ULTRASOUND AND CANCER

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We would like to express our sincere gratitude to Professor Henri Tagnon, Professor of Cancerology at the Université Libre de Bruxelles and President of the E.O.R.T.C., for accepting the Presidency of this Symposium.

Organizing Committee

Preface

The diagnostic use of ultrasound energy and its properties has been increasingly developed over the past twenty-five years for an impressive variety of indications and for almost all medical specialties. With ultrasound techniques, the contours of superficial and deep structures in the body can be defined noninvasively and without harmful effects. Furthermore, their content and architecture can be characterized qualitatively. Active work is also in progress with a view to obtaining quantitative information. The feasibility to diagnose cancer, or at least to aid in diagnosing, has often been demonstrated but in a dispersed manner. The goal of the Symposium and of its published proceedings is to present collectively the actual results obtained in the endeavour to diagnose cancer with ultrasound. The survey of the methods and results is supplemented by discussion around the problems encountered when criteria corresponding to cancer lesions have to be defined. The problems arising from ultrasonic cancer detection and the diagnosis methods are seldom restricted to a limited field or specialty: most of the criteria used for cancer detection or tissue characterization are based on physical features related to sound-tissue interaction; they can be applicable, with some small differences, to the majority of human tissues. For those having diagnostic ultrasound as a primary interest, all subjects, all organs or fields are of interest. For the others, more involved in only one specialty, knowledge about the use of some methods developed for diagnosing cancer in other, more or less restricted areas, is worthwhile and could give invaluable information if applicable on their own. The reasons to gather, under the common denomination Ultrasound and Cancer, chapters related to many different organs and functions are thus more obvious.

This book contains invited papers reporting the experience of diagnostic ultrasound practitioners; most of them have a worldwide reputation due to their outstanding merit and valuable contribution to the progress in diagnosic ultrasound, and due to their first-class publications and presentations. Diagnostic ultrasound started quite early in Belgium – in 1966 the Editor was among the few using A-mode and then B-mode ultrasound in Europe – and to hold such a Symposium in Brussels was an opportunity to become acquainted with some skilled Belgian ultrasonologists who have good experience in cancer diagnosis.

A call for papers from various authors concerned with Ultrasound and Cancer was made with a view to ensuring a wide and comprehensive coverage of the subject and, after an inevitable selection, to avoiding duplication as far as possible. The readers of this book will have the invaluable advantage of the very short interval between the preparation of the manuscripts and the publication of the proceedings: they are published at the time of the public presentation of the papers. Support and criticisms are welcome for improving the next, II International Symposium on Ultrasound and Cancer.

The Editor

Foreword

Does ultrasonography help, facilitate or allow to give a precise diagnosis in the field of oncology, whatever may be the organ or tissue involved in the cancerous process?

This will be asked to the participants of the 'First International Symposium on Ultrasound and Cancer' held in Brussels the 23rd and 24th July 1982, organized by Salvator Levi, M.D., head of the Unité de Diagnostic par Ultrasons de la Clinique Obstétricale et Gynécologique de l'Hôpital Universitaire Brugmann and supported by the European Organization for Research on Treatment of Cancer and the Belgian Society of Diagnostic Ultrasound.

The subject is ambitious and one can ask why such a symposium covering all aspects of oncologic ultrasonography is promoted by gynecologists. The reason is, that in our department, S. Levi started to study, ten years ago, how to characterize tissue texture in vivo, noninvasively, in order to elucidate – or trying to do so – the nature of pelvic or abdominal masses. At that time, with the help of a commercially available equipment, S. Levi gathered interesting results presented for the first time in 1974 at the Institut de Génie Biologique et Médicale de Vandoeuvre (France): 'Essai d'Analyse Quantitative des Echogrammes de Tumeurs Pelviennes'. The results were encouraging enough to carry on the experiments with more sophisticated method, granted by the Fonds National de la Recherche Scientifique and the Fonds Lequime-Ropsy.

Later, J. Keuwez, Physicist, joined Dr S. Levi's team. The computerization of acquired ultrasonic signals combined to the automation of scanning are now in progress.

The Fondation pour la Recherche en Endocrinologie Sexuelle et l'Etude de la Reproduction Humaine (F.R.E.S.E.R.H.) supported Dr Levi's work in order to carry on his original experiments, with the aid of the new tools, because of the interest brought to the work, more particularly in the U.S.A. where he received the title of Senior Research Scientist from the Indianapolis Center for Advanced Research. The Department of Physical and Natural Sciences of the Commission of the European Communities also became interested and concluded in 1977 a research contract with our ultrasound laboratory.

The noninvasive, in vivo, analysis of tissue texture, appears to be promising for all kind of tumors in the whole body: therefore the F.R.E.S.E.R.H. and the OB-GYN Department of the Université Libre de Bruxelles, support as much as possible the research of ultrasound in cancer diagnosis.

Prof. R. Vokaer
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de l'Hôpital Universitaire Brugmann (U.L.B.).
Administrateur-Directeur de la F.R.E.S.E.R.H.

Introduction

Our subject today is ultrasound and cancer. More specifically what is the contribution of the ultrasound technic to the diagnosis and treatment of human cancer. The answer to this important question will be given by the speakers of this symposium brilliantly organized by Dr Salvator Levi and sponsored by the service of gynecology and obstetrics of the University of Brussels.

We oncologists are often asked 'when will the cancer problem be solved?' The answer to this question is that it is being solved every day, progressively like all medical problems. The year 1981 marked the tenth anniversary of the *National Cancer Act* of the Government of the U.S.A. which dramatically put the emphasis on a renewed and expanded effort to study and advance the treatment of cancer in the U.S.A. This is the country which has a real vision of science. We all here have confidence in the scientific method, whether applied to clinical studies and in the laboratory. Good work and discoveries come from every country from all parts of the world but especially from countries which make good use of their intellectual potential. The man who signs a paper describing an important discovery is indebted to all humanity past and present for over 99% of the ingredients of the discovery. We in Belgium should be thankful to countries with vision.

What are some of the important advances of the last 10 years in terms of practical results, leaving out for today's occasion the tremendous explosion of biological laboratory research which prepares an even brighter future: in children, long-term survival increased from less than 10% to over 50%. By 1980 many of our children patients have become healthy adults and have families of their own. It would be instructive to analyze in detail the many factors which have contributed to this victory, among which should be noted first the development of cytotoxic chemotherapy to the point that chemotherapy became a full partner, with radiotherapy and surgery, for the care of cancer. We all realize of course that the problem of curing cancer is bound to this strange property of cancer to metastasize and more often than not to metastasize before the primary is or can be detected.

Therefore, treatment addressed to local disease to the exclusion of systemic treatment rarely achieves cure and then only in specific cases. This is well exemplified by breast cancer in which any type of operation with or without radiotherapy produces the equivalent rate of *failures*, amounting to over 70 to 80%. Therefore a systemic treatment appears indispensable and physicians who scorn at chemotherapeutic research should remember this and assist in finding other modilities of systemic treatment, perhaps chemotherapeutic, perhaps of different types, some of which are of immense interest and cannot be discussed here.

Not only in children but also in adults has systemic treatment in the form of chemotherapy following local treatment by X-ray given gratifying results: Hodgkin's disease (70% survival at 10 years), lymphosarcoma, testicular tumors (over 90% cures with certain regimen), many others. These tumors had a very high mortality as recently as 20 years ago.

There is a second factor: the development of improved radiotherapy and especially of chemotherapy would have been impossible without the parallel development of a precise and reliable methodology for the evaluation of clinical results. Such development is necessary in all fields of clinical medicine but nowhere more than in cancer medicine. Cancer therapy, cancer cure is the repository of the hopes of mankind and represents the supreme temptation for the honest physician to mistake his hopes for reality. Hence the vagaries and the unreliability of early clinical investigation in cancer therapy. The important present day evolution is the advent and generalization of the controlled clinical trial.

One of the sponsors of this meeting is the European Organization for Research on Treatment of Cancer. It is a non-governmental organization which comprises the most important cancer hospitals and research centers in Western Europe. It is not a society in the usual sense, but it is a working association to promote clinical groups for the clinical evaluation of the new treatments created in the laboratories. There are over 1500 participating physicians in 150 hospitals and clinics. 9000 patients per year are registered and treated according to carefully worked out and detailed protocols of treatment uniformly applied. The results are assembled in a 'Data Center' located in Brussels. There the data managers supervise the normal flow of incoming results from the participating hospitals; the statisticians verify the validity of the conclusions. Quality of life and ethical obligations are also studied and strictly supervised. The clinical trials of the E.O.R.T.C., working hand in hand with similar organizations in the U.S.A., are an irreplaceable instrument for progress in cancer treatment.

I now realize that I should say something about ultrasound and cancer. I will tell you that we in the Cancer Center of Institut Jules Bordet and our radiological department like the ultrasound technic and apply it extensively. Dr Levi who is a pioneer in this field and the founder of the Society deserves our admiration and gratitude. However the speakers in this symposium are the ones who know much on ultrasound and I now shall let them tell you their story.

Prof. H.J. Tagnon
President, E.O.R.T.C.

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IMPEDIMENTS IN TISSUE CHARACTERIZATION FOR CANCER DIAGNOSIS

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I. INTRODUCTION

Ultrasonography is an imaging technique based on the reflection, by the human body, of sound pulses. Sound penetrates into the body, interacts with the encountered tissues. Sound tissue interactions have name scattering, absorption, refraction and diffusion. Reflected sounds are received back by the emitting transducer during its long non-emitting periods. Special technical procedures display into an image the received signals arising from the insonified area. Spatial display and relative intensity of echoes constitute the basement of echography and diagnosis.

A diagnosis is suggested through the interpretation of image, based on sound-tissue interaction. Only a few facets of interaction are taken into account: mainly the backscattering and the attenuation because they may strongly alter the echo-formed image. However, the basic information is mainly morphological, qualitative, somewhat quantitative but rather subjective.

As mentionned above, the sound wave is disturbed by various mechanisms. If their respective contribution to disturbances is different from tissue to tissue and from a healthy tissue to its pathological state, the quantification of these mechanisms and of their combinations, should constitute the acoustical signature of a given tissue.

When a catalog of signatures from the different human tissues will be available, as well in normal as in different pathological conditions,diagnoses of diseases affecting the properties of tissues will be made through the determination and identification of their signatures.

Everybody forecasts that the main hope put into ultrasound tissue characterization is related to the possible ability to perform non-invasive "biopsies". Sonic biopsy is a sampling of ultrasonic information which has to be analyzed in order to distinguish objectively and accurately between benign and malignant lesions.

II. BASIC CONCEPTS

PHYSICS

Sound waves are mechanical waves, energy which propagates into a medium, human tissues for example. That energy is partly **reflected** to the transducer: this is the fundamental phenomenon which produces signals and then an image or **echogram.**

Reflection occurs where sound waves pass trough the **interface** of two media. Reflection is strong, more especially as the media impedances are different (impedance = product of **density** and **sound velocity**).

The **transmitted energy** (i.e.the non-reflected part), somewhat **refracted,** is damaged by a serie of sound-tissue interactions: a.**scattering**, or spreading of the energy by non-uniformities in the medium, even particles smaller than one wavelenght; b.**friction forces:** a part of the wave energy is transformed into heat. The resultant of wave damages is called **attenuation,** which appears to be easier to measure than any of its components. Therefore, determination of attenuation could be one of the best approach for tissue characterization by ultrasound (UTC).

CHARACTERIZATION BASED ON IMAGE

To a certain extent, UTC is feasible on images. **History of ultrasound imaging** for the past 12 years could be summarized into three stages:

1. Interest for A-Mode trace as well as the possibility to display it have diminished. This is explained by the fact that A-Mode traces are rather difficult to interpret, despite the fact they contain much information.

2. Grey-tones images have supplanted the black and white where all printed dots are equally bright, whatever their amplitude is. The only condition to appear on the echogram is to reach a predetermined level of amplitude. Grey-tones (8 to 64) display more information. Grey-tone image permits a visual characterization, very subjective, non-quantitative. Its quality depends, between many other factors, on sound **frequency** which acts on **resolution,** on scanning mode (simple scan, compound, with or without **overwriting**), on the different settings and on equipment.

3. Beside static B-Scan, dynamic B-Scan or real-time imaging, contributes specifically to make better diagnosis. Real time has two main advantages: easy handling and detection of movements. For example, a bowel loop cannot be interpreted as an ovarian or salpinx cyst lesion if peristaltic movements are detected. Abnormal movements could also be a powerful aid for diagnosis. The immobility of an organ compared to the others can be a sign of adherences. They are also important features which restricts sometimes its use (1).

IMAGE FEATURES OF TISSUES

Many influences - some of them out of control - modify the aspect of images, but careful observation bring valuable information on the particular nature of some tissues. **Adipose tissue** is an organized compound fat and fibrous tissue producing non-, low- and strong echoic areas. The image texture is characteristic of that adipose tissue (Fig.1). Between fat and muscle, **aponevrosis** reflects very well ultrasounds. **Muscles** are irregularly echogenic. **Bones** reflect sounds highly, thus transmitted energy is very low; they are almost perfect reflectors. On the borderline of gas containing tissues - **lungs, bowels** - sounds are reflected and penetrate a few; gas bubbles scatter the transmitted energy. Homogeneous liquids do not reflect neither scatter sounds (Fig.1,2,3). Secretions, exsudates and transsudates, filtration products, urine, gall, ascitis, are homogeneous liquids in normal conditions. As sound velocity is lower in liquids than in tissues, sound-attenuation is also weaker and refractions could be more important (2). Low attenuation and refraction have some effects on image: echo-amplitude enhancement at distal part of liquid area and shadowing on its lateral edges.

Blood is not visualized but scatters ultrasound: indeed circulating blood is detected by Doppler effect. Blood is acoustically comparable to other tissues: density and sound velocity are equivalent to those of the liver: 1.06 and 1560 m/sec respectively. **Other liquids** as pus, sebaceous substance in teratomas, may have a marked scattering effect and are more attenuating than water. **Liver, pancreas, spleen, placenta** and **fetal lung tissue** contain many very small size reflectors which are responsible for typical echograms, with regularly distributed echoes of even amplitude. Echo-distribution is only disturbed by "foreign" structures belonging to the organ: vessels and excretory canals for example. Some physiological factors can modify echodistribution and echoamplitude (placenta ageing, fetal lung maturity) as well as pathological ones (inflammation, calcification, fibrosis, infarcts, ...).
The contrasts between the organs or between tissues in the organ may be enhanced by fat tissue and liquids (Fig.3). Foreign bodies and wall abnormalities (of stomach, gallbladder, urinary bladder) may be seen, even if their size is very small (ulcus, papillary tissue, small tumors). Visualization of these is greatly improved by the contrast brought by liquids (acoustical window) and therefore better studied by characterization techniques. Oedema and blood infiltration into tissues modify also their image. Calcium deposits may produce high reflections but the size of calcification is predominent for absorption as for reflection and/or scattering.

The peculiarities of the image, when they are correctly described and interpreted - with a good knowledge of the technical conditions applied for echogram building - are

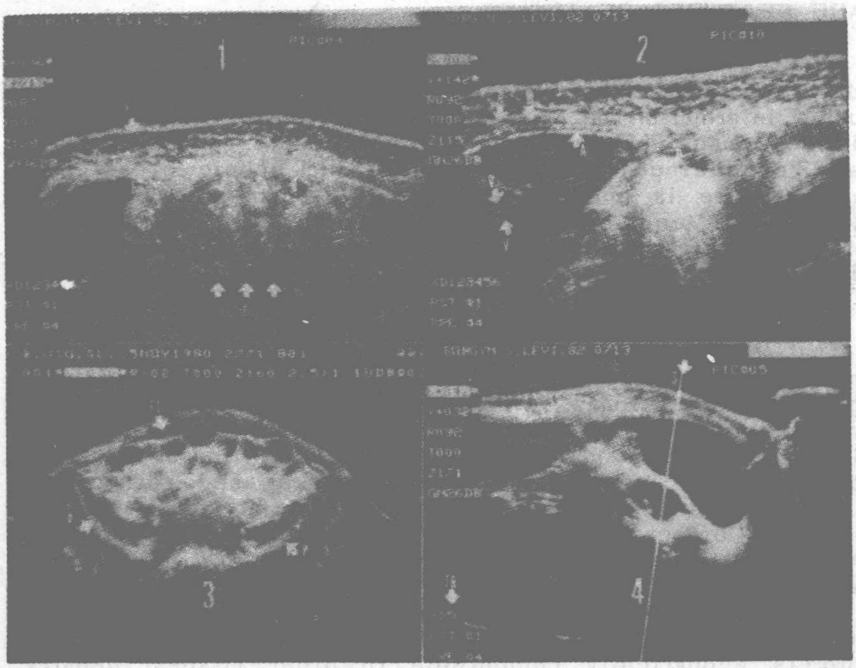

Figure 1. Longitudinal scan of the abdomen. Skin and adipose tissue lie between the two arrows F. Under muscles and aponevrosis, bowels loop are visible (B); sound energy is not transmitted to the spine because attenuation by gazes (arrows T).

Figure 2. Abdominal wall layers, liver and duodenum (D); A = aponevrosis, M = muscles, V = vessel within the liver.

Figure 3. Ascitis and bowels filled with liquid (transverse scan); FL = fluid, P = pelvic bones.

Figure 4. Pelvic tumor submitted to sonic biopsy. The line of sight (S),from which samples are collected, is the axis of the transducer 5 (TR) (All the pictures were tooken on U.I.Octoson).

informatory enough to give or approach a precise diagnosis. Sonar information have to be added to other collected data (anamnesis,physical examination ...), to knowledge of anatomy, physiology and pathology, all factors which are to be harmoniously integrated in the brain mechanisms leading to diagnosis. Diagnosis approach,as described above, gives very satisfactory results on a statistical point of vue, very close to the real situation in most of cases.

Analysis of transmitted energies could be added to analysis of reflection. Very useful **in vitro** in order to determine most of the acoustical parameters of tissues, it appears presently to be much less applicable **in vivo.** Indeed, transmission does not bring any information on the localization of studied interactions and is very often too weak because sound penetration is difficult throughout the whole human body (Fig.1,2).

Yet, image is sometimes not informative enough to chose between different situations and to decide for one conclusion with an acceptable risk of error. The space occupied by the uncertain diagnoses, when image may fit with many different lesions, could certainly be reduced if the evaluation of sound tissue interactions could be approach differently and by priority by quantitative ultrasonic tissue characterization to differentiate between normal, benign and malignant tissues.

III.OBJECTIVE AND QUANTITATIVE MEANS TO CHARACTERIZE TISSUES

A.**Pattern recognition:** The image represents only a limited part of the echographic information (mapping, signals levels). Moreover, the sonologist perceives it only in a restrictive and subjective way.
An automatic image-processing can present objectively to the sonologist a deal of the imperceivable information: as for example, the echo-density and its distribution. Analysis could be performed on the raw image; it can also be performed on an image modified either to accentuate some of its features,or to extract information which could hide other. These techniques were applied successfully to improve the diagnosis of prostatic cancerous diseases (3).

B. The **Doppler effect** is effective to determine blood flow in vessels, even quantitatively using pulsed sounds. Texture changes may induce modifications of blood flow, especially in breast cancer. The tissue infiltrations is followed by increase of blood flow in the abnormal breast compared to the heterolateral breast. The Doppler effect could be useful in the detection and identification of breast tumors but also for other organs (4) : the tumoral part of a pancreas shows different Doppler signals than the normal part.

C.Cancer affects the **elasticity and compressibility** properties of tissues; the response to external forces is modified. Moreover when cancerous and peripheral tissues are submitted to mechanical oscillation, the cancerous tissues respond differently. This method, named echosysmography (5), has been tested on liver, pancreatic, renal tumors and accessorily could be useful for breast investigations.

D.Sound-tissues interactions

a)Velocity: sound velocity measured by transmission techniques is different in normal and cancerous parts of various organs, as it has been shown **in vitro** for hepatic and breast tissues. This change has a special interest for **in vivo** examination of breast, better adapted to transmission method than other structures. Maps of velocities profiles in the breast can be constructed (6).

b)Scattering: the backscattered energy is dependent on the frequency and structure of the medium. The structure may be modified by some diseases. Trials were made to detect changes in the backscattered energy to diagnose liver and thyroid anomalies (7). This approach would be interesting for early detection of pathology because scattering could be modified before attenuation.

c)Attenuation: much attention has been focused on the attenuation of sound energy to characterize tissues. Attenuation was evaluated on echograms and the first practical applications were made by the Japanase School. The **graded tomography** (8,9) is a quantitative evaluation of attenuation. Although approximative, it gives a surprising high rate of correct diagnosis in breast cancer. The increase of attenuation with frequency is a property of sounds used for **in vivo** characterization (10). Noteworthly results were obtained for the differentiation of liver diseases (11) by **spectral analysis**. A similar method is under development in our laboratory.

The central part of the amplitude spectrum, of a pulsed sound wave, has the shape of a gaussian curve. The modification of this part with depth penetration is the mark of the various interactions, already described during the propagation in the medium. The characteristics of the decrease of the amplitudes are supposed to characterize the medium.

The amplitude spectrum of echoes, arising from two reflectors located on the same pathway, are compared with the aim to calculate the attenuation in the medium. One single value obtained by this comparison is not representative of the attenuation by the medium. Attenuation can be determined only from the distribution of these values. Significant differences between spectra are obtained when the distance between echoes of each pair is large enough. But when the distance becomes to long, the points generating the echoes are not similarly perceived by the transducer. Indeed, the shape of the sound field changes with the depth. The best appropriate distance depends on frequency and attenuation of the medium. The use of high frequencies allows to reduce the distance and to characterize smaller structures. However, with high frequencies, the attenuation in the intervening tissues is burdensome for the measurements.

To insure the independance of the samples, sampling should