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Chapter 24

Life-Cycling of Cancer: New Concept

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Additional information is available at the end of the chapter

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1. Introduction

The best way to deal with a tricky and unpredictable disease is to understand its essence, causes and triggers.

- Why and how become some normal cells "rebellious" and aggressive? Are there any common processes and rules that govern the transformation of normal cells into malignant neoplasm?
- What is the main cause of cancer diversity and individualism?
- Why do some cancers give metastasis and some do not?
- There are overlaps between benign and malignant lesions. Can we define cancer accurately? Is there a clear margin or a criterion that differentiates benign and slowly progressing malignant neoplasm?

The basic questions about cancer must be answered to demystify this scary disease and solve the "Oncogenic Paradox" described by the Nobel Prize laureate Albert Szent-Gyorgyi [1]: "The malignant transformation of tissues … is a very specific process which must involve very specific changes in a very specific chemical machinery. Accordingly, one would expect that such transformation can be brought about only by a very specific process, as locks can be opened only by their own keys. Contrary to this, a malignant transformation can be brought about by an infinite number of unspecific influences, such as pieces of asbestos, high-energy radiation, irritation, chemicals, viruses, etc. It is getting more and more difficult to find something that is not carcinogenic".

A new promising way of understanding malignant neoplasia and its paradoxes rests upon integrating biomedical and physical knowledge. Several years ago the US National Cancer Institute funded a major research program to bring insights into the cancer problem from the

standpoint of physical science; the hope was that physicists could introduce some radical new ideas to the table. In the manuscript we focus mainly on the physical aspects of cancer origin pushing aside biochemical, immunological and gene-associated findings that do not presently add much to the conceptual framework for cancer theory. Our model of carcinogenesis incorporates certain recently discovered physical phenomena [2-4] that elucidate many peculiarities of malignant processes.

New concept of cancer origin is a particular example of the more general model of system-genesis published last year [5]. According to this hypothesis, a malignant neoplasm originates within a small isolated area of a larger organism as a new functional unit with its individual mechanisms of self-control and self-regulation; the cells that are deprived of nutrients and oxygen do pass through several stages of dramatic transformations that lead to the formation of toti- or pluripotent cells with altered genetic makeup. The future fate of this "potential neoplasm" depends on a combination of some physical factors and on the proper timing of successive events that include the unification of enclosed cells and their preparation for aggressive expansion through the physical effect of "Random Lasing" [2]. Hence, contrary to a widely spread opinion of cancer being a chaotic and poorly controlled pull of rebellious cells that are "driven mad" by some mutations, we consider malignant neoplasm to be a strictly controlled and adaptive system of cooperatively acting primitive cells. Some researchers share this point of view regarding cancer as a self-organizing adaptive system or a parasite-like organism [6, 7].

Our model of carcinogenesis is the result of 12-year-long experimental and clinical work in the emerging scientific field of Biological Holography. All illustrations presented in the manuscript are obtained with the computer-assessed device (CID-system) developed specially for cancer detection and visualization [5]. This hardware-software system is the ever first cancer-detecting and monitoring tool convenient for mass-screening purposes; it is capable of detecting and monitoring of any malignant process disregarding its type and location in the body. The non-invasive and automatable method of any cancer detection through a single and short-term procedure is already implemented in diagnostic practice: the patients with and without malignancies are distinguished by spectral information emitted from their body surfaces.

2. Cancer origin theories: State-of-the-art

Malignant neoplasia of normal cells remains a source of misunderstanding and controversy. There is a vast literature on cancer theories. In this section we briefly describe only some of the most acknowledged and interesting ideas. Although none of the debatable hypothesis of carcinogenesis elucidates the general scenario applicable to all cases of cancer, they are nevertheless helpful in generalization of the state-of-the-art knowledge.

A central feature of today's view of cancer is that it does not develop all at once but evolves as a result of complex succession of events over time. According to Hanahan and Weinberg [8] there are several essential alterations in cell physiology typical for malignant cell growth. These

hallmarks of cancers include: 1) Self sufficiency in growth signals, 2) Insensitivity to anti-growth signals, 3) Evading apoptosis, 4) Limitless replicative potential 5) Sustained angiogenesis, 6) Tissue invasion and metastasis, and 7) Genome instability. It is also widely accepted that cancers express aerobic glycolysis regardless of their tissue or cellular origin [9]. Abnormal segregation of chromosomes during mitosis (aneuploidy) and genome instability are found almost in all cancers [10], though the reason(s) of these abnormalities are not clarified.

The somatic mutation theory of carcinogenesis has been dominant since the beginning of the 20th century. It is known that cancer cell genomes carry somatic mutations in DNA that may include base substitutions, small insertions and deletions, rearrangements, and copy number alterations. As the tumor progresses, mutations accumulate and the cell eventually becomes cancerous. Apart of successive alterations in genetic material (somatic events), some germ-line mutations can also predispose a person to heritable or familial cancer. Certain defects in DNA are known to be responsible for a variety of hereditary cancer predisposition syndromes including non-polyposis colorectal carcinoma, Bloom syndrome, ataxia-telangiectasia, Fanconi anaemia, etc. [11,12]. Molecular genetics has identified some oncogenes that, along with tumor suppressor genes, can reproduce many aspects of cancer progression. In fact, each tumor is unique in its genetic makeup [13] and, correspondingly, has a unique phenotype akin to an individual organism. Many researchers consider the above theory unsatisfactory because no strict correlation exists between gene mutations and malignancy; besides, it is unclear which factors trigger the gen-associated events that lead to neoplasia. Evidently, the genomic instability per se is not sufficient to initiate a malignant tumor. The somatic mutation theory can explain neither genetic variability within individual tumors, nor many other observable phenomena in cancer biology.

The **cancer-stem-cell (CSC) concept** is becoming increasingly popular, since non-differentiated, relatively primitive and pluri- or totipotent cells have the ability to self-renew and to give rise to distinct types of malignant cells. It is now generally accepted that the CSC sub-population of cancer cells plays significant role in initiation, progression and recurrence of cancer. The CSC concept was first demonstrated in the study of leukemia, which was found to be associated with the "stem-cells" having specific surface antigen profiles [14, 15]. Italian researchers who spotted CSCs in human primary bone sarcomas highlighted CD133 as a pivotal marker for their identification [16]. In recent years similar cells were found in human cancers of brain, breast, colon, pancreas and other tissues [17]. Kornelia Polyak from Dana-Farber Cancer Institute (Boston, US) demonstrated that the frequency of tumor cells positive for stem cell–like and more differentiated cell markers varies according to tumor subtype and histological stage [18]; the question whether malignancy arises from normal stem cells due to maturation arrest or due to transformation of mature cells into CSC is still open.

The Viral/Microbial Theory of Cancer that regards viruses/microbes as potential triggers of a neoplastic process has long history. First finding concerned the avian leucosis virus as a cause of leukemia in chickens [19]; Two years later after this discovery P. Rous presented his theory about ultramicroscopic organisms capable to induce cancer in humans and animals [20]. Since then many viral infections have been linked to malignant processes. Recent studies have

provided cogent evidence that some "oncoviruses", e.g., human papillomavirus, hepatitis B and hepatitis C virus, Epstein-Barr virus, etc. are indeed associated with increased incidence of human cancers [21, 22]. Over the years, scientists have proposed a number of mechanisms to explain this link. However, numerous cases of cancer can originate and develop independently of any viruses, fungi or bacteria.

A major cohort of scientists supports the **embryonal theory of cancer.** A type of similarity between embryogenesis and carcinogenesis was first mentioned by John Beard, who put forward The Unitarian Trophoblastic Theory of cancer [23]. The main idea behind his theory is that certain fetal cells or atavistic genes give rise to a neoplasm. Prominent physicist Paul Davis argues that ancient genetic toolkit active in the earliest stages of embryogenesis gets switched back on, re-activating the Proterozoic developmental plan for building cell colonies [7]. Rippert [24] suggested that cells expressing embryonic potential arise due to the process of dedifferentiation. According to the proponents of the embryonal theory, some immature cells such as the remnants of fetal tissues, become eventually malignant due to altered blood supply, e.g., after tissue traumas or mechanical isolation of a small area from nutrients and oxygen. Remarkably, the development of the zygote up to the blastula stage is more or less the same in all mammals, so one can assume that the early phases of cancer "prenatal life" would be of the same nature. Whether we should blame the atavistic genes or there are some other factors that eventually "fertilize" the host-cells producing neoplasm remains an open question.

The embryonal theory is closely related to the hypothesis dubbed **the "speciation theory"** that regards cancers as new species. Duesberg and his UC Berkeley colleagues, who studied aneuploid nature of a cell karyotype across numerous cell cultures, came to a conclusion that some cell-destructive events cause chromosomal mutations and result in cells with totally new phenotypes [25]. The authors argue that carcinogenesis is initiated by a disruption of chromosomes that alters the balance of tens of thousands of genes. The result of these processes is a cell with new traits – that is, a new phenotype or a new organism. According to these researchers, "cancer is comparable to a bacterial level of complexity, but still autonomous; … it doesn't follow orders like other cells in the body, and it can grow where, when and how it likes" [ibid]. M. Vincent [26] also considers cancer as a programmed and evolutionarily conserved formation rather than just a random series of disease-causing mutations.

Malignant neoplasm develops within host tissues, so the state of entire body and traits of **the micro-environment** of a "cancer-nursery" must be taken in account while searching cancer initiation factors. Gene mutations are only part of the process that leads to cancer, which involves an interaction between neoplasm and surrounding tissue. The importance of changes in the micro-environment during tumor progression has been recognized thanks to pertinent enthusiastic scientists, who were moving against the mainstream science to prove their hypothesis [27-29]. The existence of histologically abnormal tissue beyond a neoplastic area that predisposes to tumor formation is a characteristic feature of many cancers. Interesting data were published by a team of American researchers who established that in the course of tumor development the normal cells in tumor stroma may lose more regions of DNA than do the cancer cells [30]. Another team of American scientists demonstrated that stromal cells

actively participate in carcinogenesis [31]. Sonnenschein and Soto from Tufts University in Boston [32] put forward the tissue organization field theory arguing that dynamic breakdown of cellular communication and signal transduction prompts disoriented cells to mistakenly revert to pro-growth patterns of behavior.

The theoretical considerations listed above are substantiated by empiric evidence, but they deal with particular events and manifestations of carcinogenesis. These hypotheses are essentially complementary to each other rather than contradictory; they describe various contributing factors and peculiarities of a neoplasm but no data are available concerning the general scenario and common physical processes that take place at early stages of any cancer genesis. No doubt that there is an urgent need for such a theory capable to reconcile existing hypotheses and empiric findings by establishing the reasons and physical laws that drive normal cells towards malignant neoplasia.

3. Malignant neoplasm as a new organism

Our model of cancer origin has much in common with the embryonal and speciation hypotheses mentioned above; however, it brings new insights into physical mechanisms of cancer emergence and elucidates some details of its "prenatal" life. In this section we will discuss the general peculiarities of complex adaptive systems and show that malignant neoplasm being a system of cooperatively acting cells, behaves as an autonomous organism with its own mechanisms of self-control and self-regulation. Evidently, the whole spectrum of distinct cells, tissues and organs in human body comes out from a bunch of initially identical cells produced by a single zygote - the same processes would be expected in cancers. Lloyd J. Old has found common genetic programs at work in tumor cells and gametes that led him to describe cancer as a "somatic cell pregnancy" [33]. In sections 6 and 7 of the manuscript we will search an answer to the question: how a normal and well-differentiated (somatic) cell becomes "pregnant" in the absence of fertilizing agents?

One can suggest that a cluster of young cancer-cells would not survive in the heavily populated competitive environment unless their development is driven by powerful autonomous mechanisms of self-regulation and adaptation. Such self-organizing entities belong to the class of complex adaptive systems (CAS) which are capable to learn from their experience while functioning in variable ambience. Adaptive evolution (evolvability) and the emergence phenomenon are their yet unexplained characteristics. Emergence implies appearance of certain unpredictable and qualitatively new functions that pop up out of the multiplicity of relatively simple interactions.

It is widely accepted, that all CASs share the following common characteristics: 1) robustness – the ability to maintain a basic level of dynamic equilibrium; 2) resilience – all CASs are capable to restore the quasi-equilibrium state after various perturbations; 3) multi-level organization in terms of complex structural and functional hierarchy; 4) self-organization that implies creation of more complex internal structures without external resources or information and, of course, 5) adaptability in the sense that any CAS can vary its strategy and tactics according

to a new or previously experienced situation. The listed hallmarks of autonomously functioning systems are unimaginable without synergy, which implies an orchestrated, synchronized and interdependent behavior of all system-components.

We argue that cancer has all the traits typical for any CAS: cancer cells are hard to destroy even by chemical toxins and radiation, since they coordinate their action in order to survive as an entity. Only united and self-organizing system of cooperating cells would be able to start the vital struggle against the powerful host-organism. The cancer-system shares the phase-space with the host-CAS which is its rival and breadwinner at the same time. New organism should either defeat its host, or, alternatively, obey its rules and commands adapting to the variable ambience.

3.1. Adaptive behavior and diversity of cancers

There are about 200 types of cancers each type comprising multiple "families" and sub-types of cells. The scientists from the Wellcome Trust Sanger Institute in Hinxton, England, recently announced 73 different combinations of disease-causing mutations in the breast tumors each involving up to six different genes from a set of 40 driver genes [34]. Canadian researchers have shown that the cells taken from patients with acute lymphoblastic leukemia are actually composed of multiple families of genetically distinct leukemia cells [35]. No doubt, that the treatment of such a diverse pathology would not be efficient without understanding of the most general regulatory mechanisms common for all cancers.

What is the reason of cancer diversity? Are its cells the clones of distinct "cancer-stems" that originate simultaneously, or they emerge as new cells due to clashes with surrounding cells that produce odds and ends of damaged cellular components?

We assume that an interaction of poorly differentiated cells with the bystander elements of stroma can yield various karyo- and phenotypes through the same mechanisms that take place in the first "nursery" of emerging cancer. The tumor micro-environment is a complex system of many cell types, including endothelial cells and their precursors, smooth-muscle cells, fibroblasts, granulocytes, lymphocytes, macrophages, etc. Taking into consideration the features of CAS, one can suggest that adaptation of young, meta-stable and extremely motile cancer cells to variable and heterogeneous micro-environment plays crucial role in the process of cell diversification; however, there is another possibility to provide diverse "stems" and their clones. This "fresh" idea about recurrent (iterative) cycles of carcinogenesis that imply successive production of less complex generations of malignant cells is described in section 7.

Many cancers adapt to chemo- and radiation therapy: according to some researchers, the clonal selection leads to the resistance of recurrent tumors [36]. If "cancer-embryos" are nurtured in various conditions before they proceed to active life-cycling, they might give birth to distinct "clones". This process cannot be considered as selection, but as the emergence of new organisms by the same scenario as in the first act of carcinogenesis.

It should be noted that the adaptation itself is not a well understood phenomenon. Elusive non-molecular processes of information exchange between the cells/tissues are difficult to study. As a result, we often ignore an obvious fact that no process of learning (gaining

experience) is possible without data storage. No doubt that some mechanisms of data memorizing should exist in all, even in simplest entities capable to adapt and develop: ambient information has to be perceived, processed and stored in a readily accessible (usable) form. We argue that a kind of associative memory must be an embedded feature of all adaptive systems, among them, of cancers, since autonomous functioning, adaptation and development are unimaginable without the available information on previously experienced states [5]. The physical basis of a system memory is closely related to real-time holographic mechanisms that are basic for any CAS. These poorly understood mechanisms that imply the wave-wave and wave-matter interactions ensure the unification and integration of many separate elements into an autonomously functioning system of interdependent agents (see below).

3.2. Collective behavior of malignant cells

Cells and other elements of complex biological systems are functionally interdependent – they exhibit evident signs of collective behavior being organized as a hierarchy [37-39]. If cancers are integral and adaptive organisms, the action of malignant cells should be strictly coordinated. Indeed, nontrivial spatial correlations between malignant cells have been found by various researchers. The cooperative behavior, namely, collective migration of malignant cells during their invasion into healthy tissues seems to follow essentially the same pathways as healthy cells that participate in embryological development and damaged tissue reparation [40]. Cells performing collective migration share many biological characteristics with independently migrating cells but, by affecting one another mechanically and via signaling, these cell groups are subject to additional regulation and constraints [41, 42].

Experimental and clinical observations support the suggestion that cancer cells form a complex and integrated system. G. Lambert studied the collective response of breast cancer tissues to drug-induced stress and found a similarity between the rapid evolution of drug resistance in cancers and the behavior of bacterial colonies under starvation conditions [43]. Professor P. Davies, principal investigator of a major research program funded by the National Cancer Institute, argues that cancer is not a random bunch of selfish rogue cells behaving badly, but a highly-efficient pre-programmed response to stress, honed by a long period of evolution. [7, 44].

Hence, one can regard cancer as a life-tenacious organism created by and incorporated into relatively mature tissues of the host-body. This complex adaptive system, which is doomed to conduct a life-long battle with its superior ancestor - parental body, has its own powerful self-regulation mechanisms, a flexible primitive structure and enough power to hunt the preys – host cells.

4. New approach to the cancer non-invasive study

Cancer remains an elusive, unpredictable and scary disease mostly because the malignant processes are difficult to detect and monitor. The most efficient methods of cancer conventional diagnostics are either harmful or too costly to be used in vivo as often as necessary. Oncologists lack a non-invasive, reliable, user-friendly, automatable and non-expensive test for tracking

the malignant processes on the organism-level. We were lucky to find the solution to this problem thanks to an unexpected discovery of a previously unknown physical effect - "the holographic diffraction" which turned out to be characteristic of all biological objects [4-5, 45]. Detailed description of the innovative technology developed and tested by the authors was published earlier [46, 47]; in this manuscript we present concise information about this principally new approach to the detection and monitoring of malignant processes for a better understanding of our empiric data.

The computer-assessed diagnostic system "CID" provides reliable and comprehensive spectral information valuable for non-invasive detection and monitoring of malignant processes of any location and type [5]. The CID-system belongs to the class of the imaging technology dubbed BHT (Bio-holographic tomography) which is both – a diagnostic and research tool. The device is not cumbersome or difficult to operate: examinations can be conducted right at a patient's bed and the interface is so simple that even novice users can collect data in the form of BHT-grams. The whole procedure of the BHT-examination lasts several minutes: distal body-parts (usually 10 fingertips) are exposed to the pulsed electric fields that are strong enough to initiate the discharge of air; the relaxation of excited atoms and molecules in ionized gas produces optical radiation, which is captured for further processing and analysis; cancer-specific optical signatures are determined by analyzing effects of electric impulses on the body distal "terminals". A computer operates the device and performs analyses of recordings (fig. 1).

Figure 1. BHT-examination implies the recording of ten fingertips' emission that takes only 2-3 minutes.

In observational research, results can be changed or biased by the act of measurement itself. The distal areas of human body are used as a source of information because they provide less distorted spectral information about entire body-state avoiding "an observer/measurement effect". A set of images-tomograms of 10 fingertips (each showing a 2D momentary "slice" of the 3D system) is recorded for the detection and monitoring of malignant processes in human body. The fingertips are exposed to electric impulses of distinct frequencies, so that one gets comparable information on the character of resonant responses to electric impulses of particular frequencies in 10 distant areas of human body (necessary for mapping of pathological process). The harmless and short-term procedure of a person examination can be conducted as often as necessary.

In clinical practice various modalities are used for imaging of body parts, including radiography, computed tomography, magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). All these modalities focus on particular areas of human body in order to get the images of organs/tissues that physicians need to examine. In BHT there is no necessity to screen entire body part by part, since the holography-based mechanisms spread the scaled information about the deviations from normal functioning of cells and tissues throughout the whole body acting akin to a wireless system of bio-communication. Experimental and clinical study of various patients (with and without diseases) enabled us to reveal some cancer-specific spectral signatures in fingertip BHT-grams [5, 48] that prompted subsequent research in oncology. The CID is a portable, easy-to-use and non-costly tool of the whole body examination; it allows the determination of the spatiotemporal distribution of malignant processes throughout an intact organism. The CID-system is already implemented in routine diagnostic practice.

Pre-existing devices of the same class [49, 50] failed to provide reliable and reproducible information on cancer-specific emission and on the dynamics of systems. In order to stabilize the air discharge plasma and obtain the informative optical data it became indispensable to modify the device and alter the examination procedure. We have filtered out the most variable and non-informative spectral components thus getting reproducible and comparable recordings of fingertip emission. Stabilization of the discharge plasma and improvement of data quality have been achieved through the limitation of the gas transit-time across the discharge zone, the restriction of particle upward scattering/dissipation, etc.

It became necessary to conduct a plethora of probes on hundreds of patients with distinct types and stages of cancer before we understood the principles of the holographic imaging and developed the system of data interpretation. Close collaboration with clinicians made it possible to define the matrix of correlations between clinical diagnoses and spectral information obtained in various conditions of data acquisition. Experimental and clinical work conducted during several years led us to the conclusion that interference patterns emitted from body surfaces in response to high frequency electric impulses carry encoded information on the shapes, densities, complexity and dynamic features of the most problematic areas/processes disregarding their type, size and location in human body (fig. 2).

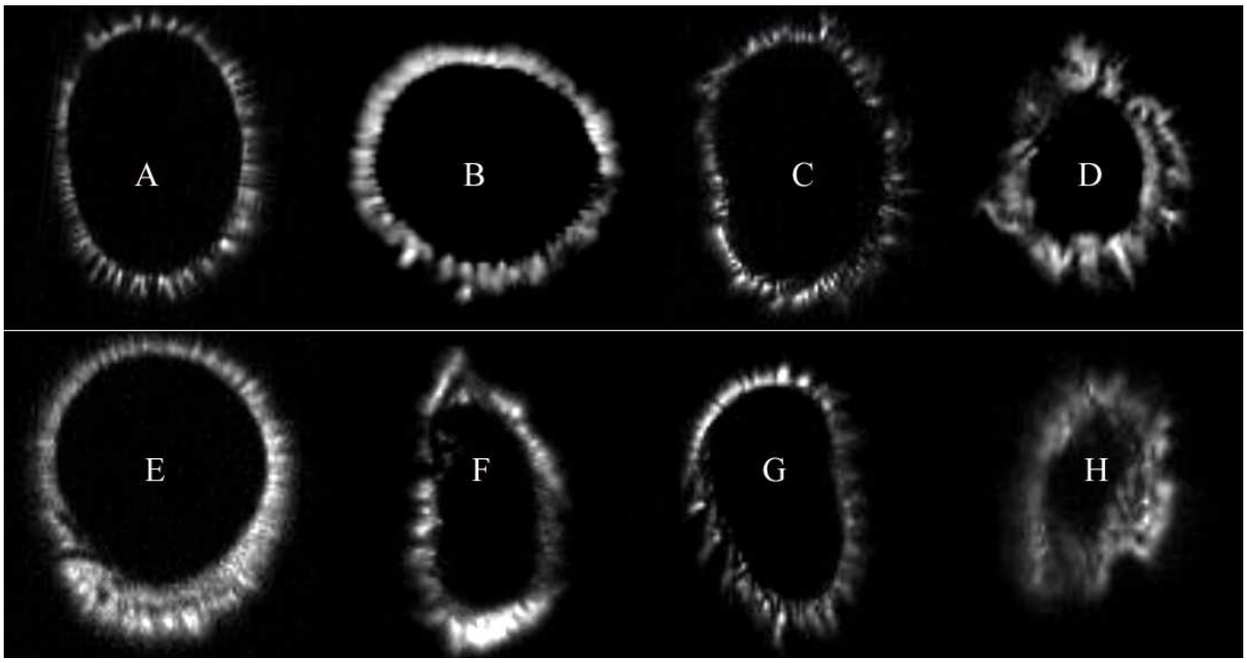

Figure 2. The geometry and texture of fingertip BHT-grams is altered according to certain characteristics of the most affected tissues and organs: A - a healthy person's uniform emission; B – a case of prostate cancer (a chestnut–like flattened shape); C – cancer of the left kidney (the shape of a bean); D – the lactation state; E – gastrointestinal cancer; F – the shoulder malfunctioning (complex elongated shape); G – lung cancer, advanced stage; H – colorectal cancer (terminal stage).

A system in a quasi-balanced state radiates evenly thanks to intrinsic processes of the destructive interference (similar waves propagating in opposite directions cancel one other and do not affect neighboring waves), whereas any perturbation caused by pathological processes results in constructive interference and phase-shifts that upsets the whole system of interdependent waves. Actually, all non-uniformities on fingertip BHT-grams represent the interference patterns, namely the replicas-holograms of the most malfunctioning tissues and cells – the source of wave-imbalance.

This extraordinary capability of system-waves to scale the information on any abnormal process and to deliver it to all body-elements enables the BHT-analysts to observe many structural nuances of pathological areas like in a microscope (fig.3).

The discovery of the astonishing peculiarity of biological systems that act like "bio-microscopes" became a great stimulus for subsequent theoretical and experimental research. This natural phenomenon enabled us to get and analyze the interference patterns/holograms of real anatomic structures using human fingertips as a source of the otherwise invisible and non-measurable information. New approach to the evaluation of the body problematic areas can be referred to as the "Holographic Imaging". Owing to non-locality of holographic information and because of spectral differences between immature cancer-cells and differentiated host-cells, it has become possible to detect malignant pathology with high accuracy [45]. It should be noted that contrary to the spectral analysis of BHT-grams, the visual interpretation of the holographic replicas is not an automatable task.

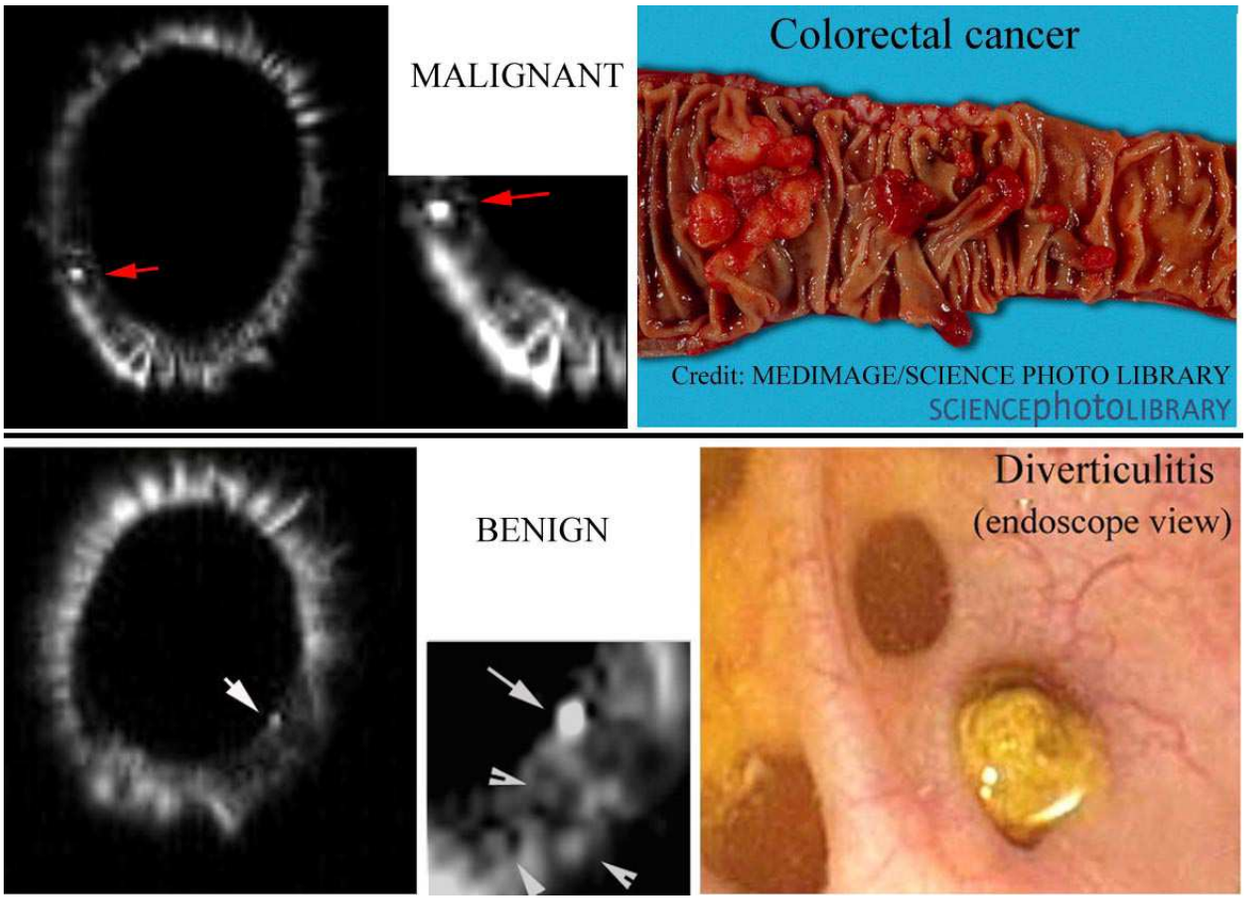

Figure 3. Holograms of the small body-structures are displayed on BHT-grams like in a microscope (see section 5 for explanations of the scaling effects). Two fingertip "coronas" and their enlarged parts are shown next to photographs of similar pathologies. Red arrows (upper images) point to a very bright inclusion embedded into a dark zone. Such a contrast between bright "spot" and dark background is typical for invasive cancer: the degrading host-cells around invasive tumors emit weakly. In the case of benign diverticula (bottom image, white arrows) no signs of degradation are present next to rounded inclusions and the center of relatively intensive emission.

5. Spectral information is distinct in benign and malignant cases of pathology

Waves play enormous role in integration and self-organization of complex adaptive systems, though their contribution to the functioning of human body is still grossly underestimated. Some oscillatory and cyclic bio-activities are studied in the process of functional diagnostics in conventional medicine (e.g., ECG, EEG, etc.); however, organization of nonlinear waves within intact body (especially on micro- and nano-scales) was never explored experimentally.

All physical objects radiate in response to incident electromagnetic waves that are always present in the environment. The spectrum emitted by simple objects such as particles, atoms, molecules and chemical substances, can be recorded and studied much easier than that of complex dynamical systems where internal waves interact with each other. Natural radiation

of human body is extremely variable and weak; besides, any perturbation of observable waves causes their instant change, so direct measurements cannot provide reliable spectral information. Only resonant enhancement of body emission and its distant probing can bring the relevant data on the dynamics and character of intrinsic processes. In our model of carcinogenesis we focus mainly on dynamic processes and interactions rather than on various participants (the solid components) in biological processes.

The hardware-software system "CID" records a resonant response of a body to applied electric impulses of high frequencies. This spectral information is valuable for investigation and understanding of yet unknown functional mechanisms in human organism. An elusive and extremely fragile system of organized and interdependent physical waves of various types ensures not only the self-control and self-regulation of the system, but also its interaction with ambient waves and fields [5].

Waves are carriers of energy and information, so their internal "life" and exchange with environment is worth to study. One can ask whether various non-molecular signals, waves and their interference patterns emitted by nontransparent and dynamic organisms carry non-distorted (and interpretable) information on the state of various tissues, cells, intercellular communications and other peculiarities of internal processes. Experimental findings of many researchers prove that the answer to the posed question is positive: G. Hyland has shown that some biological objects emit highly focused coherent electromagnetic waves of ultra-low intensity. The author assumes that such an emission is an outward sign of an orderly functioning metabolism [51]. Japanese researchers caught sound waves generated by bacteria and showed that bacterial cells can enhance the proliferation of neighboring cells through acoustic waves. It is suggested that sounds can function as growth-regulatory signals for entire colony of cells [52]. The alteration of bacterial growth and the synchronization of light emission of adjacent cultures were observed by M. Trushin [53]. An ability of placental mammalian cells to generate pulsating light signals in response to near-ultraviolet light irradiation was discovered by G. Albrecht-Buehler [54]. Such a reversible enhancement of autofluorescence can be used by cells for the "quorum sensing" and coordinated action. And finally, our own experimental and clinical data provide arguments on behalf of the well organized system of interacting waves whose rules and mechanisms are already disclosed (at least partially). The coordinated vibrations and waves of a system medium turned out to be crucial for system integrity and self-regulation via real-time holographic mechanisms (see below).

Although the study of weak radiation of complex biological objects is still in its infancy, spectral analysis of cells, tissues and entire organisms offers great potential being a source of readily automatable biomedical information. The development of spectral methods for Biomedicine was prompted by recent advances in computer sciences, since enormous amount of spectral data requires specific tools and appropriate concepts for data interpretation. There are many approaches to spectroscopic studies of biological samples. Here are some examples that demonstrate the usefulness of spectra for medical studies:

- American researchers developed a novel microscopy technique, called nonlinear interferometric vibrational imaging (NIVI) intended for quantitative analysis of tissue specimens [55]. The NIVI can differentiate cancer versus normal tissue sections with greater

than 99% confidence interval in a preclinical rat breast cancer model and define cancer boundaries in fresh unstained tissues.

- Extremely detailed study of cells in their natural state without the need of fixatives has been performed through Raman spectroscopic analysis [56].
- Surface-enhanced Raman spectroscopy in conjunction with imaging was found to be informative in the studies of the chemical composition of the live cells [57].
- Fluorescence emission spectrum of blood components was found to be efficient in distinguishing normal from early-stage and advanced-stage breast cancer. The sensitivity and specificity of the method are 80.4% and 100%, respectively, in distinguishing subjects with breast cancer from normal controls [58].
- Fourier Transform Infrared (FTIR) spectroscopic studies and Fluorescence Emission Spectroscopy (FES) have been effectively employed in the qualitative and quantitative analyses of rat tissues. The study showed that the spectral profiles are different when the tissue of a particular organ is affected with tumor [59].
- Near-infrared light (NIR) is used to differentiate oxygenated vs. deoxygenated forms of hemoglobin and myoglobin. Illumination of intact tissue with NIR allows qualitative assessment of changes in the tissue concentration of these molecules [60].
- Over the last few years infrared microspectroscopy has been used to study cells and tissues. Research work is now aimed at characterizing spectral biomarkers for cancer diagnosis [61]. Dynamic IR imaging with image-processing-guided frequency analysis is a promising modality for breast cancer detection and may not have the tissue-dependent limitations of mammography. The IR imaging process recognizes the cancer area independently of tissue density, cancer size, and cancer appearance on mammography [62].
- Photoacoustic tomography (PAT) is an automatable emerging technique for spectroscopic analysis and imaging live tissue at depths up to 10 cm for detecting tumors and cancer research. The method enables in vivo study of melanomas with both exquisite sensitivity and high specificity [63, 64]. Besides, it can provide anatomical, functional, metabolic, molecular, and genetic contrasts of vasculature, hemodynamics, oxygen metabolism, biomarkers, and gene expression.
- Angle-resolved low coherence interferometry (a/LCI) during endoscopic examination has been found to be convenient for esophageal cancer diagnosis [65]. Physicians shine short bursts of light at locations of suspected disease and sensors capture and analyze the light as it is reflected back.

It is evident that spectral characteristics of actively developing immature cells differ from the emission of normal cells due to increased metabolic rate and proliferative activity of cancer-cells. Much more difficult is to explain how a small cluster of malignant cells alters the emission of distant body-parts, e.g., human fingertips.

The "Holographic Imaging" of abnormally functioning internal structures through non-transparent body is, in fact, a mind-boggling effect. Nobody could ever imagine that it was

possible to observe the structural and functional nuances of internal cells, tissues and microscopic areas via assessment of fingertip emission; neither could it be suspected that our organism is able to scale the holograms of real anatomic structures and to expose on a huge scale only those cells and tissues that do not obey the general rules of entire system. This "holographic imaging" is a physical phenomenon and it has been explained as a manifestation of background activity of the system nonlinear medium (phase-space) that acts akin to an organizing holographic grating of a body [5].

In complex adaptive systems (CAS), where all components are well-controlled and there exists a strong subordination between the levels of a system hierarchy, a permanent interaction of "each" and "all" (non-locality) is of utmost importance. In order to achieve interdependence of all agents of a CAS, the periodic grating and synchronicity of vibrations within whole medium must be set from the very first moments of a new system emergence. In the next section we will discuss the role of focused coherent waves in the processes of a system-unification that makes it possible to create an integral system of cooperatively acting agents out of separate elements.

Can the waves generated within human body affect the motion of small neutral particles, molecules and cells? Physicists know that certain waves (e.g., light) can serve to bind neutral matter in new organized forms. It has been established that high frequency oscillations of intense fields interact with micron-size dielectric objects trapping and bounding small particles. The artificial holographic/diffractive setups allow the simultaneous production of very high numbers of such traps generated by superimposing coherent beams either through the wave-interference or through the interaction of several beams previously fanned-out by diffractive optical elements [66]. Hence, a kind of feedback interactions really exists between the waves and solid particles of a CAS. If the suggestion about interdependent action of all system-waves and solid "particles" is correct, the medium waves of a biological system would mirror the state of corresponding solid elements (atoms, molecules, cells, etc.) as all these "agents" are enclosed in the partially bounded space. Any alteration in one of these two complementary realms would affect another - either directly or via some intermediate mechanisms; so, one can evaluate the system-wave behavior/patterns (interference) in order to get information on both - the features of background waves and the state of their complementary (solid) structures.

The permanent wave-wave and wave-matter interactions within a bounded space can explain the effect of the "holographic imaging" discovered by our team 12 years ago; it was an exciting day when we were all huddled round the computer puzzled by the similarity between some BHT-grams and real anatomic structures (see section 8).

As mentioned earlier, an integral system of interfering waves is too sensitive to be studied directly: the wave functions collapse as soon as an observer tries to probe this fragile "structure". That is why we take only the most distant minor areas of human body for BHT-examination – the minor "terminals" of a system provide us with less perturbed system-information.

The background order within the medium/space of a system can explain many peculiarities of CASs. This unifying and organizing realm of a system must be preserved during the whole life-cycle; obviously, the ordered motion of a system-medium and the wave interactions set at initial stage of the system-genesis become more and more complex in parallel with its growth and development. The invisible activity of waves in the phase-space occupied by a CAS can be considered as a "wireless" system of communication between all system-components.

Information propagates in the form of a signal or a message that cannot alter behavior of the solid matter directly but can instead be sent simultaneously to all system-waves. Obviously, diverse "recipients" of information would not react to one and the same message in a similar way; however, weak interactions ensure delivering of a message to a large "audience", actually to the whole system, so that the instructions and commands would not miss their targets.

The question arises whether there are any specific mechanisms that a biological system utilizes for the reinforcement/amplification of the most urgent and/or essential information; it is also very important to understand how a system controls its "misbehaving agents" and which mechanisms are able to transform weak signals into an effective force? We have reasoned that the system-mechanisms of self-control and self-organization require the interaction between weak (information-associated) and strong (energy-associated) waves; powerful or focused waves can play the role of mediators between the information-associated processes and the processes that affect distinct particles, molecules and cells. The reinforcement of information without actual participation of the solid matter in the process of signal amplification is possible via the holography-based mechanisms.

The holographic principle and real-time holography are the only concepts that can explain the imaging of scaled internal structures on the surfaces of autonomous systems. A characteristic feature of any static and dynamic hologram is that any part of a holographic record can be used for the reconstruction of the whole recorded scene. In physics the principle of holography implies that information about a 3D space-volume is encoded in 2D form on its boundary [67-69]. We argue that permanent encoding and decoding of information is a natural phenomenon specific for all autonomously functioning systems; it should not be confused with the conventional process of technical holography.

The real-time holography enables a rapid successive recording and read-out of the information (interference patterns); in the case of a CAS the amount of the processed information can be very high (terabits/s), since the operation is performed in parallel within the entire volume. When creating a hologram, the ordered reference waves (aka the ordered medium-waves of the body) interfere with disordered waves generated by perturbed waves/particles. This information can be reconstructed if the reference waves are subtracted, e.g., by conjugated waves that propagate in the opposite direction. The original object's field/image is reconstructed when the waves deflect in the hologram structure. The refresh rate (update) of information correlates with the periods of phase-conjugated waves, so the reaction of the entire system to any disorder in a high frequency range would be much more "acute" than in the case of a mismatch in slower processes.

We argue that the holographic mechanisms play crucial role in the self-organization of any CAS. These mechanisms imply existence of a hidden order in the background medium where all waves comprise a harmonious structure of vibrations and standing waves; the same mechanisms are critical for the adaptation (decentralized memory) and the resilience of biological systems. Any perturbation, disregarding its actual cause and culprit, would result in constructive interference and phase-shifts of corresponding waves thus altering the entire (scale-invariant) system of background harmonics. Besides, the principle of holography makes it possible to observe the most disordered tissues and organs via assessment of their holographic replicas on distant surfaces of a system (e.g., fingertip BHT-grams), since the "whole" and its "part" can equally reconstruct the entire "holo-image".

The scaling of information in a system of natural origin depends greatly on the frequency/wavelengths of the most perturbed intrinsic waves. Thanks to the fractal nature of body wave-structure, its self-similarity and scale-invariance, the high frequency signals from excited cells (short waves correspond to small structures) can reach the body surface only after their scaling through the waves of lower frequency (longer waves correspond to larger structures of a system): the fingertips BHT-grams display the interference patterns with the resolution that is proportional to the frequency of constructively interfering waves.

On the way towards the body surface, the upward propagating waves of high frequency (complementary to cells and other microscopic structures) are scaled through the doubling of their amplitudes and periods at each successive level of the hierarchy; that is why the interference patterns/holograms of cells and their constellations are emitted with higher resolution compared to holograms of larger parts of the body. This peculiarity of the multilevel and self-similar structure of interacting waves enables us to observe and analyze the most active processes and also malignant cells/tissues via assessment of fingertip BHT-grams (see section 8 for examples of the cell-holograms).

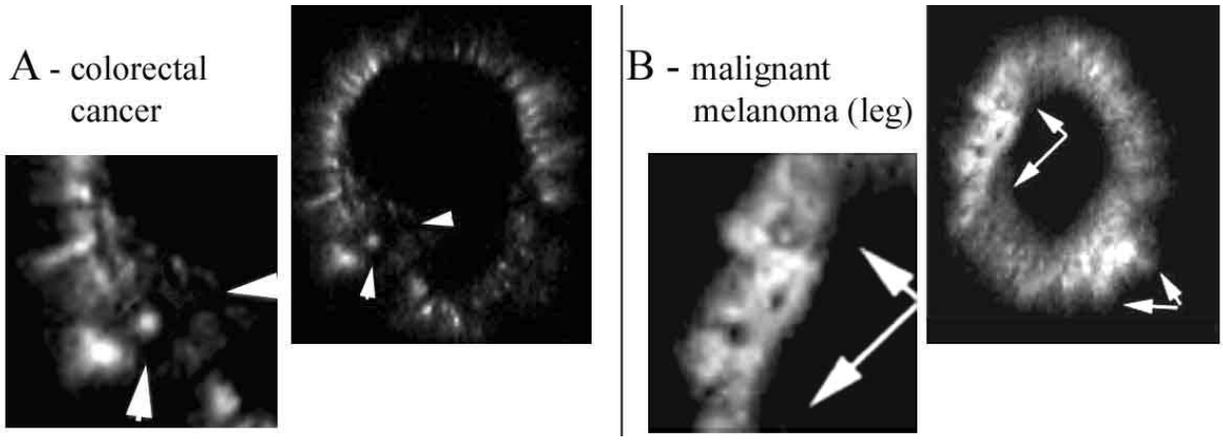

Figure 4. Examples of cancer-signatures on fingertip BHT-grams. In the case of colorectal cancer (A) a part of growing neoplasm paves its way through degrading surrounding tissues (dark zone around to bright inclusion). In the case of malignant melanoma (B) the rapidly proliferating cancer-cells produce an effect of diffuse illumination. The multidirectional radiation that illuminates major parts of BHT-grams is a hallmark of the high frequency coherent emission generated by large conglomerates of poorly differentiated cells (see section 6 for more explanations).

In the cases of cancer, two autonomously functioning entities occupy a shared phase-space and compete for available resources. The conflicting organisms that are "trapped" within a shared body are not able to synchronize their individual rhythms and achieve a state of a quasi-balance. Hence, the BHT-grams of the patients with cancer would display the replicas (interference patterns) of aggressive neoplasm with huge resolution. In certain cases of malignant pathology the fingertip "coronas" demonstrate dark areas around brighter inclusions that present the "remnants" of cells destroyed by cancer-cells (fig.3 and fig. 4,a); The effect of illumination by diffuse light is a BHT-characteristic of actively proliferating non-differentiated cells (fig. 4,b).

6. Emergence of cancer via random lasing

Waves – the carriers of energy and information - are the sole candidates to perform the task of information reinforcement in living systems. In a bounded system of interdependent mechanical and electromagnetic waves of various intensities, wavelengths and frequencies, any perturbation propagates throughout the entire system. The higher coherence and intensity of waves the greater their influence on the solid matter. The interaction of the information- and energy-associated events ensures synergy and coordination of all system-components.

The recently discovered physical effect of "Random Lasing" [2, 3] which implies the focusing and amplification of light in a non-uniform and disordered medium, e.g., in biological tissues, casts new light on the interaction between information and energy-related biological mechanisms. The reinforcement of information through the real-time holographic mechanisms differs from the principles that focus and amplify waves in random lasing; the random lasing implies a complex process of wave-trapping and releasing by disordered excitable material. Emitted waves become much more focused and coherent than those that have been initially "arrested", which explains the term "lasing" (light amplification by lasers).

Conventional lasers that amplify light through the stimulation of photonic emission, require an excitable medium (gain medium) and some feedback mechanisms that temporarily trap the light before emitting a narrower spectrum beams. Usually the gain medium in lasers is excited by pumped energy supplied as an electrical current, or as light of different wavelength, while the photons are confined between mirrors in optical resonator.

Back in 2000, several teams of researchers announced the creation of microlasers exploiting a disordered dielectric material as gain medium [70, 71]. A disordered material that comprises the scattering elements in random positions was found capable to exhibit a laser-like behavior [72]. Electromagnetic waves bounce from one scattering center/cavity to another and such a recurrent scattering on a microscopic length scale temporarily traps light. Hence, the random lasers do not possess large cavity or mirrors typical for conventional lasers; they contain only multiple non-uniformities that scatter light (or other waves). Small irregularities in the material act just like artificial mirrors in laser resonators preventing the light from escaping too quickly. These non-uniformities can be presented by particles, bubbles, droplets of dye, density fluctuations in fluids, surface roughness, cells in organisms, textile fibers in clothing, etc. In

polymer films and biological tissues the lasing effects take place because of naturally formed cavities and non-uniformities that temporarily trap energy of waves through internal resonances.

Coherent amplified emission and dramatic spectral narrowing take place only if excitable medium gains energy above the threshold of its excitation [73, 74]. The random micro-laser characteristics can be tuned by varying the geometry of the scatterers' clusters, since each cluster operates at its own specific wavelength, depending on its shape and size.

In some cases constructive interference of backscattered waves brings transport of light to a complete halt (Anderson localization). Philip Anderson was awarded the Nobel Prize in physics for the theory of light localization in disordered medium [75]. In principle, not only electrons and photons, but actually any wave can be localized in a similar way: successful experiments aimed at the sound-wave localization in the strongly disordered 3D samples (composed of aluminum beads) have been described in 2008 [76].

The effects of light amplification and lasing have been found in various vegetable and animal tissues as well as in human tissues from various organs [77]. Even individual cells are capable to produce narrowband laser emission remaining alive after prolonged lasing action: these data were published by researchers from Harvard Medical School, who created biological cell "lasers" based on green fluorescent protein [78]. The team engineered human embryonic kidney cells to produce this protein; when they placed such a cell in the optical micro-resonator and exposed it to pulsed blue light, the cell started to emit a directional laser beam visible with the naked eye.

We have described the random lasing effect and wave interactions in detail because these findings elucidate the energy-mediated mechanism by which information in the form of weak waves affects inert material and creates an "order out of chaos" within the whole system (essential for the system-resilience); besides, the random lasing can account for the appearance of anaplastic cells – the process referred to as the "dedifferentiation" [79]. The spectra narrowing and light amplification are equally important for the understanding of cancer aggressive behavior as the focused light can readily destroy surrounding tissues and facilitate the neoplasm progression.

Indeed, intensity and character of lasing in malignant neoplasm were found to be distinct from benign tissues of the same origin. The Utah University researchers have demonstrated that the malignant colon tissues, when soaked in the laser dye Rhodamine 6G and excited by laser light, emit many more coherent lines than benign tissues in the same colon [2]. The disorder in cancerous tissue was much more chaotic than that in a benign tissue due to a mixture of distinct cells and processes of degradation; however, the increased intensity of coherent radiation in cancerous tissues is indicative of the aggressive behavior and active signaling between elements of neoplasm. The Utah University scientists have experimented with various healthy and cancerous colon tissues taken from different patients, as well as from other parts of the human body such as kidney, with very similar results.

It is acknowledged that the radiation pressure from the focused laser beams is able to trap and physically move small dielectric particles acting like a kind of tweezers. S. Kawata and T.

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Sugiura were the first to demonstrate that the field can be coupled to the particles in proximity on the order of 100 nanometers [80]. Optical interaction forces are able to organize microscopic objects with sub wavelength accuracy; they can be very long range and oscillate in sign at the optical wavelength [66, 81]. Continuous evanescent field that originates in conditions of multiple internal reflections within a small bounded area can guide a large number of particles into a preferred direction.

The field-wave-matter interactions discussed above can be considered the key mechanisms of the self-organization in live cells, since a complex system of organized waves is able to direct and unify diverse elements into an indivisible "whole".

Random lasing creates a perfect order out of extreme disorder. This effect takes place in a chaotic excited medium and it might facilitate creation of a new ordered system out of "ashes" of the host-body degrading cells. Such "Phoenix Paradigm" was proposed by researchers of the Pittsburgh Cancer Institute: their experiments with the Kaposi Sarcoma-associated Herpesvirus resulted in the conclusion that excessive cell death, rather than its absence, may be a defining force that drives the cancer emergence [82]. In a stressful situation, e.g., when deprived of energy and oxygen, living cells can act as a gain medium for wave reinforcement. The increase in internal pool of energy that results in excitement of cellular matrix can be caused by many "cancer-promoting" factors: the degradation of intracellular substances, intrusion of some toxic substances or viruses/microbes into cells, increased temperature during inflammatory reactions, etc. can contribute to random lasing within a small bounded area; however, all these factors should be evaluated from the standpoint of their energy-associated effects upon an emerging system.

Coherent radiation of any cellular constellation can reach the body surface if cellular emission is strong and distinct from less intensive radiation of surrounding tissues. The signatures of random lasing are especially prominent on BHT-grams of the patients with aggressive malignant processes (fig. 5).

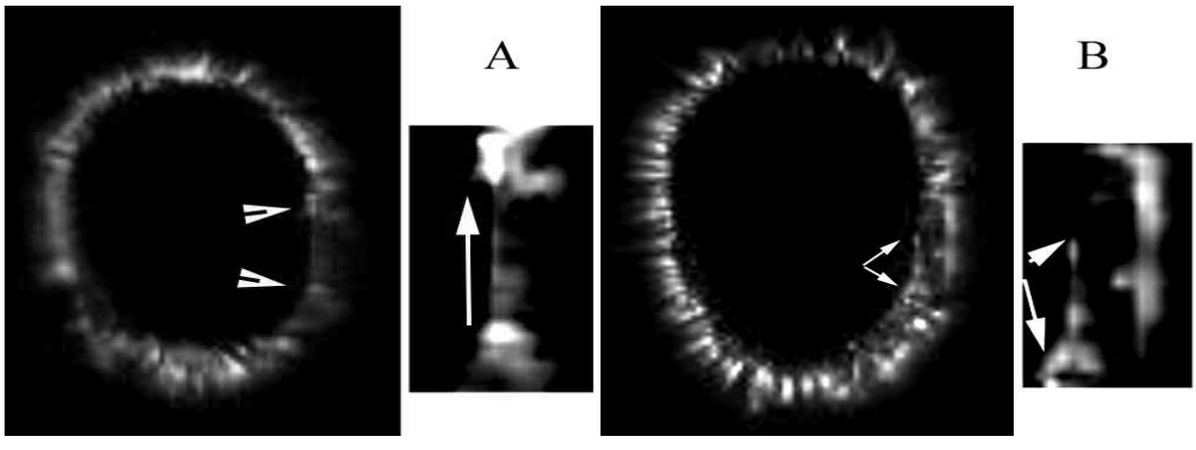

Figure 5. Examples of coherent beams produced by cancer cells. Enlarged and slightly contrasted parts of fingertip coronas are shown next to the raw BHT-grams. A – gastrointestinal cancer, ongoing radiation therapy; B – non-treated renal cancer with spreading metastasis. White arrows point to the scaled holograms of straight tiny lines (focused light).

7. New concept of cancer origin: Dramatic events within a "cancer-nursery"

Cancer, as a new system with altered karyo- and phenotype, originates within a larger and more mature host-system only if a cluster of genetically altered cells builds up its real-time holographic mechanisms of control and regulation. The physical processes within a bounded area of the host-organism play critical role in the cancer-emergence.

We argue that the early carcinogenesis is a multistep process and it starts in a small "nursery", isolated from the matter, energy and information. Such a segregated "nursery" is deprived of oxygen and nutrients having no access to blood supply for this or that reason (a trauma, fibrosis, etc.). A number of starving ischemic cells undergo a chain of metabolic and structural alterations that include the shift of metabolism from aerobic to anaerobic glycolysis, significant increase of Hypoxia-Inducible Factors [83], activation of cell-death programs, disruption of cellular membranes, release of energy from complex substances through their degradation, and other dramatic events typical for metabolic and hypoxic stress in "cut out tissues".

A growing body of evidence supports the view that hypoxia can contribute to the development of cancer. Some researchers established that hypoxia drives cancer progression by promoting genomic instability and that inactivation of apoptosis is essential for tumor-cell survival during this process [84, 85]. Chinese researchers demonstrated that hypoxia inhibits serum withdrawal-induced apoptosis in endothelial progenitor cells [86], while Australian scientists determined that certain monocyte/macrophage populations survive better under conditions of low oxygen [87].

Low oxygen levels characterize the micro-environment of both stem cells and rapidly growing tumors. Moreover, hypoxia is associated with the maintenance of stem-cell–like phenotypes and increased invasion, angiogenesis and metastasis in cancer patients [88]. Recent observations demonstrate the parallelism existing in hypoxia responses of embryonic, adult and cancer stem cells: the mechanisms involved in hypoxia-dependent processes related to stem cell features and tumor progression include the maintenance of the undifferentiated state, cell proliferation, tumor neovascularization, extra-cellular matrix degradation and motility factor up-regulation [89]. Hypoxia often leads to increased aggressiveness and tumor resistance to chemotherapy and radiation [90]. All the findings about the effects of hypoxia and starvation on the state of bounded cellular constellations were taken into account while working on the new concept of cancer emergence.

According to our hypothesis, not only hypoxia, but also isolation from other environmental processes should be considered as the key factors that initiate carcinogenesis. The degradation of starving cells should be tightly regulated in order to rescue at least some of confined cells. It is well known that autophagy is a highly conserved self-digestion process to promote cell survival in response to nutrient starvation and other metabolic stresses [91-92]; however, the role of autophagy that may lead either to cell survival or to cell death is poorly understood in the context of early carcinogenesis.

The autophagy is the chief machinery for bulk elimination and reutilization of aberrant cell components - constituents of cytoplasm and organelles. In the cases of cancer this "self-

digesting" mechanism plays an essential role at all stages of the disease, since it helps to prevent tumor cell necrosis by mitigating metabolic stress while acting in concert with apoptosis [93]; the autophagy provides an alternate energy source by degrading damaged proteins and organelles that allow some tumor cells to survive during extended periods of starvation [94]. In the absence of phagocytes, apoptosis would be less efficient as the debris cannot be eliminated from the isolated "nursery" (the disposal of debris is necessary in apoptosis). So, the autophagy seems to dominate over apoptosis in early carcinogenesis though cooperation or alternated action of both mechanisms is not excluded especially just after cessation of the blood supply. Increasing evidence points to the selectivity of autophagy: it helps to "sort" vacuolar enzymes, to remove the aggregate-prone proteins and to destruct only excessive organelles [95].

There is a kind of similarity between neoplasm and budding primitive organisms (see fig.11 in section 8 – holograms of proliferating cells). A key role of recycling of cellular organelles via autophagy and *de novo* purine biosynthesis was found while studying caloric restriction effects on the longevity of budding yeast (Saccharomyces cerevisiae). This yeast is an effective model for the analysis of genes and cellular pathways. Researchers have shown that additional genes appear to contribute to the restriction of either amino acids or sugar, and that defects in autophagy prevent lifespan extension induced by limitation of nutrients in the growth media [96]. An international team of researchers found that the autophagy helps some starving cells to recover, whereas the cells with a disrupted mitochondrial transmembrane potential inexorably die even under optimal culture conditions [97].

Taking all the above findings into account, one can speculate that a complex action of death-programs maintains viability of some cells at the expense of others and that debris of sacrificed cells serve as the sources of energy and nutrients for a cluster of rescued cells. The most viable cells with primitive organization, increased pool of free energy, altered genetic material and the capability to proliferate without additional resources, start to colonize the "nursery" and prepare themselves for the cooperative functioning.

New genetic makeup of surviving cells might have many reasons, such as partial degradation of cellular DNA, abnormal mitosis due to metabolic stress [98], fusion of cells or their "remnants", functional impairment of DNA repair pathways, the shattering and rebuilding of chromosomes named chromothripsis [99, 100], etc. In chromothripsis the chromosomes exhibit a Humpty Dumpty-like behavior: multiple fragments of chromosomes stuck back together after almost complete "pulverization". Such a massive genomic rearrangement acquired in a single catastrophic event can lead stressed cells towards neoplasia [ibid]; however, the effect of coherent waves on the genetic material of cells should not be ignored, since extreme disorder in overexcited biological tissues would initiate the random lasing processes and the laser-like coherent beams would be able to cut/weld distinct macromolecules and other cellular structures.

Thus, dramatic events within a bounded area are accompanied by the release of free energy that excites the trapped mass of degrading cells. Random lasing takes place in the extremely disordered overexcited medium full of debris where the clusters of nanoparticles, macromolecules and the remnants of cells have their own unique sets of lasing frequencies

[73,74]. Intensive motion of the enclosed mass becomes ordered thanks to the organizing effects of powerful waves in the medium [66, 80, 81].

The wave interactions and the motion of solid matter within an isolated area inevitably reach a state when all dynamic processes become synchronous and coordinated. Increasing laser-like radiation of excited cells can help them to break through the isolation and invade host-tissues. "Cancer embryos" do not and cannot manage their logistic problems at the stages of division, compaction and unification that take place in isolation (prenatal phase); such a neoplasm needs to gain power and become "armed" with laser-weapons before it proceeds to the stages of expansion and growth. At the stage of unification via ordered vibrations and organized motion, the entire cluster of new cells acquires its individual rhythm of functioning and becomes a self-organizing entity ready to grow and struggle for resources.

Duration and timing of all "prenatal" stages are the factors of great importance in any system-genesis. For example, one can deduce that if a "cancer-embryo" is ready for independent functioning but the barrier around its nursery cannot be breached yet, the cells would continue to "chop" internal structures and eventually die. Without supply of nutrients, oxygen and some "building blocks" from surroundings, the trapped energy would be spent on the self-destructive work yielding a cyst filled with fluids/semi-solid material; if, on the contrary, the passage of nutrients through the isolating barrier is open earlier than enclosed cells become integrated and "armed", the neoplasm would grow and develop like a benign tumor.

In the manuscript we do not discuss the "postnatal" behavior of the neoplasm in detail; however, once adaptive malignant organism left its nursery and started the life-long battle with its host-rival, it would repeat the same (formerly experienced) scenario whenever possible by blocking blood supply to minor areas and creating the nurseries for new "generations" within the host or its own tissues (the latter is a source of metastasis). Cancer easily adapts to variable situation thanks to the holographic mechanisms of data storage [5] and its first "experience" determines the behavior of its clones. This proclivity of the neoplasm to execute the learned schema of action multiple times in the same or in a slightly changed form can explain the exponential progression, diversity, resistance to the stress posed by "aggressive treatment" and other yet unsolved peculiarities of cancer. The arrangement of new nurseries in various host tissues can be regarded as a kind of adaptive de-evolution: malignant cells produce new generations of "stems" whose structure becomes more and more primitive in each successive cycle.

The schema presented on figure 6 describes the main stages of such an iterative carcinogenesis.

It is established that non-differentiated stem-cell-like sub-populations of cancer (CSCs) are resistant to chemo- and radiation therapy [101]. Since a "cancer-stem" that yields CSCs originates from the remnants of partially degraded progenitor cells, a kind of genetic kinship exists between the host and malignant tissues. The same can be said about a relatively mature neoplasm and its metastasis: the features of metastasis though distinct from primary cancer cells are usually distinguishable from the metastasis of other types of cancer.

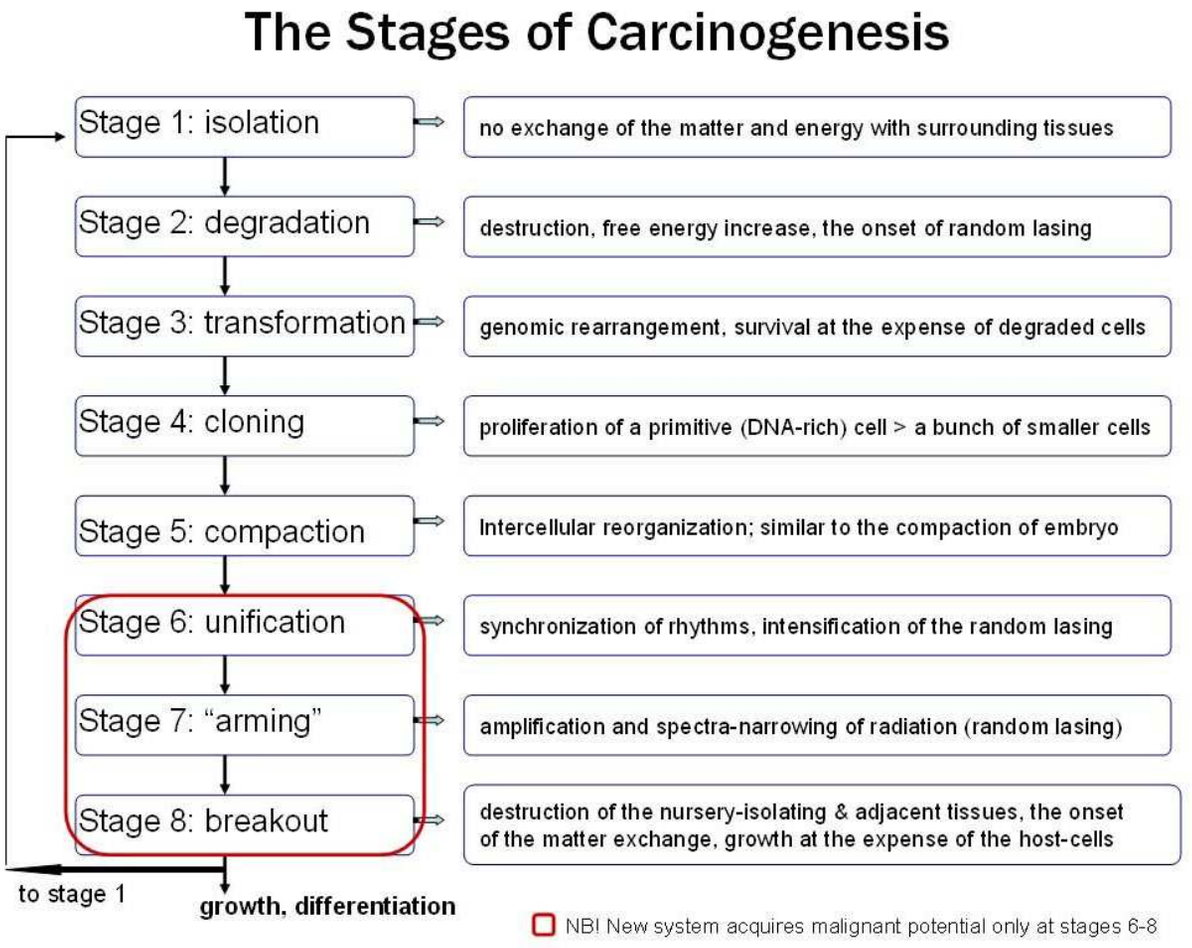

Figure 6. The host-cells should pass through "prenatal" stages before the malignant system leaves its "nursery". Note, that some malignant tissues can start the whole process anew. Each successive cycle would generate less differentiated cells.

To summarize, we argue that malignant neoplasia presents an iterative process of the recurrent system-genesis: one and the same scenario is repeated multiple times within various tissues, in various conditions and with accelerated "prenatal" periods. Such course of the disease can explain the capability of many types of neoplasm to give metastasis through successive rejuvenation of its "daughter-spores". Multiple execution of described tactics of the self-reproduction and the creation of new (younger and less differentiated) generations enables the primary clone of malignant neoplasm to progress exponentially, conquer more and more space at the expense of diverse tissues, resist new stresses and ultimately destroy its breadwinner host. From this point of view, certain stresses posed by standard chemo- and radiation therapy should be considered as the factors that in some cases facilitate the genesis of extremely aggressive and resistant clones of new primitive "organisms".

An unpredictable nature of cancer and dubious efficiency of the methods of its treatment often raise the question whether intervention into the disease course is better than the watchful waiting. For instance, the breast ductal carcinoma in situ, which is a low grade (well differentiated) malignant tumor, can become invasive after more than 30 years since its first manifestation [102]; many patients with low-risk prostate cancer lead a normal life for about 10 years without any treatment: "some prostate cancers might never have developed into serious disease… surgery or radiation therapy may not outweigh the substantial side effects of these treatments" [103].

No doubt, it is urgent and critical to understand the most common rules and principles of malignant neoplasia. We hope that an interdisciplinary approach to the problem and fresh ideas would help everyone involved in healthcare and medical decision-making to plot a clear course through the cancer-paradoxes.

8. Holo-imaging: Some examples

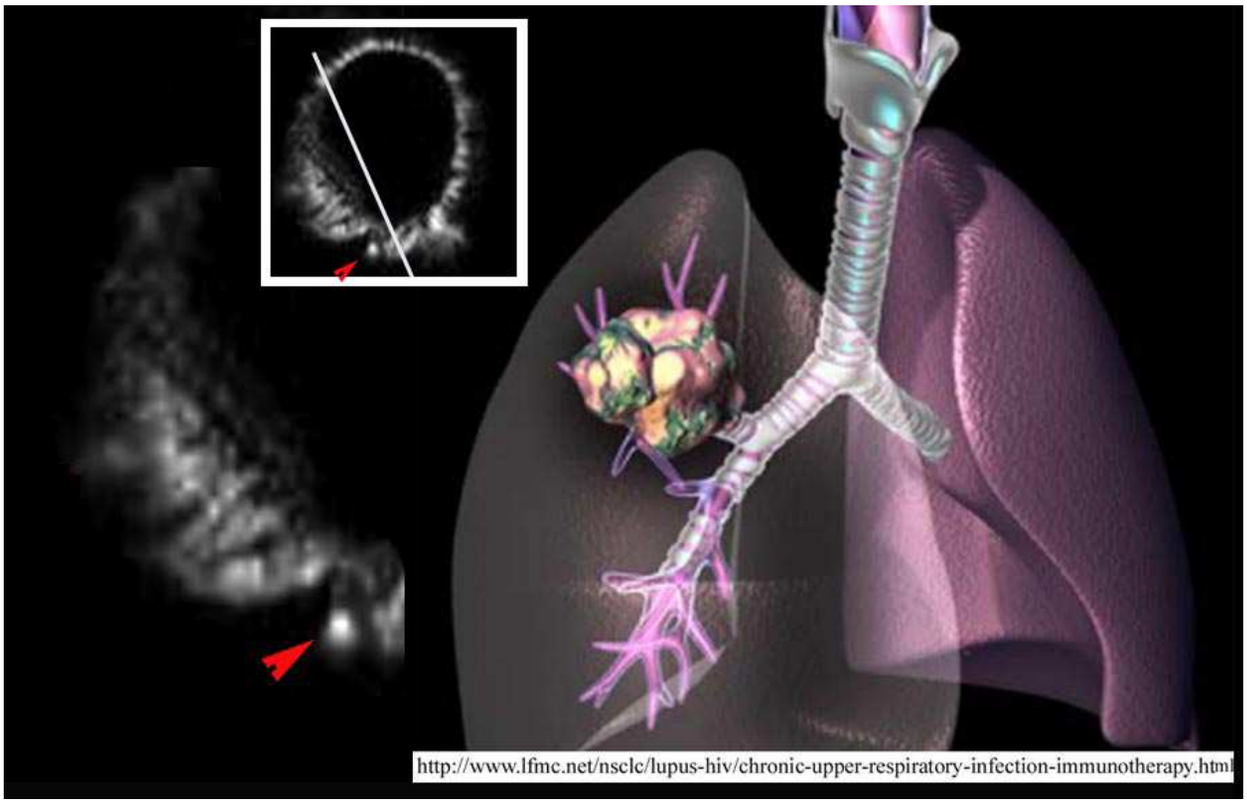

Figure 7. BHT-gram of the patient with treated lung carcinoma. Prominent functional and/or structural disorder in large areas of the body alters major parts of coronas displaying characteristic features of affected tissues in a slightly distorted form. The holographic replica of the most affected lobe of the lung occupies 2/3 of the index finger BHT-gram. Red arrow points to the replica of a growing metastasis.

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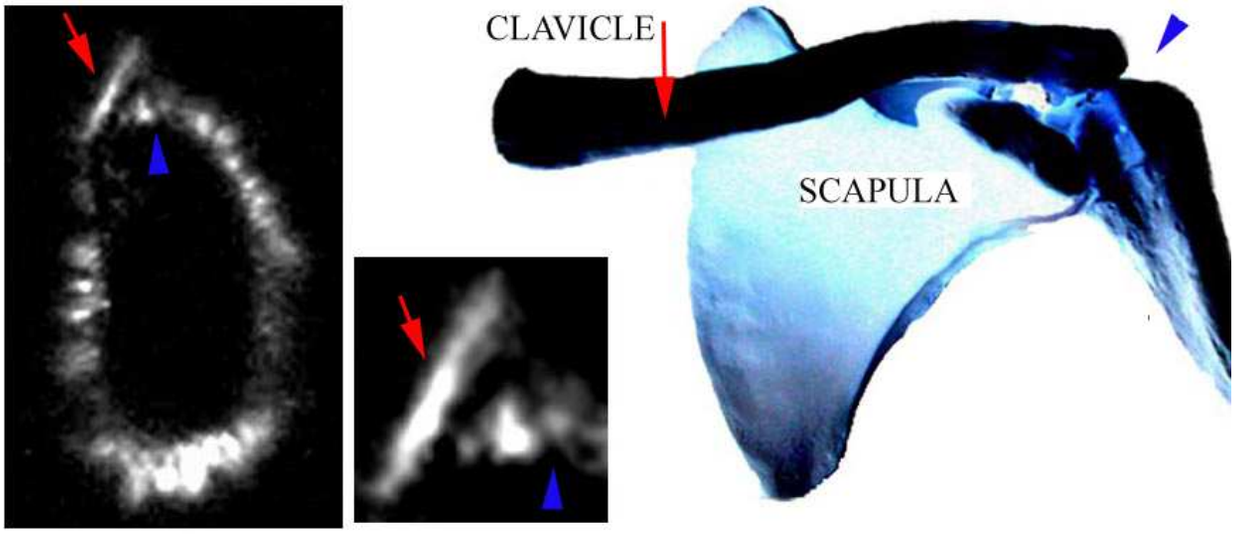

Figure 8. Shapes of presented corona's parts are distorted resembling a shoulder joint (blue arrows); a replica of the most affected bone – clavicle - is displayed with higher quality (red arrows). This is a case of the shoulder malfunctioning (former trauma).

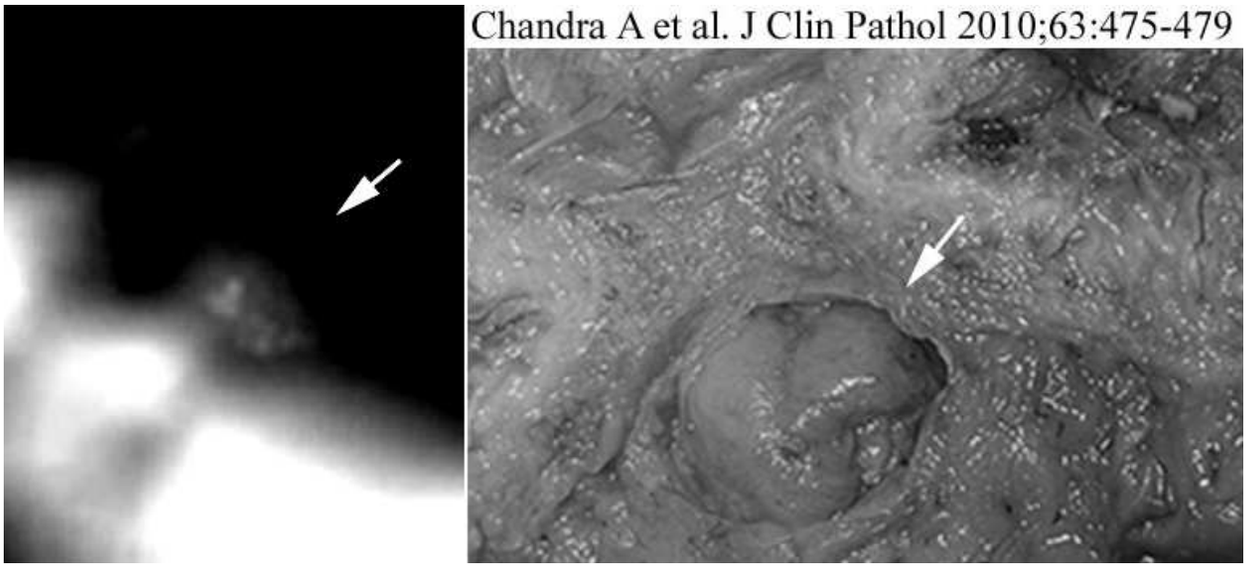

Figure 9. Small areas provide their holographic replicas with higher resolution than the large ones. A case of malignant polyp in the urinary bladder (left) is shown next to the photograph of the bladder cancer.

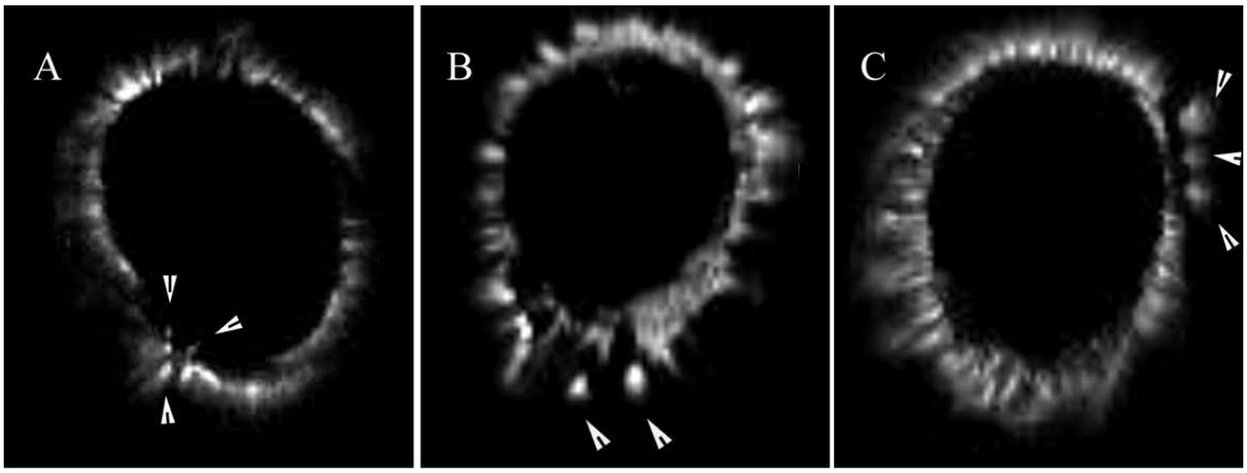

Figure 10. Spreading metastases are displayed on BHT-grams as bright balls on a dark background (indicated): A – Colorectal carcinoma with liver metastasis; B – Colorectal carcinoma with regional metastasis; C – Renal carcinoma with metastasis in regional lymph-nodes.

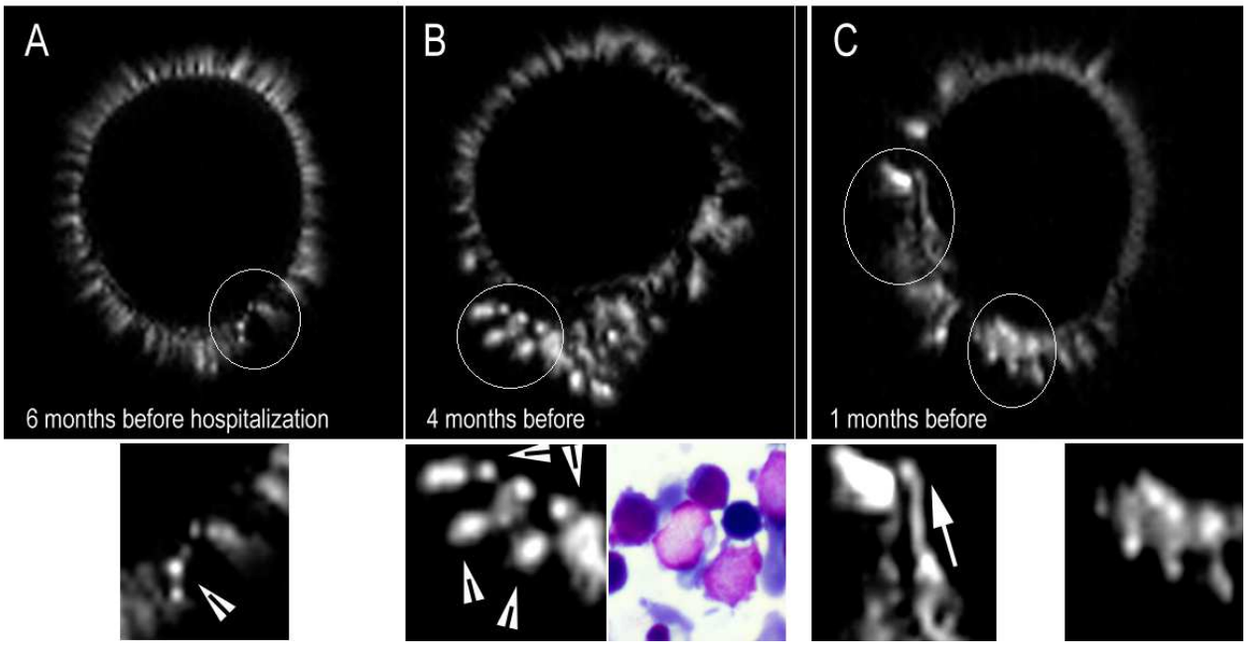

Figure 11. A case of refractory dysmyelopoietic anemia transformed to acute leukemia and liver metastasis. BHT-signs of the disease aggravation have been revealed 4 months before the clinical manifestation of acute leukemia (B). Lab-analyses were not informative a month prior to urgent hospitalization of the patient (C). Abnormally proliferating cells are displayed with huge resolution (B, enlarged part). Compare these holograms of "budding" cancer-cells to the bone marrow smear of a patient with acute leukemia (color-image from http://www.washington.edu/news/2011/09/06/gene-defect-that-predisposes-people-to-leukemia-discovered/).

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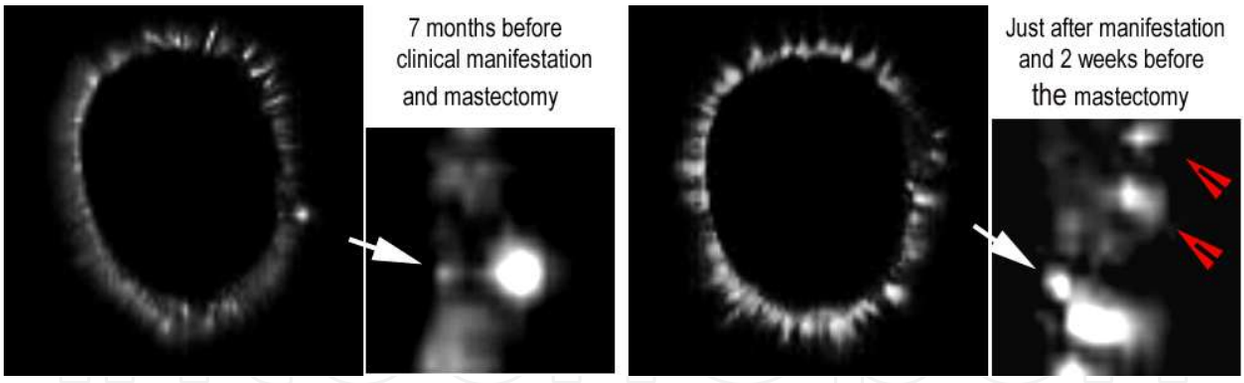

Figure 12. The case of the breast cancer (relapse). BHT revealed the tumor 7 months prior to its detection by conventional imaging methods. Pay attention to powerful diffuse light that consists of multidirectional coherent beams. Such a "fireball" is typical for the neoplasm that just came out of its "nursery" (dark surroundings). Several months later the neoplasm became less uniform and poorly outlined; it grows, multiplies and creates the nurseries for new generations (red arrowheads).

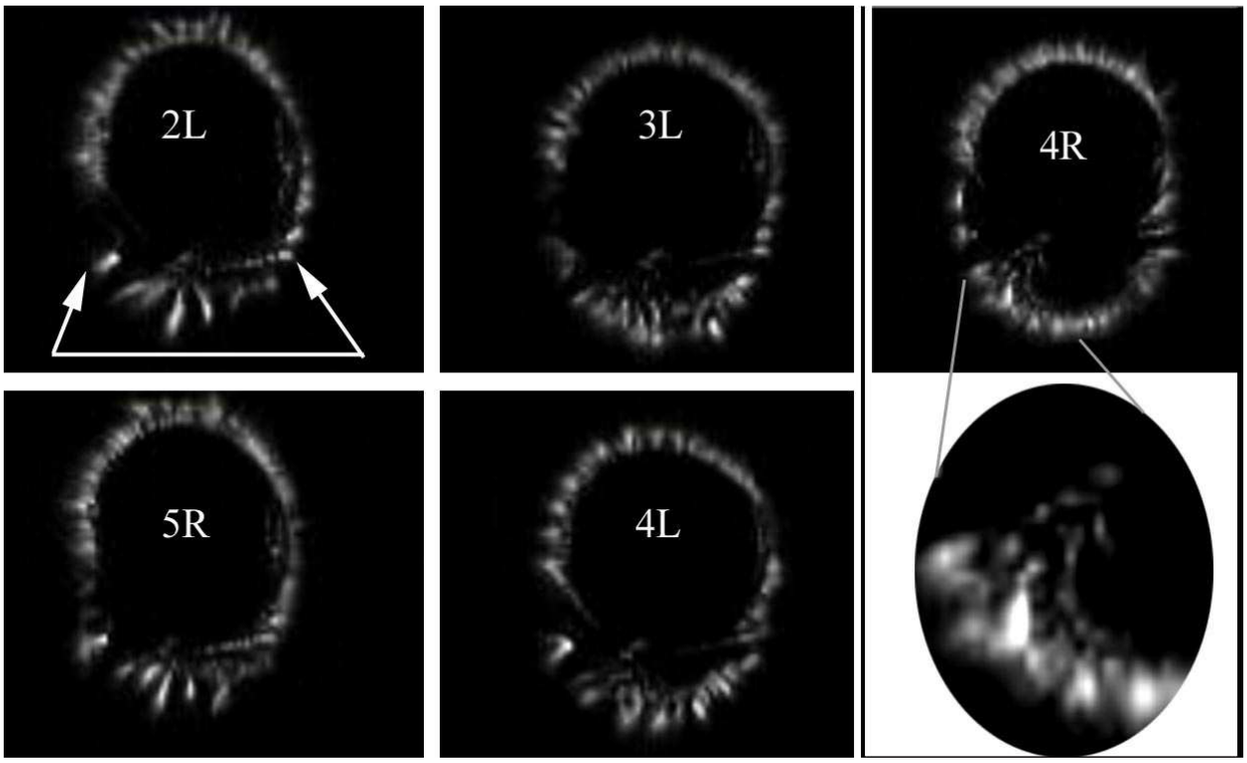

Figure 13. A case of the breast cancer (treated). Almost all BHT-grams display similar replicas of unusually shaped structures. Such a similarity of disordered coronas is typical for an aggravating (sub-acute, transitory) state. A chain of enlarged lymph-nodes in the upper thorax-neck was found to be responsible for the similarity of interference patterns.

9. Conclusion

Presented work was inspired by the discovery of previously unknown physical effects specific to complex adaptive systems of natural origin [5]. The model of carcinogenesis discussed above is a particular example of the more general scenario of system-genesis [5]. According to our data, the "prenatal" life of malignant cells starts in isolation from normally functioning host-tissues. This segregated "nursery" of cancer cells can be compared to a closed box with the famous "Schrödinger's cat" whose fate is totally unpredictable: no direct observation is possible unless the box is transparent to the observer's eye. Conventional biomedical approaches to *in vivo* diagnostics and monitoring are not efficient in such cases. However, we managed to look into the "cancer-nursery" with the help of the waves that in autonomously functioning systems of natural origin act as "wireless" means of the communication between all system-components; back in 2000 we found that cancer provides specific spectral signatures and that aggressive behavior of its cells can be detected via non-invasive analysis of the body-surface radiation. Thanks to complex nonlinear mechanisms of information scaling and transfer across the system, it became possible to conduct a non-perturbing observation of some physical processes that take place in early carcinogenesis. Presented hypothesis focuses on very early stages of cancer emergence; however, we suggest that the described scenario of the system-genesis within more mature organism is equally responsible for the generation of distinct clones and metastasis.

The general model of iterative carcinogenesis reconciles many existing hypotheses and also significantly reduces the number of possible causes and triggers of malignant neoplasia; besides, it opens wide horizons for new experiments and theoretical considerations that can result in the development of more targeted methods of cancer treatment. Apart of the widely known facts about biochemical and genetic features of cancer cells, our model takes into account some physical aspects of malignant neoplasia.

Fragile non-molecular processes within biological systems were largely ignored by official science due to their elusive and non-measurable nature. The findings of the physicists who demonstrated the ability of live cells to manipulate and focus intra- and intercellular waves (e.g., light) should be acknowledged as a giant leap forward, towards the official recognition of the critical role that background nonlinear processes play in the system life-cycling.

We hope that empiric generalization of the biomedical and physical information together with the new possibility to study the "secret" life of the neoplasm would cast light on many puzzles and paradoxes of malignant processes and also help to build foundation for more efficient diagnostic and cancer-treatment strategies.

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