mortality and even morbidity represent undeniable advantages and undoubtedly outweigh some of their disadvantages (all these investigations cost time and money and often they provide high sensitivity with low specificity). Since these diagnostic imaging techniques are non invasive, they are ideally suited for screening, follow-up investigation and can be applied to the work-up of an immense variety of clinical problems independent of age or sex of the patient and degree of progression of the disease. Since nuclear medicine imaging investigations and X-ray tomography techniques derive their information from the utilization of ionizing radiation (gamma rays and X-rays), radiation dosimetry is still a factor to be considered during their application. Two important rules should be applied: a patient should be submitted to an investigation only if the benefit from it outweighs its risk (even if this is minimal) and in general the «ten day rule» for investigations involving ionizing radiation should be applied to female patients during their fertile span of life.

Mechanisms involved

It should not come as a surprise to the reader that each of the non-invasive imaging techniques has its advantages and limitations. Applied to the diagnosis of space occupying disease in different organs, different degrees of sensitivity and specificity will be obtained for each of these imaging modalities and it is clear today that for each of them a variable percent of false positivity and false negativity will occur. It is therefore important to appreciate the basic mechanisms involved in the different imaging approaches and for this reason a few basic considerations will be outlined at this stage relevant to the recording of nuclear medicine scans, ultrasound and computerized tomography transmission or emission images.

Nuclear Medicine. The basis for a nuclear medicine scan is the in vivo and biochemical interaction between a more or less specific radiopharmaceutical and the tissue, organ or structure one intends to image. A nuclear medicine scan offers therefore, primarily, biochemical information and only secondarily, structural information. In a few situations, such as cardiac blood pool imaging, an additional mechanism is involved in the derivation of information from the scans, and that is the detection of relevant edges. The left ventricle is therefore analyzed by nuclear medicine techniques primarily via edge detection, since the radiotracer remaining in the blood pool does not establish a biochemical interaction with the organ to be scanned. This situation is, however, the exception to the above-mentioned general rule.

Ultrasound. Ultrasound images are basically obtained via edge detection. Bodily structures are scanned and imaged by outlining the different acoustic interfaces ultrasonic waves encounter during their path through the body. The information obtained is therefore, primarily, of morphological and structural nature and only secondarily can functional information be derived (when functional information is obtained via ultrasound techniques, this is usually a result of the analysis of ultrasound against time).

Computerized transmission tomography. Since in this case X-rays are shone through the body and the different organs and structures will absorb X-rays to different degrees, the scan obtained is a consequence of the detection of these different X-ray absorption coefficients in tissue. The information obtained is again of morphological nature and not of functional nature. When tomographic techniques are applied in nuclear medicine (computerized emission tomography), then the mechanism involved in the recording of an emission tomographic scan will be basically due to the biochemical and in vivo interaction of the radiopharmaceutical and the organ to be studied.

It is vital to keep these basic notions present when an attempt is made to interpret the scans of these different techniques. The concept and scope of resolution (clinically defined as the smallest lesion to be imaged with each of these techniques) will therefore be entirely different for nuclear medicine, ultrasound, or computerized transmission X-ray techniques.

Resolution

Nuclear Medicine imaging. Resolution here is heavily dependent on the availability of a more or less specific radiopharmaceutical. Theoretically, it would be possible to see a point source as long as the source were radioactive enough. With good radiopharmaceuticals, such as those utilized for bone scanning, lesions as small as 3 mm can easily be seen. However, with less specific radiopharmaceuticals, lesions as big as 2 cm may be missed (liver scanning) and if the lesion does not take up the tracer, even very large space occupying masses may not be visualized (brain cysts). It is therefore important to realize that size of the lesion is not necessarily the most important factor which determines the resolution of a nuclear medicine scan. Progress in nuclear medicine imaging will therefore be dependent on developments of new radiopharmaceuticals. Work on labelled lipid membranes, specific antibodies and hormones suggest the future lines of application.

Ultrasound imaging. In the case of ultrasound, the resolution is almost already at its best, that is to say, approximately 1-2 mm. In the foreseeable future there seems to be no indication that this figure will be improved. Modern ultrasound scanners, and in particular real time scanners, have the advantage of imaging moving structures in real time at the cost of some resolution degradation. Since ultrasound has to be transmitted in order to obtain information, certain structures and organs escape its application. Examples can be given for the brain, the lungs and the skeleton.

Computerized transmission tomography. With present machinery, beam intensities and imaging time per slice, the best resolution is approaching 1 mm. Improvement in the future is unlikely to lead to faster imaging times (data acquisition for one slice is already down to one second); smaller beam intensities, and improvement in display and data manipulation can be achieved. In terms of resolution, however, no significant improvement is expected in the future.

Although the resolution for ultrasound and computerized transmission X-ray techniques is down to the millimetre, not always will structures of this size be imaged by these techniques (Fig 1 and 2). This highlights the difference between physical or theoretical capability of a technique and clinical resolution — it is now known that most of all liver secondaries smaller then 1 cm will be missed by ultrasound techniques. As already indicated above for ultrasound, a number of organs will not be able to be imaged by these techniques and it is known that in abdominal scanning approximately 10 % of patients cannot be diagnosed. Interference of overlying structures such as fat and gas will prevent diagnostic information from being recorded. Similarly, if the X-ray absorption coefficient of normal and abnormal tissue is very similar, transmission X-ray techniques will fail to image differentially. This explains the known phenomena of false negative liver scanning with liver secondaries and the late diagnosis of space-occupying disease in the pancreas. Once the basic mechanisms of image reconstruction are understood, the clinical problems in the application of these techniques will cease to cause surprise.

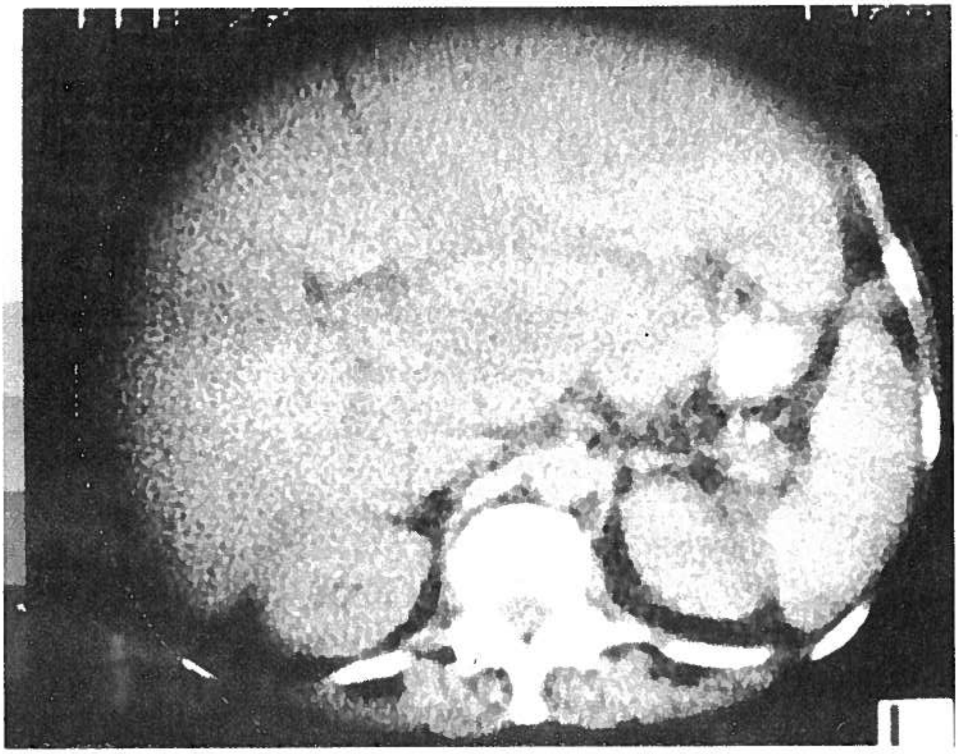

Fig. 1 — *An EMI X-ray transmission scan of the body is shown at the level of the upper abdomen. The liver, speen, kidneys and other organs are exquisetely seen in detail. Apart from hepatosplenomegaly, no other abnormalities were reported on this scan*

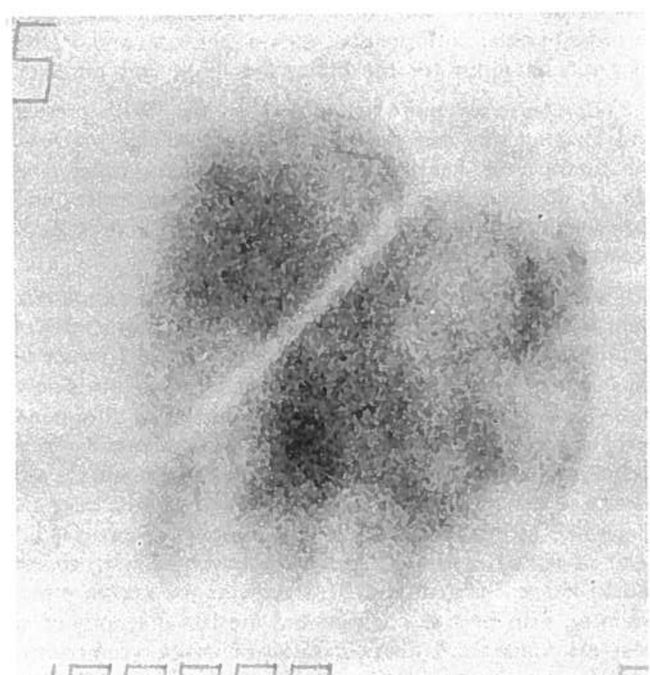

Fig. 2 — *An anterior projection of the liver of the same patient is seen on a standard 99 m Tc-sulphur colloid scan which images, the R. E. S. cells of this organ. The scan reveals large and multiple filling defects compatible with liver secondaries. The costal margin is shown for reference, as a white line*

Clinical Strategies

In a number of circumstances, one single diagnostic test provides the best answer for the clinical problem (even when on frequent occasions additional information has to be obtained via other diagnostic methods). In the diagnosis of skeletal secondaries, nuclear medicine bone scanning is the test of choice. A whole body X-ray survey for bony secondaries is now a test of the past. However, a pelvis X-ray is often performed in addition, due to the higher incidence of false negative bone scans in this area. In the diagnosis of acute pulmonary embolism, nuclear medicine ventilation and perfusion studies are the tests of choice. Pulmonary angiography has been replaced for this purpose and is now performed if surgical treatment of embolic lung disease is considered. If a placenta praevia is to be diagnosed and localized, ultrasound imaging is the technique of choice. Nuclear Medicine scanning has been replaced in this context. If the movement of the mitral valve is to be studied with a non-invasive imaging technique, again ultrasound via echocardiography offers the best answer. Computerized axial transmission tomography is the technique of choice for the differential diagnosis between cerebral haemorrhage and cerebral infarct and offers the best solution to the diagnosis of cerebral atrophy or dilation of cerebral ventricles. It would not be difficult to increase a list of problems which are best approached by one particular technique.

For a number of different clinical problems, the solution is best approached by a combination of diagnostic investigations. Examples can be given as well. In the work-up of a solitary thyroid nodule, a nuclear medicine scan will highlight the presence or absence of function in that nodule, whereas an ultrasound scan will reveal the presence or absence of liquid and permit the easy aspiration of fluid. The implications for patients' management become clear. In the work-up of a patient with carotid stenosis, carotid angiography will beautifully demonstrate the site and extent of the stenosis and nuclear medicine perfusion studies will highlight its relevance to cerebral perfusion. Space-occupying disease in the pancreas is best approached by combined ultrasound and transmission X-ray tomography.

In a variety of more complicated clinical problems, one or even two investigations cannot always provide a definite answer. This is well known, but not always is the approach and the solution to such problems based on objective lines of thought. To achieve this, the concept of clinical strategies is put forward.

A typical example can be found in the assessment of thyroid function. The clinican is often confronted with the question of the status of the thyroid (euthyroid? hyperthyroid? hypothyroid?) In this case, the establishment of normal ranges (the tests used to ascertain these are commonly known as the serum thyroxine measurement and the free thyroxine index) will allow definition of those parameters within which a particular result is considered euthyroid. Applying general statistics to these normal rangers, three additional areas or zones can be defined. One will contain those values which fall within the definitely «high» range (hyperthyroidism), a second area which will define those which will definitely belong to a «low» range (hypothyroidism) and to either side of the normal range, results may fall into grey areas of doubtful «high» or doubtful «low». A clinical strategy is then defined by sending a particular blood sample, no longer for the performance of a particular test, but for the solution of the problem, entiled «State of thyroid function». If the results fall within the definitely normal range or the definitely high or low ranges, no further tests are required. If, however, the results fall in the doubtful high or doubtful low ranges (commonly defined by standard deviations from normal), then and automatically a further test is done for the borderline high result (namely, the measurement of total serum T_3) and a further test is automatically performed if the result falls in the borderline low area (namely, the measurement of serum TSH). With such a scheme, we now have a well defined approach to the question of the status of the thyroid function, which will cover all the possible referrals. A particular attraction of this scheme is the fact that normal ranges can be reasonably well established for each laboratory and particular population. Since the test measures reasonably well defined amounts of hormone levels, expressed as a particular quantity, clinicians will tend to rapidly accept such an approach.

In the case of space-occupying disease of several organs in the body, such a concept, although viable and advisable, is necessarily more complicated. Clearly, the obstacle is derived from the fact that normal ranges are more difficult to define and that, as previously stated, each test has certain characteristics of sensitivity and specificity. To add to the problem, it is easier to define a strategy for a population rather than to define a strategy for a particular individual. The following concepts, however, have emerged to help in the definition of a clinical strategy for an individual patient. The «sensitivity» of a test is the fraction of all cases which the test calls positive. The «specificity» of a test is the fraction of non cases that the test calls «non cases», in other words normal. The «predicted value» of a positive test is the fraction of all positive reports that turn out to be cases. In similarity, the «predicted value» of a negative test is the fraction of all negative reports which turn out to be «non cases». Finally, «accuracy of the test» is defined as the sum of all correct outromes divided by the total number of tests done. Once these indices are known for the several imaging modalities which have been outlined before, clinical strategies for the diagnosis of space-occupying disease in the liver, the brain, the kidney or other organs can indeed be established.

In the case of space-occupying disease of the liver, it is now understood that isotope liver scanning has higher sensitivity of detection than ultrasound imaging but has lower specificity. It is also known that transmission X-ray tomography has in this case the highest positivity of all three imaging modalities, but with the lowest sensitivity (Bayan et al 1977; Bragg 1977; Cosgrove and McCready 1978). It follows from here that if the clinician refers to the imaging specialists the problem of space occupying disease detection in the liver, a nuclear medicine liver scan should be the first imaging technique performed. Depending on the answer obtained and the degree of confidence on this answer, a further test (ultrasound imaging of the liver) should be performed, and only in the last instance, if doubts persist, the third imaging modality (computerized transmission X-ray tomography) should be performed. Based on similar data, flow diagrams for the liver, the brain and the kidney have been proposed and discussed elsewhere in the literature(Ell et al 1978).

It is vital to understand that a clinical strategy will only apply in a particular setting and a particular community. No general rules can be outlined if a number of factors are not taken into consideration. These include: availability, cost, time, degree of automization, radiation dosimetry, time of operator, repeatability and reproducibility.

In terms of availability, it is clear that not every hospital in every region will have available all three imaging modalities. It is also understandable that the degree of available expertise will differ from centre to centre, depending on the degree of individual knowhow for each imaging technique. Only very rarely will centres be equipped with the highest degree of expertise for each of the imaging techniques. It is also to be understood that cost and time will be linked and will influence to a varying degree the type of strategy which must be defined. Cost effectiveness considerations will have to be borne in mind and these are often dependent on the operative skills required for each technique. Where, for instance, for ultrasound imaging quite often a skilled and highly trained individual is required for data acquisition, this aspect of the technique is now almost fully automated for nuclear medicine and transmission tomography procedures. This will in the end have implications, since if one is developing screening techniques, the less operator dependent the method, the easier it will be to apply to large numbers of patients. Similarly, in certain circumstances, the radiation dose will have to be a deciding factor, and quite clearly in obstetric diagnosis ultrasound has the advantage over the other two imaging modalities.

In Table 1 and in order to outline possible future applications, a number of «personality traits» are attached to each of the three imaging modalities which have been the subject of this paper. An arbitrarily chosen dot score highlights the relative advantages of each of these imaging modalities in terms of whole body imaging capability, static or dynamic imaging capability, and the ability to achieve quantitative information, and functional and metabolic data.

With nuclear medicine investigations, the future will lie in the analysis of tracer uptake and the development of metabolic image information. Cross-sectional distributions of thallium-201 uptake in the heart, fluorin 18 deoxyglucose uptake rates in the brain, furnish examples of such applications. Ultrasound and computerized transmission X-ray techniques excel in the display of detail and structure. As an example, one may mention the ultrasound display of the biliary tree and its inherent capability to demonstrate the presence of obstructive jaundice. For computerized transmission X-ray techniques, an example can be given in the detailed visualization of the retroperitoneal space and the mediastinum.

TABLE I

	Nuclear Medicine	Ultrasound	X-Ray Transmission Tomography
Whole Body images	***	**	*
Static images	***	***	***
Dynamic images	***	***	*
Functional studies	***	**	*
Metabolic studies	***	—	—
Quantitation	***	***	***
Availability	***	***	*
Cost	**	***	*
Time	***	***	*
Automation	**	*	**
Radiation dose	**	***	*
STARS (the more the better)	30	26	15

CONCLUSION

Each of the imaging modalities has a role to play in diagnostic medicine. Often, they will have to be used in conjunction to solve a particular clinical problem. A basic understanding of the mechanisms involved in the production of images and the analysis of the sensitivity and specificity data for each of the techniques will allow clinical strategies to become useful and effective. A certain degree of organization at home, however, may be required (creation of non-invasive imaging units) in order to make this desideratum possible in practice.

RESUMO

Discutem-se os mecanismos que presidem à obtenção de imagens por métodos não invasivos (medicina nuclear, ultrassonografia, tomografia computorizada de transmissão e de emissão). Introduzem-se definições para sensibilidade, especificidade, valor de previsão e precisão. Defendem-se estratégias de diagnóstico clínico para lesões ocupantes de espaço e sugerem-se orientações para futuro desenvolvimento.

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