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Supportive and Palliative Care in Cancer Therapies—Path from Tumor-Driven Therapies to Patient-Driven Ones

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Abstract

Cancer patients frequently report a set of symptoms including fatigue, pain, and physiological and social distress. Families and other personal lay relations give proposals to take supportive drugs and supplemental nutrients, without professional knowledge about their actions. Internet search engines and social networks serve up most of the treatment proposals, opening wide possibilities for quackeries and predatory money-making practices. Medical professionals have a responsibility to clear this field and concentrate on patients' well-being and personal needs. According to our approach, the integration of supportive and palliative care with conventional therapies needs a change of paradigm from tumour-driven to patient-driven treatment actions. Supportive/palliative care includes a broad spectrum of applied methods, including medications, nourishments, electrical effects, and psycho and social supports. Our goal is to discuss the possibilities for combining conventional oncotherapies with additional supportive/palliative care and to give suggestions on a professional basis.

Keywords

Cancer, Vitamins, Minerals, Fungi, Immune, Phytomedicine, Complexity, Electric-Stimuli, Hyperthermia, mEHT

1. Background

Cancer patients frequently report a complex syndrome of the disease, a set of symptoms including fatigue, pain, and physiological and social distresses. Families and other personal lay relations give proposals to take supportive drugs and supplemental nutrients, without professional knowledge about their actions. Internet search engines and social networks serve up most of the treatment proposals, opening wide possibilities for quackeries and predatory money-making practices.

The application of supportive and supplemental drugs for cancer patients is a hot topic not only in the relevant professional literature, but also in patients' self-help groups and traditionally formed societies, and among patients' family members who would like to help their ill relatives. Supportive care (SC) is a general category of attention regarding the patient throughout the complete course of cancer treatment, involving self-help support, information exchange, physiological and psychological support, symptom control, social support, rehabilitation, complementary therapies, spiritual support, palliative care, and end-of-life care too [1]. SC could be provided at all stages and on all pathways of cancer treatment from the established diagnosis and therapy process onward. SC is a necessary condition for accurate cancer treatment, and, of course, SC is very personalized. Due to the absence of a standard protocol of SC it has a risk of non-reproducibility, so even the best supportive care (BSC) cannot be simply adopted as a reference for any clinical trial [2]. SC is focused on the well-being of the patient, improving the quality of life (QoL) and decreasing adverse effects of ongoing treatments or preparing conditions for planned therapy.

The growing incidence of malignancies drives the cancer therapy market. Cooperation in academic research, mergers in the pharmaceutical industry, and the gradual harmonization of the activities of various organizations make the field of supportive therapies massively influential in the global market [3]. An estimated 16.9 million cancer survivors were registered in the United States on the 1st of January 2019 [4]. Due to increasing survival rates a huge number, 22.1 million patients, are estimated for the 1st of January 2030 [4]. Two thirds of cancer survivors (67%) have 5+ years of overall survival, and 18% were diagnosed 20+ years ago, and also nearly 2/3 of cancer patients are 65+ years old [4], so the demand for SC is massively growing with these numbers. Consequently, many uncontrolled patient's practices of SC (pSC) grow rapidly, supported by massive advertising and "mouth propaganda".

The hopes and beliefs in traditional healing practices and pSC are supported by information reported about various spontaneous regressions. As early as the beginning of the last century, 185 spontaneous regressions were collected [5] and another collection of cases was published in the early 1960s: 202 cases were collected within four years [6], while 98 cases were also shown in the middle of that decade [7]. Many surprising spontaneous remissions were described in a monograph [8]. The literature on the spontaneous remission of cancer is impressive

[9] [10] [11] [12]. A large number of clinical cases have been collected to study the topic: 176 cases between 1900 and 1960 [13] [14]; 489 cases described from 1900 to 1987 [15], and a large meta-analysis was applied to about 1000 cases [16]. The topic was brought into focus again a few years ago by the "Armstrong effect" [17]. These published data give special (sometimes illusionary) hope to cancer patients and also to professionals. However, statistical evaluation is not possible on the sporadic facts, and pieces of weak evidence may give false hopes, supporting the belief that the patient often self-heals with the help of unprofessional healers.

The main realistic expectation of SC is the improving of the QoL, and by this progress the establishing of a condition of well-tolerated and elongated overall survival time too. Health professionals must pay more attention to patients' fear and complaints during therapy. Professionals have to offer appropriate SC, explaining the disadvantages of the uncontrolled intake of drugs in pSC, and clarifying the possible advantages of the regulation of diet and supplements by experts.

Nevertheless, the uncontrolled pSC became common in the self-care of cancer sufferers. Statistics show that a vast number of cancer patients use various herbal products without questioning the physician or nurse in connection with conventional cancer therapies [18]. Unfortunately, many of these intakes of additional drugs are not reported to the oncologist, though their interactions with chemotherapy could limit the benefit of the full therapy. The numbers are high: 81.7% of patients use herbs uncontrolledly during the various chemotherapies, and 94.3% of patients take herbs/vitamins before their surgery. The influence to use herbs intended to help with complaints concerning the conventional therapies came 39.8% from the media and 20% from internet searches, the patients' own physicians recommending of the applications in only about 1% of cases [16]. The results of another survey [19] also showed that patients having chemotherapy frequently use pSCs believing in their advantages. Some supplements are harmless, but many have interactions with the actual conventional therapy and could have significant disadvantages too. Almost one third (28%) of the patients were at risk due to the harmful interactions of pSC intake with the chemotherapy they received [20]. The vast use of pSC is based on various hopes and beliefs. The use of supplementary herbs or vitamins is rarely documented; frequently patients rely on their friends and naturopathic providers who are many times not in complete knowledge about the actual status of the patient his/her basic therapy. Despite the weak documentation and the small number of pieces of evidence, patients and their families massively request pSC, creating a not negligible demand for the doctors. This "grey zone" of treatment has to be investigated and a definite evidence-based approach established to put pSC in its place among the cancer therapies.

The patients in this way become easy targets of the misconceptions of unprofessional laypersons or, in more serious cases, they become the victims of quackeries, fake information, and harmful cheats. Frequently the leading causes of

imbalance in patient's decision-making are:

- a massive fear of the side-effects of conventional therapies;
- suffering from declining quality of life;
- the vast number of irresponsible advertisings by various information resources in society, including via modern information technology.

The high-level demand for supportive care of cancer patients in physiological and psychological help and in getting information about appropriate changes to make to their lifestyle is massively under-satisfied [21] [22]. The absence of an appropriate understanding of supportive care for cancer patients results in its under-utilisation in medical applications. The non-appropriate pSC accompanied with a lack of knowledge among healthcare professionals. Consequently, the sometimes inappropriate evaluations of physicians significantly limit the development of the cancer-supporting therapeutic industry and sometimes push disoriented patients to unproven, uncontrolled courses of treatment. Another unrecognised and uncontrolled source of herbs and supplemental drugs are the local historical diets and traditional habits which may interact with drugs [23]. The disease and its therapy may drive patients to seek a change to their regular every-day lifestyle, including a change to their traditional diet, which could be culturally inherited according to national character or individual family lore. Psychosocial distress could be an additional factor in the lifestyle change of the patient [24]. Due to this complexity, SC varies by country due to cultural differences and available resources [25]. The change in diet could involve not only an alteration to the set of nutrients consumed but in fact a complete rearrangement of the usual daily life of the patient, forming a new lifestyle and preferences.

The need for effective supportive cancer care increases with the longer survival times and with the transformation of previously fatal cancers to chronic disease [26]. The further development of the field requires a reliable and valid evaluation of global needs for supportive care with standardized guidelines [27], which could differ according to specific challenges in various countries [28].

The increase in the number of patients affected by various anti-cancer therapies, or by those therapies having become ineffective, pumps-up the global market for palliative and supportive care, which is a clear market for home-care too [29]. pSC is a special and considerable part of the SC market, pumping up the need for herbs, supplementary drugs, and vitamins by mass marketing and the extreme attention of social media. The time is ripe for a change of paradigm.

The meaning of SC by clinicians drastically narrows in everyday patient practices, becoming limited to the simple addition of dietary supplements, diet-protocols, herbs, vitamins, teas, decoctions, and other "home-made" practices, without the assistance of medical professionals. Proper SC is based on cooperation between the patient and the doctor, the therapist, who knows well the applied protocol, the possible adverse effects, and the actual support needs. The objective of our article shows for professionals the complexity and great potential in the SC.

2. Change of Paradigm

The patient demands for SC met with the medical needs of the broad range completing the curative therapies. A high number of patients strongly request such complementary pSC services despite these mostly having mere shreds of evidence. The Guideline of the National Health Service (NHS, UK) [1] focuses on the needs of patients, expressing the importance of providing reliable information for proper decision-making, and taking care that patients can access these therapies safely when they insist on a therapy. Interestingly, end-of-life care does not increase the survival when the therapy directly includes the patients (or "the family members") preferences [30].

SC has to consider the complexity of cancer and its embedded value in the family and society. However, its proper application needs a change of paradigm from cancer-driven to patient-driven therapy. This refocused attention becomes strong only when the conventional cancer-driven approach is limited or has failed, and then palliative treatment (PT) will be at the centre of considerations, with concentration on the QoL and the easing of the suffering of the patient. The PT is this phase the only help, and in the meaning of the patient support this phase is an intensive and medically controlled SC. Unfortunately, PT has no unified definition [31], but the common meaning generally reached is that it does not follow a curative approach but concentrates on the elimination of symptoms. It is the active holistic care of patients with advanced, progressive illness, managing the pain and other symptoms, predominating in end-of-life care [32]. More detailed definitions have been elaborated by the NHS (UK) [1], listing the needs for SC and PT for medical professionals. The key idea of SC is not a distinct specialty but is the responsibility of all health and social care professionals delivering care. It requires a spectrum of skills, extending from basic skills to highly specific expertise and experience. PT is described thus [31]: "Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families". The importance of SC/PT is widely recognized and is provided not only by medical experts, but the family, the social environment, and other care-providers have a part in the complex process.

The WHO defines PT more widely [33]: "Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness and is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life."

Despite the above definitions, some confusions between palliative and supportive care exist in medical practice. The main attempts to distinguish SC from PT point to apparent contradictions between them, listing that PT is passive care, is relatively cheap, and is applied for a short time during the end-of-life care; while SC is an active intervention, chronical, and expensive [34]. In this approach, it looks as if SC and PT are complementary, but in the complex pa-

tient-oriented therapy these are not distinguishable into disjunct groups, so we cannot formulate these independently from each other. In general however, supportive care is rather oriented towards helping the patient to achieve remission as long as it is feasible by the "holistic" combination of therapeutic and supportive interventions.

2.1. Challenging Present Conventional Consensus

The actual challenge of SC/PT is the inherent complexity of the human being and in consequence the complexity of human medicine. The rigid conventional consensus in oncology, which is oriented towards the tumour, somehow forgot that the lesion belongs to an individual patient. This conceptualisation has led to overly simplistic therapeutic protocols. There is a slogan sometimes quoted by doctors to patients who are suffering from the side effects of the actual medication: "The drug which has no side effect has no effect either". This opinion mirrors the missing complexity of the therapy; the drug which is administered focuses on one effect, ignoring its embedded interconnections to the complex system. SC/PT has to complete the therapy, compensating for the missing apprehension of complexity in the approach of the primary treatment.

SC and PT focus on the patient, who is the host of the malignancy, while oncology concentrates on the tumorous lesion, ignoring the complexity of the disease. The missing complexity has to be found again, answering the question as to "where medicine went wrong" [35]. The medical paradigm of oncology has to focus on the complexity of the malignant situation and evaluate and treat the patient as a whole.

The aim of this article is to summarize the recent achievements of pSC applicable in the PT process and to firmly embed the importance of general SC in everyday oncological practice. We want to point to the responsibility of those health professionals showing the optimal way to use pSC, giving stable support for disoriented patients, preventing them from becoming victims of quackeries or simply of their own beliefs.

The SC of individuals could start with the prevention of malignant diseases by advising on lifestyle and diet, as well as by proposals for checks depending on the individual's various life-conditions, habits, and environmental circumstances, including the actual daily risk factors and the ages of the subjects. In diagnosed, established malignant disease, supportive care focuses on the treatment of cancer-related diseases, comorbidities, and side effects of the active therapy [36]. Palliative care usually follows supportive care, when the support is not enough, and in many cases when the active curative approach has failed [37]. The goal of both is to keep the QoL as high as possible. This is the final turning point from the tumour-oriented to the patient-oriented concept. We have to have a certain change of paradigm. Interestingly, artificial intelligence and robotic technologies started to enter this field too [38].

To meet patients' demands, there are three major categories of pSC to be applied in the frame of the general SC:

1) Increase the efficacy of conventional cancer therapies, maximizing their curative effect.

2) Decrease the adverse effects of conventional therapies, increasing the quality of life of the patient.

3) Regarding the newest developments of immuno-oncology, the support of the immune system, and the revitalizing of the toxic degradation of immune effects is a new goal.

All of these categories are focused on the patient-guided treatment plan instead of the tumour-guided methodology (Figure 1). The curative effect must consider the patient's personality and individual factors (like comorbidities, allergies, disease history, environmental factors, dietary factors, life-style). Local treatment has to be effective systemically too.

Anyway, the change from tumour-focused to patient-focused therapies is inherently included in the definition of malignancy. Cancer is a systemic disease from its early beginnings in the body. By the conventional view the PT period of the treatment starts only in advanced cases, when the metastases limit curative interventions. Patients suffering extensively by the intensified illness need extended support. Hope and sometimes false advertisements and unprofessional bits of "helpful" advice make the patient vulnerable and could orient the patient towards uncontrolled pSC and PT. It is the task of healthcare professionals to keep the patient on a safe course of treatment together with providing patient satisfaction. The satisfactory condition is mostly related to the QoL and, of course, the elongation of the life-span with acceptable living conditions.

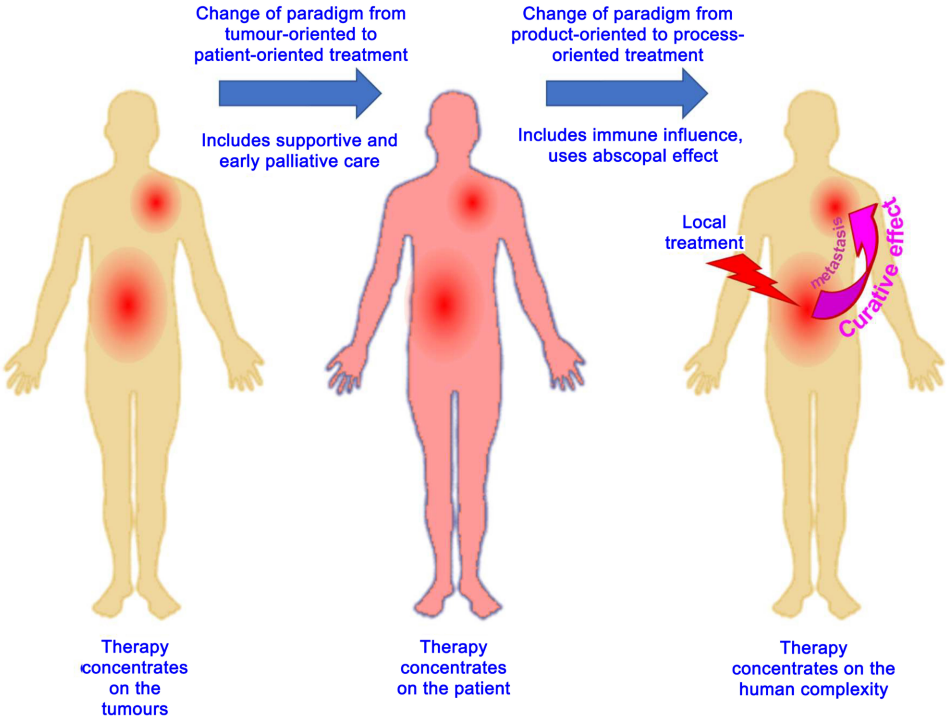


Figure 1. It is time to change the paradigm of cancer therapies, and take the patient as whole in the centre of actions.

The patient-oriented attitude of the therapy concept re-establishes the complexity in the mind of therapist and offers for the patient the possibility of a better prognosis, longer survival, and higher quality of life. The integration of SC/PT into oncology relies on specific knowledge and skills [32]. The two existing models of SC and PT have to be integrated, challenging a certain "dualistic perspective" [32]. The classical cancer treatments are tumour-oriented, focusing their attention on eliminating the malignant tissues. These intensive processes can cause extensive side effects and may cause irreversible comorbidities too. The growing number of serious adverse effects and the lack of effective approaches to managing them raises new challenges [39]. Such new, high-hope treatments as targeted therapies have serious side effects [40] and can decrease the QoL of the patient [41]. Immunotherapy may even worsen cancer development, causing hyper-progression [42], well showing a double-edged sword effect of immuno-therapeutics in cancer treatment [43].

The conventional therapies, led by chemo and hormonal remedies, have lost their overall primacy. According to a WHO consultation publication [44], the classical chemo and hormonal therapies can be grouped into five categories by their effectiveness: 1) potentially curative, 2) adjuvant with benefit for local disease, 3) palliative in metastatic stages, 4) local control enhanced, and 5) chemotherapy is ineffective. The ten most frequent cancers (lung, stomach, breast, colorectal, cervix, head and neck, lymphoma, hepatobiliary, oesophagus, and prostate) are all in category 3, which well supports the importance of the PT processes. Most of the essential high priority drugs are developed for the top ten cancers [44], and despite the mostly improving overall survivals, the results are not satisfactory yet. It is obvious that in most of the disease manifestations PT/SC is not an alternative treatment to the curative conventional chemotherapies but it is a part of the therapy.

Expectations of a simple situation in a system which has multiple regulatory feedbacks and interactions which request a harmonic coexistence of the regulatory actions is unrealistic. Chronic inflammation often promotes tumour development, including the dissemination and formation of metastases too. Acute inflammation, however, could act oppositely, causing a dilemma [45]. The accompanying pain, depression, psychosocial stress, fatigue, and other bad conditions of patients combine to accelerate their loss of QoL and shorten their survival. It could be a matter of slowing the acceleration of symptoms when PT/SC care starts at the first diagnosis of a fatal malignancy [46]. Even sophisticated PT/SC is not able to be superior over combined SC and conventional therapy. This is statistically proven, for example, in advanced metastatic colorectal tumours [47].

As an actual example of the need for complexity-oriented approaches in both CT and PT, one is directed to e.g. the presently extended discussions about the "miraculous" effect of medical cannabis [48], treating the symptoms, relieving the pain, decreasing nausea and vomiting, and so increasing the QoL. Currently

there is no scientific evidence for these results, but in any case it is unlikely that one single herb could solve the complex problem of PT/SC.

Cancer presents a massive challenge for patients, their families, and their social environment. The medical challenge for professionals is complex, and they have to consider the involvement of SC/PT actions too. A natural consequence of such consideration is to apply it much earlier than the conventional palliative phase. Many aspects of PT are also applicable in conjunction with other treatments from the discovery of the malignant transition [30]. It could be given equal priority alongside diagnosis and treatment [49].

While traditional PT starts when symptom management massively demands it, in the new paradigm early palliative treatment (ePT) starts at diagnosis, in the very early stages [50], and increases its dominance with the expansion of the disease [33]. The integration of ePT into therapy has three levels: linkage, coordination, and full integration [51]. Presently ePT integrated into oncology is in its infancy, while a few clinical trials reveal that ePT may have beneficial effects on QoL [52]. The integration of ePT into the treatment of cancer patients is recommended [53] [54] [55], but presently it is limited mostly to inpatient services [54] [56] [57]. Due to the complexity of cancerous diseases and the growing number of high-line treatment applications, ePT is having a gradually stronger effect on treatment protocols [58]. Due to this trend, general SC is receiving a growing emphasis and is making the complete process integrative, taking care of patients in its complex unity. At this point supportive and palliative care are united, the ePT component being adequate within the SC, unifying the care domains in physical, psychological, social, spiritual, cultural, end-of-life, and ethical aspects [59]. This integrated treatment approach, one which includes the oncotherapy being integrated with the SC and ePT, is the complex treatment approach (CTA). Cancer causes a complex local and systemic change which needs a complex answer to reestablish the healthy homeostatic control.

Meta-analysis shows that ePT improves the QoL significantly compared to standard cancer-care alone, and no extra adverse effects appeared [52]. ePT delivered in parallel alongside the conventional standard treatments increases the survival time [60], which together with better QoL is a great support for patients and their families [61]. The American Society of Clinical Oncology (ASCO) gives special attention to ePT too [62], and has expressed the opinion that the optimal care needs to include palliation [63]. There are further efforts requesting the integration of oncology and PT [64]. It is shown that ePT could even start at home. The meta-analysis of palliative home-care shows the benefits, but general attention and the partnership of family and medical professionals have to be improved for its success [29]. The standardizing of PT and the improvement of its quality are general wishes for the new concept of oncology care [65], including for the psychosocial aspects of this activity [66]. More attention to PT practice in rural areas is necessary [67], and in poor countries as well, fitting the actions to the actual availability.

Clinical decision-making requires prognosis estimates, which must include the PT too [68]. Some models for clinical prognosis including PT have been developed, such as the Palliative Prognostic Score [69], the Palliative Prognostic Index [70], and the Glasgow Prognostic score [71].

The harm is relative: "no action" is harmless compared to intervention, but its consequence could be harmful, leaving a disease uncontrolled. The "action" of treatment, however, could cause harm, but compared to the benefit this harm could be evaluated as low. Tumor-oriented "action" in oncology could cause patient-oriented harm, measurable by the quality of life or by acute discomforts, pain, etc., and the clinical evaluation hinges on the harm/benefit (H/B) ratio. The complete process could have a good H/B on average, but with fluctuations the risk of causing a high H/B value could be unacceptable, and thus the "action" not be approved. The decisional fact from a medical point of view is the direction of the changes caused by "action", that is, the results: at the end of the day the patient has to have stable homeostatic control, as near to the usual healthy state as possible. The Hippocratic phrase "nil nocere" ("do no harm") also has to be understood only within this tendency towards dynamism, otherwise the meaning would be "do nothing". The goal of the "action" always has to be patient-oriented as a tendency, or else it is a medical irresponsibility. This evaluation has become central to SC/PT "actions", which have to be integrative parts of the complete therapy. Logically, when this integration of therapies is involved, the ePT concept opens the opportunity to fulfil the need for a complexity of treatment that may lower H/B values. The first line oncotherapies (like surgery and chemo- and radio-therapy) could fail without ePT. The treatment of pain syndrome by ePT is standard of course, but other factors of this complex approach are frequently absent. Indeed, presently most CTA interventions are missing in first line treatments, which can drastically decrease QoL, and this contradicts the patient-oriented dynamical expectations for H/B too.

As well as the use of ePT in seeking to implement the CTA process, the direct optimization of H/B requires natural additions to the active medical intervention. It is general nourishment that insures the basis of the complex treatment approach's potential.

2.2. The Challenge of Nutrition

Life is not in a state of static equilibrium, it is permanently undergoing dynamical changes, an everlasting transformation of energy intake maintaining the equilibrium. We have to quote Albert Einstein who formulated it very simply: "Life is like riding a bicycle: to keep your balance, you must keep moving" [72]. The energy intake comes from the environment and is focused on nourishment. As another Nobelist (another Albert), Szentgyorgyi, formulated the situation: with life-energy it is unimportant that the monkey goes through the jungle; the important thing is that the jungle goes through the monkey, in the form of nutrition, water, and oxygen [73]. The jungle becomes a part of the monkey and in

this manner all the living objects there are interconnected; we cannot discuss the energy-cycle of a species without considering the energy-cycle of the other lives in its environment. To maintain all the energy cycling functions of a healthy organism, well optimized, enzyme catalysed biochemical reaction cycles are a must. Nutritionally available micro- and trace elements (Se, B, Ni) or mesoelements (Zn, Cu, Mg) are important cofactors in the catalytic centres of these proteins. In this regard, inconclusive evidence points to the beneficial effect of Zn and Se supplementation in treatment settings for some cancers, especially for an increased quality of life [74] [75].

The culinary and medicinal use of spices and herbs has long been a part of human culture. Presently one major focus regarding diets is weight-loss, variants of which entail extreme selections of foods (like the Atkin's diet, for example). The direction of diets can be in another direction too, to keep the healthy state permanent (like the ketogenic diet), and a third direction is that of special diets to prevent and/or cure various diseases. Comparison of the various diets shows well that the extrema are not helpful in any situation [76], emphasizing the popular knowledge that "the difference between medicament and poison is only the dose". The uncontrolled take of pSC drugs causes adverse effects at incorrect dosing. For example, the extra high dose of fat-soluble vitamins (like Vit. D and E) could cause severe adverse effects, or the high dose of ion-support could produce severe alkaline-acid imbalance.

Due to the complexity of the reactions in living objects we expect well defined negative feedback mechanisms with promoter and suppressor components balancing to a dynamical equilibrium. Over- or under-dosing hurts this balance, favouring one or other of the regulatory sides, destroying the equilibrium and so acting against the homeostatic control. However, it is not only the dosing that causes dietary challenges, but also the complex variety of the nutrients needed [77], healthy homeostasis requiring a diverse nourishment containing all the supporting components in the necessary amounts for the complex processes of living.

The compounds in plants have boosted research interest towards the protection and maintenance of human health and the treatment of some previously untreatable diseases [78]. Phytochemicals in plant materials have attracted interest among scientists, producers, and consumers and have given rise to a new scientific approach, phytochemical research, and on this basis a new industry has arisen. A discipline of phytomedicine has appeared, emphasizing the therapeutic value of herbal medicine [79].

The development of the nutraceuticals field drives phytomedicine's emergence, with even the reactivation of ancient culinary cultures [80]. It makes use of the traditional values of the omnivorous feeding of hunter-gatherer humans along with modern pharma-productions and with public reference to healthy nutraceuticals too. The research in this field stimulates the industry and is also actively incorporated into human healthcare and the pursuit by individuals of

healthy lifestyles. A harmony is sought as historic medical experience (famously represented by the Far-Eastern herbal culture) and up-to-date medicine are amalgamated, in the realization that not only the target (*i.e.*, the human homeostasis [81]) but also natural medicines and the products derived from them are complex; phyto-products cannot be regarded as simple, single chemical compounds.

Traditional medicine in the Far-East, including China, India, Korea, and Japan, is traditionally popular, and its application reaches approximately one half of the human population. The dosing, however, could be a challenging point for its production and application. The natural products derived from the roots, leaves, fruits, or whole plants have a large variance in the concentration of their active substances, depending on such environmental conditions as the sunshine, weather, soil components, and bacteria involved during plant growth, so their simple standardized production is impossible. Complicated, modern investigations are necessary to create feasible products [82]. However, it is the large variations not only in the natural herbs which are challenging in the application of phytochemical products, but also in human individuals too, who show large personal variability in their gut microbiota, which has an essential role in most of the actions of the remedies. From the metabolic point of view the herb-derived products can be categorized into defined groups: carotenoids, alkaloids, polyphenols, organo-sulphur, and nitrogen compounds [83].

An increasing body of scientific literature suggests that dietary components may exert cancer preventive effects [84]. Tea, soy, cruciferous vegetables, and other foods have been investigated for their cancer preventive potential. Diets rich in polyphenols could help as prophylactics [85] [86]. However, the overdosed consumption of polyphenols could induce possible harm too [87]. The potential harm of some polyphenols leads to international regulations recommending safe levels for polyphenol consumption [88], but the appropriate dosing limit is debated [89].

Prevention-related nutritionally available mediator and hormone-like molecules such as the long-chain omega-3 polyunsaturated fatty acids (O-3s), such as EPA Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) must be accounted for. Humans need O-3s for optimal functioning at every stage of life [90], as well as their anticancer effects are also being investigated [91] [92]. Another formerly neglected, but recently rediscovered hormone-like substance, Vitamin D3 also belongs to supportive nutritional mediators of the immune system. In a recent meta-analysis of 52 trials with more than 75,000 cases, Vitamin D3 supplementation reduced the risk of cancer death by 16% [93] [94] Hypovitaminosis D is associated with a worse prognosis in breast [95] [96] [97], lung [98], colon and thyroid cancer [93] [94]. There is a significant linear dose relationship between the active metabolite 25OH-D-vitamin levels in blood and overall survival in breast cancer patients.

Like all other actions, balance is needed for the maintenance of homeostatic

equilibrium [99] [100].

The human body lives in symbioses with a large number of bacteria. The number of these single-cell organisms is greater than the overall number of the cells in tissues of the human organism [101]. A major part of these are gut-bacteria (microbiome) which make a contribution to healthy balance as well as to diseases and immune-disorders [102] too. Intestinal homeostasis is an integrative part of the whole body's well-being [103]. Many nutrients are "pre-digested" before their further digestion for human use, as well as the symbiosis making a contribution to general metabolic processes too [104]. There is an emerging research interest in the interaction of polyphenols with microbiota [85], but the present knowledge is insufficient to decide upon the optimal polyphenol intake for maximal health benefit [103]. Despite the field demanding intensive research in recent years, the prospects are great, and the modulation of the microbiota by polyphenols is one greatly focused upon [105].

Other important factors in phytomedicine are the soy phytoestrogen isoflavones Genistein and Daidzein, expected to be potent anticancer ingredients of the daily diet of eastern countries [106]. Traditional Chinese medicine favours the medical plant Astragalus too, due to its antiviral [107], anti-inflammatory [108], and antioxidant [109] properties. These properties, with an immuno-stimulative effect, make it useful for anticancer application too [110].

The traditional medicine of the Far-East, including China, India, Korea, and Japan, is historically popular, and its application reaches approximately one half of the human population. The dosing, however, could be a challenging point for its production and application. From the metabolic point of view, herbally derived products can be categorized into defined groups: the carotenoids, alkaloids, polyphenols, and organo-sulphur and nitrogen compounds [83]. As previously stated, the natural products derived from the roots, leaves, fruits, or whole plants have a large variance in the concentration of their active substances, depending on such environmental conditions as the sunshine, weather, soil components, and bacteria involved during plant growth, so their standardized production is far from simple. Complicated, modern investigations are necessary to create feasible products [82]. However, it is the large variations not only in the natural herbs which are challenging in the application of phytochemical products, but also in human individuals, who show large personal variability in their gut microbiota, which has an essential role in most of the actions of the remedies. Despite the underlying mechanisms of the effects of gut microbiota on personal homeostasis in humans being largely unknown, some hints on the regulation of metabolism have recently been published [111].

One important step ahead to accept the achievements of the traditional Chinese medicine (TCM) was the awarding of the Nobel Prize to three co-recipients in 2015 for the medicament named Artemisinin (isolated from the plant Artemisia annua, sweet wormwood) which treats malaria [112]. The history of this discovery shows well the general challenge of the complexity of phytochemical

products: the basic discovery was made by the Chinese scientist Tu Youyou, using an herb from the vast range in TCM. It was helpful for malaria, but it was quickly recognized that the malaria parasites soon develop resistance to it, so the WHO terminated its certificate [113], asking producers to halt sales. Subsequent research later developed a Nobel-winning combination therapy, based on Artemisinin. Presently the therapy is a world-wide routine treatment for malaria. Some other herbs originated from the TCM and their Japanese versions (Kampo) are widely used in active cancer therapy [114]. The most accepted member of these is the active ingredient group of Shikonin. Shikonin suppresses the oncogenic pyruvate kinase-M2 (PKM2) [115], reducing the cell proliferation in this aggressive disease, and induces cell death by inhibition of glycolysis [116]. The blocking of ATP supply for PKM2 by Sikonin allows the cytotoxic Ca^{2+} overload and promotes apoptotic cell death, proven by treating the ductal pancreatic adenocarcinoma [117], and could induce mitochondria mediated apoptosis even in cisplatin refractory ovarian cancer [118].

Polyphenols are involved in a large category of antioxidants. The polyphenol-rich foods, principally fruits and vegetables, are beneficial to healthy life. Most vegetables are rich in flavonoids, which are a branch of polyphenolic compounds and make up a significant part of the human diet, having anti-inflammatory activity together with related polyphenolic compounds [119]. Many flavonoids (anthocyanins, flavanols, flavanones, flavones, isoflavones, catechins) could suppress the effect of free radicals and arrest the proliferation activity in tumours [120].

Clinical evidence has been collected on the beneficial effects of polyphenols in colon, prostate, epithelial, endometrial, and breast cancer [121] [122]. The early research on polyphenols focused on their antioxidant activity. We will shortly review ramifications of the antioxidant effects of polyphenols here

The effect of the application in SC of various antioxidants in combination with chemotherapy has been reviewed in a comprehensive analysis [123] showing that antioxidants reduced the side effects and so that these remedies have an exceptional ability to reduce the chemotherapeutic induced toxicity, and to increase the QoL and survival time of patients.

Polyphenols can induce mitochondrial adaptation to actual ROS attack [124]. The high antioxidant capacity of vitamins and polyphenols has no overall benefit regarding mortality rate. However, the benefit of these antioxidants in sustaining health is not questioned. The apparent contradiction could be resolved by the assumption that polyphenols are mitochondrial adaptogens, defending the mitochondria from oxidative stress; however it is not a simple reduction of this kind attack, but complexly regulates the mitochondrial biogenesis [124]. Due to the well-known fact that mitochondrial dysfunction has a pivotal role in many diseases, such as neurodegenerative or cardiovascular diseases, and actually having functions in ageing, repairing mitochondrial functioning or at least improving its normal activity could have substantial health benefits.

Certain differences in the metabolic processes of malignant and healthy cells have been observed [125] and it is one of the hallmarks of cancer development; in a malignancy a primitive, simple, but fast acting, "old fashioned" metabolism is promoted that produces ATP by a fermentative process instead of by mitochondrial Krebs-cycle, so in this context the most important aspect in the origin of malignancy is a metabolic (mitochondrial) dysfunction [126]. The revolutionary discovery was honoured by a Nobel Prize for Otto Warburg. His idea has been revised [127] [128], and it is enjoying a renaissance nowadays [129], the Warburg effect returning "in a New Theory of Cancer" [130], and new hypotheses being born on this basis [131] [132]. A malignancy is usually hypoxic because of the intensive fermentative metabolism. This hypoxic environment is a possible selective factor for medical targeting [133].

The response of mitochondria to hypoxic stress is a changing of their sub-cellular localization. The hypoxia ignites mitochondrial fragmentation, forming perinuclear clustering [134] [135] around the nuclei [136]. The hypoxia-induced nuclear relocation of mitochondria is associated with increased nuclear ROS, which can suppress the electron flux and so further increase mitochondrial ROS production [137], and it may allow the ROS signal to directly affect the nucleus. Furthermore, the "wasted" energy of the low efficacy anaerobic ATP production heats the lesion. The increased local temperature helps diffusion processes, as well as inducing higher blood flow and supporting the permeability of the vessel walls. The diffusion coefficient depends linearly on the temperature [138], so the diffusion of intra- and extracellular electrolytes is likely to be higher than in healthy counterparts. The development of ROS has again a complex balance, showing that the way bactericide antibiotics act is possibly connected to ROS [139]. The regular use of antibiotics could be a risk-factor for cancer [140], and in general has a risk of shortening survival [141]. The main disadvantage of antibiotics is that they do not differentiate between pathogenic and beneficial (gut) bacteria [142]. The homeostatic balance of gut microbiota is essential for antitumour responses, and could directly impact tumour outcomes [142]. Again, a complex balance has to be considered; pathogens can cause cancer, but the gut microbiota could impact the immune-system and so the cancer's progression [143].

Another large and extensively studied category of phytomedicine is that of the mushrooms used for culinary and medical purposes. It has been used in the treatment of infections for centuries, and is very popular in Far Eastern medicine. In recent decades medical mushrooms have been a part of the regular treatment of cancer in China and Japan [144]. Presently medical mushrooms are in use in more than 100 medical applications [145]. Two of the crucial ingredients of these are Polysaccharide Krestin (PSK) and polysaccharo-peptide (PSP), also used recently in Western medicine too [144]. PSP is a protein-bound polysaccharide extracted from the edible mushroom Coriolus versicolor [146]. Hundreds of studies have been conducted on the immuno-stimulating and anti-

tumour effects of mushroom polysaccharides [138].

The active ingredient of the mushroom Grifola frondosa (Maitake) is a protein-bound polysaccharide, a bioactive extract (proteoglucan) [147]. The purified soluble b-glucan has immunomodulatory and anticancer activity [148] [149] and could inhibit metastases [150]. It stimulates immune activity in experimental models [151]. It has synergetic effects with vitamins, especially when it is intravenously applied [152], as well as increasing bone marrow colony formation, reducing the toxicity of doxorubicin [153].

The mushroom Lentinula edodes (Shiitake) improves gut-immunity and well reduces inflammatory symptoms [154]. A clinically approved intravenous pharmaceutical for third stage gastric cancer with the active ingredient branching polysaccharide, beta-1,3-1,6-D-glucan. Lentinan has been on the Japanese market between 1984 and 2004, manufactured by Ajinomoto and then Taiho Pharmaceuticals. It was successfully applied for inoperable gastric cancer treatment in combination with some chemotherapies [155], but later was withdrawn due to skin-related side effects. L. edodes also showed antiviral activity [156] and immune support [157], as well as improvement of quality of life being observed when it was applied complementarily to other cancer immunotherapies [158].

The mushroom Ganoderma lucidum (Reishi) helps prolong cancer survival [159] in adjunct to conventional treatment to potentiate conventional therapies, enhancing tumour response and stimulating host immunity. Reishi shows immunomodulation in cancer [160] and enhances the response of the tumour [159]. However, its toxicity is also measured on leukocytes [161], as well as hepatotoxicity also being detected [162] [163]. There are some other commonly consumed medical mushrooms, such as Agaricus bisporus (button mushroom) [164] [165], Agaricus blazei (almond mushroom) [166], and Pleurotus ostreatus (oyster mushroom) [167], which are nowadays studied intensively [168] [169].

Various forms of mistletoe extract (Helixor®, Iscador®, Lektinol™, Cefalektin®, Eurixor®, etc.) are extensively applied in various cancer treatments [170] [171]. Its immune-stimulating effect probably plays a pivotal role in its anticancer applications [172], which is probably combined with a tumour-inhibitive action as well [173]. Again complex in its action, balancing the dose for proper homeostasis is of great importance in mistletoe administration too: it could be found to be anti- or pro-proliferative, depending on the dose [174].

A relatively cheap and effective drug of natural origin is the Metformin, which is a long time accepted first line standard clinical drug to treat type 2 diabetes. It was developed from a natural product, Galega officinalis as the natural source of galegine, used for natural medicine [175]. Metformin is a guanidine analog, product in the synthesis of N,N-dimethylguanidine [176]. It was recently observed that application of Metformin in cancer treatment lowers the incidence of tumor development and the risk of mortality [177]. Studies proved the direct antitumor effect of Metformin, by inducing apoptosis and suppressing the malignant. It was tried for various cancers like breast [178], lung [179] and leukemia

[180]. Metformin limits the mitochondrial respiration [181] and it works like the energetic stress on the cell.

The largest and most popular, broadly applied pSC group of remedies are the antioxidants. Antioxidants in their simple chemical meaning are reducing agents, taking up electrons in their reactions. Blocking oxidation is a negative when we consider that this is the fuel of energy in life, ATP being produced by oxidative phosphorylation in mitochondria in most eukaryotes. This energy-production is highly efficient, but can produce a natural by-product, the reactive oxidation species (ROS), which has an important role in homeostasis [182]. The ROS is formed as a by-product of the normal respiration process in mitochondria, as well as being produced by inflammatory processes and the myeloperoxidase action in defence mechanisms. A great many adverse reactions of conventional therapies produce ROS extensively, causing oxidative stress. The ROS, highly reactive compounds definitely being toxic in some cases, can cause significant oxidative damage of cellular structures. Antioxidants could be used as a precious tool in blocking the toxic effects of ROS. The control of ROS could have great potential in complementing chemotherapies to increase their therapeutic efficacy and decrease their toxicity [183], regulating the redox balance between oxidants and antioxidants.

Antioxidants naturally exist as vitamins, minerals, and other compounds (like polyphenols) in foods. Vitamins are natural antioxidants, too, being essential for health. Vitamin therapies are most frequently applied in the antioxidant role in general use for SC/pSC in oncology practice. The vitamins are used in the broad area of diseases in the complete range of medical activities: prevention, curative treatment, palliative application, and rehabilitation too. Most of the vitamins are taken in connection with nutrition and via the microbiome, because they are not produced naturally in the human body [184]. These can be fat soluble (like A, D, E, K vitamins) or water soluble (like ascorbic acid, pantothenic acid, folic acid, niacin, riboflavin, cobalamin, pyridoxine, thiamine, biotin). The early recognition of the importance of vitamins occurred at the beginning of the last century [185] and is currently subject to critical evaluation [186].

The application of antioxidants in cancer prevention and cure is widespread among laypersons, and a significant percentage of cancer patients use antioxidants to prevent malignancy or, very often, apply them during active cancer treatment [187]. Fruits and vegetables are good sources of antioxidants, and it is known that diets high in these sources are healthy in general; antioxidant rich diets are followed for prevention, and presently intensive research is governmentally funded [188].

Antioxidant compounds could prevent or delay the oxidation of compounds in life-processes. The discovery of ascorbic acid (vitamin C) was a great step forwards towards understanding the importance of antioxidative action and the redox balance in living systems [189]. Intensive research has identified more vitamins among which are the most known antioxidants among the general popu-

lation. The proposed mechanisms of vitamins in cancer-prevention and cancer-cure have been discussed and the ratio of the observation and expectations (O/E) of effects of vitamins collected from 102 cancers [190], measuring the plasma-concentration of the A, C, and E vitamins, which have significantly higher observed values than expected in low concentrations of the compounds.

Special attention on the antioxidative effect of vitamin C in cancer treatment has been proposed in a new concept of L. Pauling, a double Nobel Laureate. Pauling proposed using vitamin C to prevent and cure cancer [191]. The proofs of his concept were presented in retrospective clinical trials [192] [193] [194]; however, a placebo-controlled study could not find a similar effect [195] [196], and the method was not approved. Extended and sometimes emotionally heated debates on the antioxidants have appeared in recent research, inducing parallel discussions about general nourishments in which old ideas have been reborn. The application of vitamin C for malignant diseases has recently had a renaissance [197], its effect in cancer therapy being revisited [198]. Phase I clinical trials show its safety and high tolerability [199] [200] [201] and relief from the side-effects of chemotherapy [202]. Clinical trials indicated the efficacy of intravenous vitamin C (IVC) acting as a potential anticancer therapy and reducing toxic side effects when administered complementarily to chemotherapy [203] [204] [205]. Its dose escalation did not show side effects [206]. Its synergy with chemotherapy improves the QoL [207] [208]. It is also useful for the prevention of malignant diseases [209], as well as suppressing inflammation [210].

Despite the positive results the intensive debate about vitamin C continues [211] [212]. Misconceptions block a clear picture from being formed regarding the situation [213]. These deeply set beliefs have to be understood for progress to be made. All the challenges originate from the clear complexity of the topic. The action of antioxidants has to help in the balancing of the redox status of normal living processes. But inappropriate applications could cause harm, even vitamin C being potentially toxic when applied improperly [214]. It has also been shown, however, that antioxidative supplements confer no prevention of malignancy [215], while other research shows the opposite [216]. Also debate has arisen regarding preventive applications of antioxidants. The role of defensive mechanisms has been discussed in detail [217], a triple step defence activity being composed: 1) preventing the formation of new radicals; 2) capturing free radicals to prevent oxidative chain reactions; and 3) repairing the damage caused by the free radicals.

A significant shake-up in the debate around antioxidants was made by another Nobel laureate, J. Watson (the explorer of DNA). Watson published his opinion that antioxidants are harmful, may cause more harm than good, and, contrary to widespread belief, promote cancer [218] [219] [220]. This new turn was an attack not only against the application of vitamin C, but in general against antioxidant treatments in oncology. Extended systemic analyses of the clinical data show increased mortality with treatment using beta carotene, vitamin A,

and vitamin E, while vitamin C and selenium had no significant impact on survival [221] [222]. Some evidence has been collected supporting the increased mortality of patients treated with antioxidative therapies [223] [224] [225].

The heated debate was cooled down by opinions that the topic is a double-edged sword [226] [227], and that depending on the cellular concentration and micro-environmental conditions the antioxidant could have both pro- and anti-cancer potential [228]. Unfortunately, the interaction of antioxidants with anticancer drugs is not understood completely [133], which increases the challenge.

The balance of oxidative stress defines the action of the antioxidants. Many anticancer therapies, including radiotherapy and most chemotherapies, act therapeutically with massive oxidative stress [229]. Supporting the effect of these conventional therapies the naturally present antioxidant defence mechanisms in cancer cells [230] have to be controlled too. This therapeutic approach tries to maximize the oxidative stress in tumour-cells, and the out-balanced redox situation kills them. This approach emphasizes again the extreme complexity (embedded interconnections and self-regulation [231] [232]) of the living substances, where the main goal is the selectivity of cancer cells with oxidative stress, while the heathy cells have to maintain their normal redox balance. The oxidative and antioxidative impacts depend on the concentration of the natural antioxidants, acting like a "double-edges sword" in cancer, in dependence of the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) as one of the transcription factors [109].

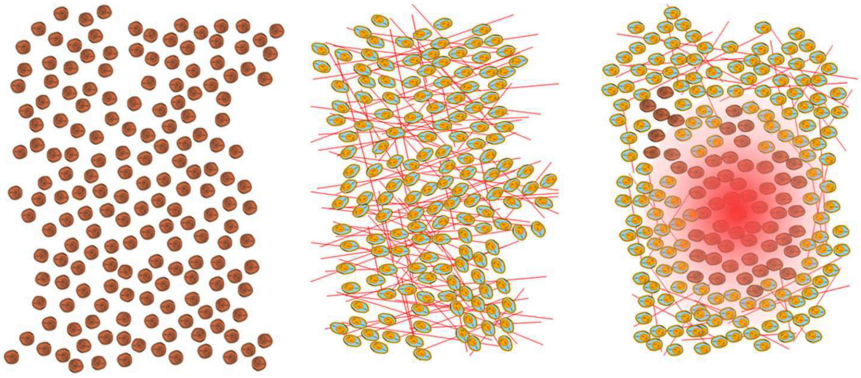
The selective factor of electron transfer, a definite clue of oxidative actions [233], could be the hypoxic environment of the cancer-cells [133]. The debate on vitamins in cancer prevention, cure, and palliation is not over yet. Results are promising, but not conclusive [234]. Intensive research and further facts are necessary to harmonize the pro and con opinions. According to our opinion, the doubtfulness is inherent, well showing again the essential complexity of the living structures and their homeostatic balance. As recognized early, the actual homeostasis is personalized [235] and also depends on the mood, and on the actual physiological and psychological condition, as well as on the stresses of the individual [236] [237]. Homeostasis depends on the gut microbiota of the human subject too [238], showing the interdependence of the parts in the symbiosis of human life [239]. To this theoretical consideration, one should add the network-based metagenomic and systems-ecology observations made recently [240]. Clinical analyses show a dependence of cancer [241], especially mucosal cancers [242] [243], on microbiomial composition. These recent reports also clearly support decreasing cancer risks with different preemptive and supportive nutritional manipulations on the microbiome, even in lung cancer [241] [244].

This extreme complexity demands new theoretical consideration, attempting to describe the adaptive dynamics of the phenomenon by cell-population calculations with emphasis on the heterogeneity of cancer cell populations [245]. Sys-

temic-Evolutionary Theory, a new interpretative model of cancer complexity, has evolved [246], as well as the fractal-physiology approach being summarized to explain cancer evolution in connection with metabolism and immunity [247], with the demand of a new paradigm, a new strategy, to win the war against malignant diseases.

Healthy homeostasis struggles to control the malignancy. The first few attempts to block the proliferation start intracellularly by controlling the DNA replication. It fails for various reasons, including genetic aberration [248], mitochondrial dysfunction [249], or other intracellular hallmarks of the cancer [250]. An additional challenge is the extracellular factors such as permanent uncontrolled stress (chemical, mechanical, etc.) [251], unhealed wounds [252], inflammation [253], and the extracellular hallmarks of malignancy [254]. The permanent proliferation could be stopped by natural apoptosis, but this mechanism is missing too [255]. Cancerous proliferations and bacteria have a lot in common [256]. The tumour itself has something like an atavism [257], in the sense that the malignant cells act like self-ruled unicellular organisms. The atavism-like process is general, not only with the loss of cellular connections, but also with the intracellular genetic structures being altered. The unicellular individualism develops great potential for adaptability to environmental changes, and in fact makes these cells more vigorous than those in the multicellular network. Disorganizing the multicellular structure is the modified genetic activity at the active boundary between unicellular and multicellular areas, promoting primitive transcriptional programs [258]. The malignancy in this general meaning is a distortion of the healthy cellular network, the rules of multicellular organization being broken. The breaking of cellular networks is a general behaviour of all the tumorous cancers independent of their locations in the body (**Figure 2**). In this sense, the cancer is an organizing (networking) disease, where the cells unleashed from their networks abandon the living advantages of collectivism, individualism prevailing [259]. The change, however, is not free from new organizing processes, because this unicellular autonomy brings its own requirements regarding environmental conditions for survival [260]; the cancer is afforded a friendly environment by the host, which tries to "heal" the abnormality, strengthening with angiogenesis, injury current, and numerous other supports.

It is interesting to note that the widely applied traditional cancer chemotherapies (anthracyclines) are in fact antibiotics derived from some species of fungi. They are topoisomerase inhibitors and act in the S-phase of the cell-cycle (disturbing the DNA synthesis). Such broadly known and intensively applied antitumour chemotherapies as Mitomycin-C, Doxorubicin, Epirubicin, Daunorubicin, etc. are all connected to the soil fungi family Streptomyces. In this regard cancer is treated like a bacterial infection, which somehow favours the supporters of atavistic ideas. In fact, a simple atavistic model cannot work in a limited environmental condition; the early unicellular organisms at the beginning of evolution had in fact unlimited nutrients from the environment. However, there



Hostile environment for each other	Friendly environment for each other, but need to pay the price	Hostile environment for each other but friendly to host
No feedback regulation	Negative feedback regulation	Positive feedback regulations
No complex	complex	Complex
Unicellular situation	Multicellular situation	Mixed situation
Cluster of cells	Network of cells	Gradient organization of cells
Neutral outside	Regulated outside	Friendly outside
No intercellular interaction	Intensive intercellular interaction	Lazy intercellular interaction
No order	Long-range order	Short-range order
Easy migration	Blocked migration	Forced migration
Short individual life long life of cluster	Controlled individual life, Limited life of network	Short individual life, Developing life of organization
Regulated by the available nutrients from the environment	Regulated by the homeostatic-immuno-surveillance	Unregulated while the host exists
Pressure is equivalent with the environmental pressure	Heterogenic inside pressure	Pressure is larger than the environmental pressure
No benefit from cell-death of others	Regulated, programmed cell-death	Benefit from cell-death of others
Homogeneous microenvironment	Dynamically changing microenvironment	Heterogenic uncontrolled microenvironment

Figure 2. The differences between (a) unicellular living clusters, (b) healthy organized clusters, and (c) malignant clusters of cells. It is clear that the atavistic approach is only formal; the interactions and the organizing of the systems are different.

is knowledge to be gleaned from the atavistic idea: the unicellular organisms were not capable of adapting themselves to broad environmental challenges, their innate adaptive facility was not enough to keep up with environmental developments, and networking started to help their overall survival by work-division, practical networks of cells having a higher survival probability than individuals.

The main development was the adaptive immune system which learned and memorized threats and the protections against them. The atavistic model could be used as a starting point, but this model does not consider all the crucial details (hallmarks) which keep the unicellular units of the cancerous development alive [261]. Both the multicellular networked and the unicellular autonomic states of cells maintain a balance which is probably realized by an electromagnetic route [262]. The FDA-approved TTF also uses this kind of interaction to arrest malignant cell-division [263]. The method of mEHT uses an electrical field to modify the polymerization process [264] with fractal noise modulation for a complex effect. The applied noise is an active harmonizing factor [265], which has an emerging application in physiology [266]. The monitoring of the noise as fluctuations in the complex system could be a factor in its surveillance [267].

The well-structured polymer cytoskeleton is missing in cancer-cells due to their permanent division. The sluggish polymerization of the cytoskeleton [268] [269] promotes huge deformability in cancerous cases [270], cell proliferation being gained with the softer consistency of the cells, which is combined with robustly increased cellular motility [271]. The higher extracellular pressure [272] promotes this higher motility of cancer cells, stimulating the spread of metastases.

The healthy networks are formed mainly by adherent connections in a chain of transmembrane proteins connecting the structure of the cytoskeleton [273] [274]. The protein-chain in the cytoskeleton is a polymerization-like networking [275], where the microfilament structure drastically changes with the electric field [276]. The protein-based networking in the intra and extra cellular milieu is extended with a high-speed network of proton (hydrogen ion) transport. The proton is mostly transported by hydrogen bridges, which allows low energy-dissipation in the transport propagation accompanied by speedy exchange (Grotthuss-mechanism [277]). The proton in this procedure tunnels (jumps) from one water cluster to another through the bridged hydrogen bonds [278]. The lifetime of the H_3O+ (hydronium ion) which is involved in this mechanism is rather short ($\sim 3 \times 10^{-12}$ s) so the speed of proton transport is approximately ten times higher than that by diffusion.

To re-establish multicellular networking we have to increase the cooperative driving force, and present a better efficacy of energy-consumption in the network than without it. The division of cells themselves does not act against the cooperative networking when it is also regulated by natural controls like apoptosis and differentiation, as in the natural healthy development of organized tissues. The structures and the functionality are interconnected [279] and define the dynamisms of the interactions which are always in a critical state [280]. The maintenance of homeostatic equilibrium defines a certain range of parameters of heathy life. The analysing of the huge set of interconnected data has opened a new scientific approach, network medicine, which tries to discover the network-

ing properties of life and of the development of cancer by big-data analysis [281]. The chemical complexity of the human diet is extremely important in regard of living processes with their environmental facilities, and the manner in which life transfers nutrients to its own building-blocks. The huge scale of the chemical diversity of food ingredients and its interactions with the broad spectrum of life remains poorly understood, characterizing a "dark matter of nutrition" [282].

The dynamic interactions in life are complex, but the chemical reactions and the transport of various species as well as the broad spectrum of signal transductions are rather unified in all the living tissues, forming scale-free networks [283]. The living complexity has a self-organized critical state (SOC) limited by the environmental interactions [284]. The dynamical fingerprint of SOC is the well-organized distribution of fluctuations (pink or 1/f noise) [231] [285]. Applied, this fractal noise could be one of the driving forces of reorganization, at least at the interface of the multi and unicellular regions [286] [287]. Usage of this special frequency distribution as a constraint for dynamism could improve success as mEHT does [288]. The electrical current of the modulated radiofrequency delivers the information through charge redistribution [289].

A quotation borrowed by Bjelakovic, Nikolova, *et al.* [247] from the Chinese military strategist and philosopher Sun Tzu states that "just as flowing water avoids the heights and hastens to the lowlands, so an army avoids strength and strikes weakness". This philosophical intention, a "target the weakness strategy", was adopted by Paul Davies and his colleagues [290], showing that one of the weakest sides of cancer's development is to the immune system. This could be a perfect target instead of the cancer's main strength, its proliferation. The lack of adaptive immunity to tumours can be revised, and the malignancy is attackable by the host system itself.

The main arrangement of the body remains networked and organized on the homeostatic complexity around the smaller tumours. Multiple robust effects, such as apoptosis and the innate and adaptive immune actions, could be naturally activated to rebuild the overall normal structure. The first step in the regular division of a healthy cell is formally similar to the beginnings of a malignancy: the cell breaks the healthy networking around it and expresses its individual demands for higher energy-intake to perform the delivery of the daughter cells, building up new constituents, creatively doubling the original structure. Its environment during this division is free from the normal networking limitations, and diffusion and osmotic activities are increased, facilitating the necessary transport of nourishments for the development. The electromagnetic properties change in the transition from the networked to the individual state [291]. However, when tumour-cells are clustered, adaptive abilities to the changed conditions are quickly developed. The tumour lesion is associated to an inflammation [292], as was first hypothesized by Virchow in 1863. The inflammatory phenomenon is a critical hallmark of many cancers [253] [293] [294] [295]. The situation is similar to that of a wound which has never healed [252], turning into a

chronic injury [296]. After a long period of silence, the inflammatory wound theory is emerging again [297]. The malignant tumour mimics a wound, stimulating the host tissue to support its "healing" [298], avoiding by this "trick" attack by the host's immune surveillance [299]. Contrary to numerous inflammatory immune cells being presented, no immune attack destroys the developing tumour [300]. The malignant cells may hide their individual behaviour from the immune surveillance. The malignant cells develop robust adaptability even to aggressive environmental conditions and also to the attack of natural immune actions. In the case of a developed malignancy even strong natural immune procedures alone are ineffectual. The definite difficulty is that the malignant character of the tumour-cells is hidden and that the immune-cells are not able to recognize these cells as a "disease"; the innate immune-attack and the adaptive immune reaction are absent.

The standard opinion in healthcare at present is that the immune system does not protect against malignant development. However, the absence of any expectation of immune action does not mean that the natural defence mechanisms are beyond consideration. The CTA constitutes a complex treatment, and a variety of antimutagenic factors could be used to prevent the malignant development in its early form or to block the development of new daughter cells in the wide periphery. There are vitamins and micronutrients (often antioxidants), such as vitamins A (in the form of b-carotene), C, D, E, D-glucaric acid, selenium, and uric acid, as well as essential oils [301], that may have roles in cancer prevention, blocking or at least limiting carcinogenesis by interfering with the malignant actions of carcinogens and mutagens as well as of other promoters of cancer development [302]. In this way the inhibitors of malignant initialization and progression become involved in a complex process within the homeostatic dynamism, preventing critical carcinogens in the metabolic processes, detoxifying the tumour-promoting factors, and limiting the possibility of cancer. Or to formulate it in other words, a properly balanced diet could maintain a healthy homeostatic dynamism, avoiding any malignant actions. The effect of course involves a complex synergy of diet with lifestyle and environmental conditions, including the avoiding of damaging habits (like smoking, consuming alcohol, etc.) which could negatively interfere with the homeostatic regulation. It has been proven that interferon-gamma with lymphocytes blocks carcinogenesis [303], which in vivo experiment was later evaluated as a "Pillars Article" by Nature [304]. The same group of researchers has published further results on immunosurveillance and cancer immunoediting [305] [306]. The research, clarifying the role of natural killer-cell (NK-cell) in cancerous processes [307] and the character of regulatory T-cells (Treg) in control of NK-cell activity [308], targets the topic of how the immune-system may prevent the development of malignant processes.

An important topic is the role of gut microbiota in immune reactions, due to a symbiotic complexity of the gut bacteria with the host system in which the transfer of ingredients of nourishment for systemic use is manipulated, which

could be used for medical targeting as well [301]. The role of gut microbiota is essential in the actions of the host immune system, working in a complex feedback frame to ensure the dynamic equilibrium of the homeostasis [309] The biota acts on the initialization of the immune effects, supporting the fight against "intruders" into the system, and has a role in the maturation of the dendritic cells to prepare the defence [310] [311].

There is currently intense research activity focusing on immuno-oncology [312]. This promising research and its medical application has a long history, starting in 1868, observing the protective effects on cancer of intentional inflammation [313], and continuing with various Nobel Prize awarded works in the field of immunology. One of the first theoretical considerations of immune surveillance in oncology was published in 1970 [314]. At this time, check-point inhibitors became the great hope as reagents in cancer therapies [315]. Soon it became obvious again that single-sided action could have serious consequences, causing the opposite effect (hyper-progression) on cancer to that desired [42], connected to immune-related adverse effects [43]. The apparent problem was obvious from the point of view of systemic complexity: a single action may modify a parameter in the complex balance, but many other conditional parameters have to be considered. The effect could be limited by simple factor too: the majority of the targeted receptors are activated, and the useful effect is saturated [316]. To avoid this problem a low dose check-point blockade has been proposed [317].

Due to the frequently mentioned complexity of homeostasis, regular immune surveillance is not the only factor which could act to achieve dynamic equilibrium. When the immune-surveillance does not recognize the malignant tumour, the well induced injury current (see above) may have the possibility to maintain some immune-attacks on the "unhealed wound" by its electromagnetic interactions.

As we have shown above, despite the disability of immune-surveillance to carry out tumour-destructive action in some cases, the general immune status of the patient is important. A well-maintained immune system keeps the general wellbeing of the patient high, could prevent comorbidities, and reduces the side effects of the therapies applied [318], and by these effects the quality of life of the patient is improved. In this sense, general immune support has to be part of the CTA and must be provided as early as the ePT starts.

2.3. Electro-Chemical Complexity—A Part of the Supportive and Palliative Care

The largest group of the components of early CTA interventions is comprised of pharma-products [319] [320] [321]. A new kind of treatment is emerging though: the bioelectromagnetic [245] [322]. The properly applied electromagnetic intervention promotes ePT in oncotherapies, as a complementary intervention to conventional therapies in any lines, including in the cases of naïve patients too. The magnetic component of the field established the popularity in

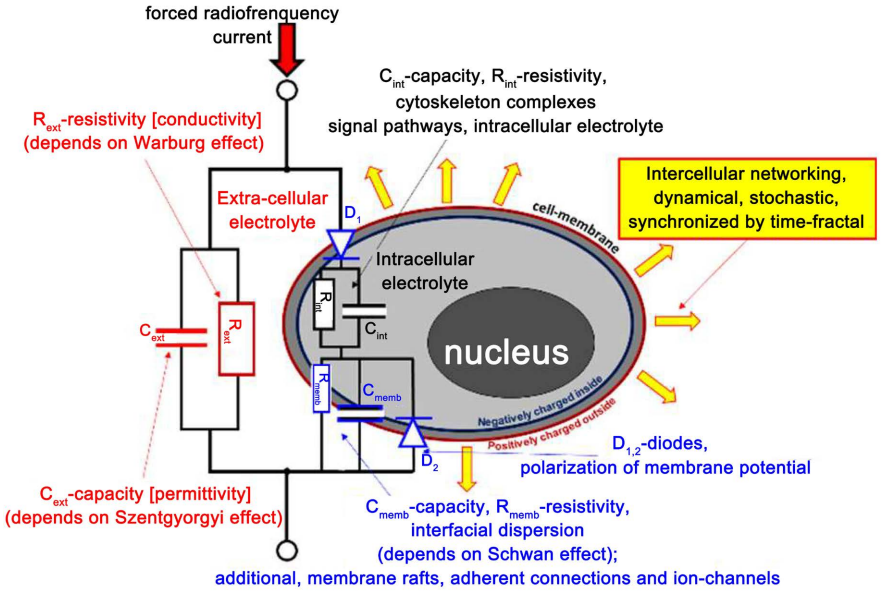
these treatments of nano-particle technologies [323], where the energy-absorption can certainly be declared heterogenic [324] in a decisive shift away from the conventional homogeneous heating concept in hyperthermic oncology [325]. The change is not drastic because the traditionally expected temperature homogeneity (isothermal heating) is quasi ensured by the rapid thermal equalization of the target. The selectively targeted nanoparticles heat up their environment, unifying macroscopically the microscopic differences.

Another nanotechnology method uses the electric field, with [326] or without [327] additional artificial nano-targets, using the absorbed energy of the field. The preclinical results show feasibility in both the artificial [328] and natural [329] nanoparticle targeting methods. The electromagnetic fields effectively arrest the malignant proliferative activities [330] by blocking cellular division [331], developing a complete therapy by an alternating electric tumour-treating field (TTF) [322]. The effect of TTF is clearly shown in clinical practice too [332] [333]. TTF is currently settled as an FDA- and EMA-approved, reimbursed tumor therapeutic intervention. A further advantage of the electric field effect is that it can decrease effusions [334], proven by a clinical trial too [335].

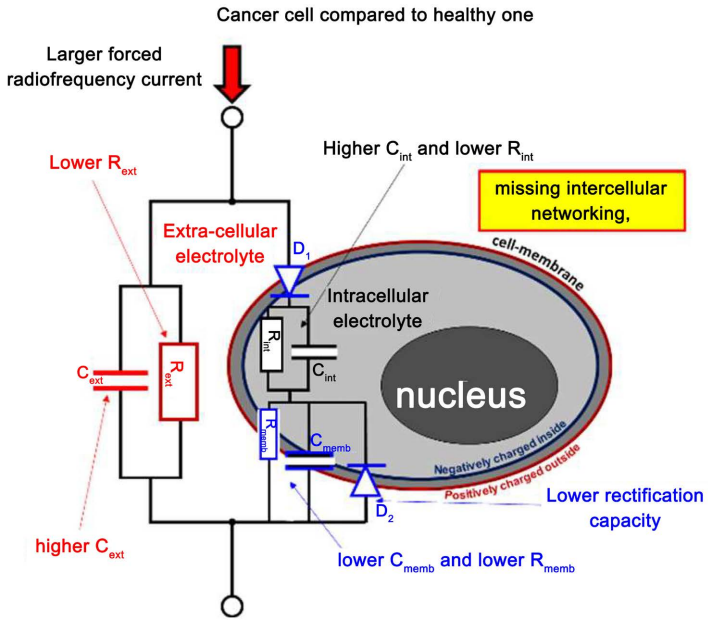
Healthy and malignant cells show a lot of differences from the electromagnetic point of view (**Figure 3**), giving rise to the possibility of recognizing them by biophysical, bio-electrodynamical methods.

The electromagnetic interactions have the particular advantage of being selective due to the electromagnetic differentiation of the malignant cells from those of their healthy neighbourhood. The more prolific than usual tumour-cells are well distinguishable by their electrolyte structure in the microenvironment of the cells. The malignant proliferation uses a massive amount of nourishments and produces more waste from them too [336]. The ionic concentration increases in the electrolytes where the chemical reactions occur, allowing the recognition of them by their lowered electric resistivity [337]. Furthermore, the characteristically autonomous tumour-cells lose their networking connections, modifying the structure of their microenvironment, and allowing their recognition by this property too [338]. These distinctive characteristics are complexly interconnected [249] and give rise to the special electro-impedance differences between the cells, permitting us to focus the energy on the malignant ones selectively [339]. In this way the absorbed energy shows heterogeneity according to the varied electromagnetic characteristics of the tissues.

There is another advantage of the electric field that could further our attempts to kill the malignant cells selectively [340]. The electrical component of the field is expected to be involved in molecular excitations by the absorption of energy [341] [342]. Using the electric field interactions with the excitable molecules defines a principally different nanotechnology, as the nanoparticles are naturally present in the tumour-cells and are used for the desired molecular excitations [343] for the well selected heating of the malignant cells and through these of the complete lesion [344] [345].



(a)



(b)

Figure 3. The electromagnetic difference between (a) healthy and (b) malignant cells is remarkable.

The impedance guided electric field opens a new paradigm of nanotechnologies by the targeting of the excitable molecular branches on the membrane of the selected malignant cells [346]. The selection is supported by the modulation of the radiofrequency carrier [347], a method named modulated electrohyperthermia (mEHT, tradename: oncothermia®) [348]. This method uses the electric field in a precisely selective way [349], there being a strong interconnection of thermal and electrical effects [350]. The transmembrane proteins of cancer cells which assure the interconnections in a healthy network remain un-bonded due

to the cellular autonomy in a tumour structure. These proteins form membrane rafts [351], which are highly populated in the membrane of malignant cells [352]. The energy is concentrated on the specific transmembrane proteins clustered in membrane rafts [353], producing the extrinsic excitation of intracellular signals [354].

The excitation of the transmembrane protein compounds helps to ignite variants of apoptotic signal pathways, destroying the tumour by the specific molecular selection of malignancies [355]. The externally oriented energy absorption may choose various pathways:

- caspase independent route through apoptotic inducing factor (AIF) [356];
- extrinsic pathway through caspase-8 (Casp8) and Casp3 [357];
- intrinsic pathway thorough the mitochondria followed by Cas9 and ending on Cas3 [358].

Additionally, the excited Septin4 [359] and Smac/Diabolo [360] proteins neutralize the apoptosis blocker XIAP helping the "avalanche-like" branches of the apoptotic signal to dominate. This complex process reintroduces the sorely missing apoptosis in tumorous development. This apoptotic method has found its way directly from the laboratory to clinical beds [361], being introduced in broad clinical practice [362] [363], and even Phase III trials have been published on electromagnetic methods in oncology [364].

The temperature dependence of the energy-absorption clearly follows the Arrhenius chemical reaction-rate in exponential development by rising temperature [365]. Certain similarities between the temperature dependence and the action of the electric field exist [366], a similar expression of chemical reaction rate being seen in both the solely temperature dependent and the solely field dependent cases. The strict similarity of the relationships defines the electromagnetic energy absorption as hyperthermia. The reality of the electromagnetic treatment is that the energy-consumption is expended on a mixture of heating and excitation. Energy analysis of the heating processes shows complexity even in consideration [367] solely from the conventional hyperthermia (heating) point of view. The comparison of conventional and mEHT heating shows well distinguishable differences [368] [369]. The temperature, however, is only a conditional parameter for the phase-transition-like excitation process while the action is physiological [370].

The electromagnetic treatments have further advantages. These are less harmful than the chemo- or radiotherapies and their H/B is lower, so their application well improves the quality of life of the patients [371] [372], which highlights again its excellence for the ePT application in CTA therapy. mEHT works complementarily with radio- [373] and chemotherapies [374] [375], increasing its already broad oncological application spectrum. The well applied electromagnetic therapy solves the long-debated problem of electromagnetic energy-absorption used in oncological hyperthermia [376]. In the conventional mode of electromagnetic energy absorption, the goal is isothermal (homogene-

ous) heating focused on the tumour as a mass in the body. Unfortunately, this heating affects homeostatic blood-flow, and by this regulation the body tries to re-establish thermal homeostasis by cooling with extra blood from the non-heated part or from the surface of the body. The extra blood-flow, however, could have the risk of supporting the tumour with glucose, this effect thus starting to compete with the anti-tumorous thermal effect. The increased blood-flow around the tumour helps the invasion of malignant cells to the vessels, distant metastases forming by dissemination of the cancer-cells [377], causing controversies in regard of clinical applications in cases where the advantage of thermal cell-killing provided excellent local control but without benefit for overall survival [378] [379]. This contradictory problem has been reported by others too [380] [381] [382]. The results show that it was probably the increased metastases that were causing the contradictions [383]. This contradictory effect of isothermal heating in the traditional hyperthermia protocol is solved by heterogenic heating, attacking the malignant cells by energy, as realized in the mEHT methodology. The selective heating could drastically reduce this risk as the complete mass is not isothermally heated, the energy absorption targeting the malignant cells.

Another electromagnetic effect is the injury current. It is a factor of natural wound healing that is physiological [384]: the injury current, which promotes redifferentiation [385], has a definite role in natural wound healing [291]; consequently, it is used for wound healing [291]. The typical value of the injury current is approximately 100 $\mu A/cm^2$ with a voltage drop of approximately 100 mV/cm in an mm extension from the wound [386]. The weak power of the current-flow (~0.01 mW/g) does not increase the local temperature [387], but it is measurable during the progression of the wound-healing [388] [389] [390]. This current is physiologically controlled and endures for as long as the wound is healing. The electric field which induces the current determines the orientation [391] and the dynamics of the cell division [392], and it forces cells to migrate [393] to heal the wound [394]. In this way a biological charge transfer promotes the tissue repair [395] [396]. Some invasive [387] [397] and non-invasive [388] [389] [390] experimental results prove the injury current experimentally.

Malignant diseases are systemic. The localization of a tumour is only a visible manifestation but not the complete disease (**Figure 4**). To achieve a complete cure, the goal has to be increasing survival time, with an acceptable quality of life, of course.

Circulating tumour cells (CTCs) are presented by invasion/intravasation from primary tumours independently of their localization, carrying the risk of metastatic developments. The sentinel lymph-nodes of the tumour are sensitive and vulnerable for the transport of malignant cells from the lesion. CTCs start their dangerous voyage from the very beginning of the malignancy, and the risk of distant extravasation in vital organs grows with time. The goal of conventional local hyperthermia is to eliminate the tumour, seeking the highest goal of complete remission (CR). Nevertheless, the disease-free status differs from local

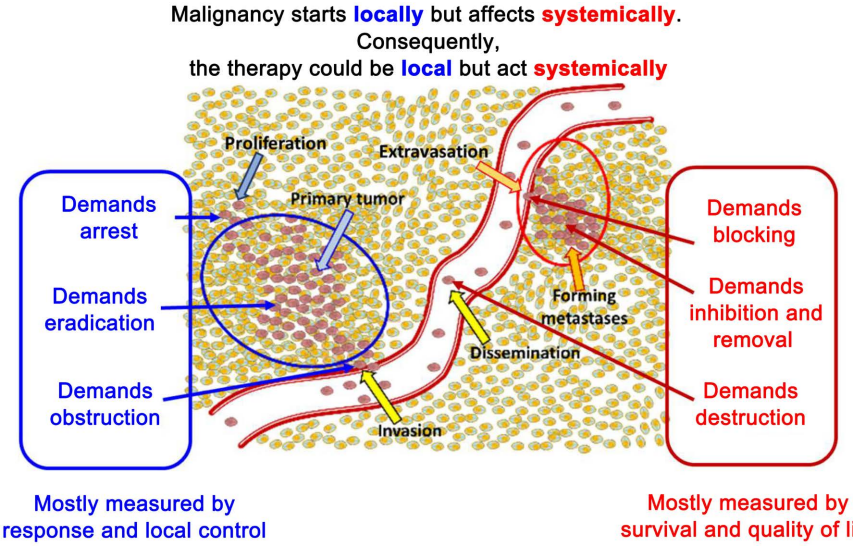


Figure 4. The tumour is a systemic disease; treating only the local tumour does not offer a complete cure, but could achieve a status of "no evidence of disease (NED)", meaning that the diseases is not visible, the malignant lesions remaining but beyond our measuring resolution.

measures. The CR alone does not guarantee the clearing of the malignancy from the whole body. This could be the reason that despite improving results with regard to local remission rates, overall survival does not necessarily increase. The development of metastases and/or local relapses considerably limits the patient's overall survival.

The conventional chemotherapies or other systematically administered compounds (check-point inhibitors, enzymes, etc.) target some products and compounds of malignant formations, but the process which produces these targets remains intact. Modern cancer-therapy needs a shift of paradigm to focus on the dynamism of the malignancy and to concentrate on the activities which form the malignant phenomena [398]. This new demand again turns our attention to the complexity of the cancer and the living objects which carry it. The previous parts of this article have emphasized the demand for a complex approach regardless of which particularity is being investigated. A review of preclinical and clinical data [399] discovered that several old anticancer chemotherapy drugs, together with radiotherapy, had effects on immune responses. Three categories of immune effects could be identified: 1) direct immune-stimulation of effector cells (like NK and cytotoxic T-cells), 2) increased immunogenicity to poorly immunogenic malignancies, and 3) blocking the immunosuppressive cells (like Treg). Among others, Gemcitabine was identified as helpful in all categories. Paclitaxel was effective in 1) and 3), and Oxaliplatin was in 2) and 3). Interestingly, even such old drugs as 5-Fluorouracil and Cyclophosphamide were active in categories 2) and 3) respectively, and the antibiotic-related Doxorubicin and Idarubicin were active in category 2).

The homeostatic dynamic equilibrium is too complex for outside constraints

to be effective in repairing it. Compactly connected feedback mechanisms regulate the system, and the reaction of the homeostatic control will be against any simple restraints. A good example of this is the response to conventional hyperthermia, which aims to kill the tumour by thermal effect. It is a valid aim, but unfortunately homeostatic control mechanisms start correcting this heating by various actions to maintain thermal equilibrium. The most effective reaction is the increased blood-flow and perfusion, pursuing the cooling down of the heated lesion. However, this feedback carries a danger, increasing the delivery of nutrients to the tumour, as well as promoting metastases by cellular invasion to the bloodstream. Consequently, any winning strategy must work together with homeostatic controls, using the natural processes and supporting the immune system in recognizing and destroying the malignant cells throughout the entire body.

Many variants exist that aim to activate personal immune defences against cancer. The key point is the immune recognition of the malignancy. The immune system needs recognizable signs to direct its actions. However, the highly adaptive hiding strategy of the malignant cells protects them from being identified by the immune cells. One effective possibility for the invading of the cancer is the NK cell's innate antitumoural immune action [400] [401]. The NK does not need information by way of MCH-I molecules of the host, and acts in case of a lack of priming too. The cytotoxic activity of NK potentially controls tumour growth [402]. As a component of phytomedicine, Panax ginseng increases NK activity [140]. Complicating the complementing of the available positive effect of NK cells, it might also promote the tumour-progression and angiogenesis [403] inducing a dysfunction by ROS [404].

Also a possibility is to initialize the innate immune action by toll-like receptors (TLR) forcing suitable signal pathways (e.g. through the Tumour-necrosis factor Related Apoptosis Inducing Ligand (TRAIL) and its death receptors (DRs) [405]) to trigger cell death, eliminating the cancer cells [406], as when helping in the fight against infectious diseases [407].

The other possible immune attack could be promoted by adaptive immune reaction. The key is to form antigen presenting cells (APCs) and produce adaptive immune-fighting against the cancer-cells all over the body. The appropriate tumour-specific genetic information has to be obtained from tumours, presenting their malignant behaviour to the immune-surveillance. The process acts through immunogenic cell-death, which is a kind of apoptosis, freeing the genetic information from the tumour. This information may mature the dendritic cells (DCs). The matured DC forms CD4+ and CD8+ (helper and killer) T-cells with appropriate tumour-specific information, preparing them for tumour-specific immune attack. We may realize in this way how to get "back to complexity", as has been recognized as a demand in medicine generally [35].

Complementary mEHT therapy is a perfect tool with which to accomplish the CTA, completing it with appropriate immune support in both the innate and

adaptive mechanisms. The heterogenic targeted energy-absorption excites a branch of apoptotic signals, as described above. The main excitation is extrinsic through TLR by TRAIL-R2/DR5, which has the possibility of innate immuno-attack on cancer [408]. The mEHT therapy has an effect on adaptive immune stimulation as well. It produces immunogenic cell death (ICD) with the help of a damage associated molecular pattern (DAMP) [358]. The molecular set of DAMP gives all the necessary tumour-specific information for APC production. The extrinsic signal-excitation triggers the release of calreticulin (CRT, an "eat me signal"), adeno-triphosphate (ATP, a "find me signal"), high-mobility group protein 1 (HMGB1, a "danger signal"), and extracellular heat-shock protein 70 (HSP70, an "info signal"). The APC (mature DC) produces the necessary tumour-specific fighters: the CD4 (helper) and CD8 (killer) T-cells. The maturation of DC cells can be actively supported by the immune-stimulatory effect of b-glucan [409]. It has been shown that the mushroom G. lucidum simultaneously increases the percentages of CD3, CD4, and CD8, with a marginal elevation of NK-cell activity [169]. Assembling and stimulating the immune system against malignancy is a direct way to eliminate the cancer and avoid recurrence and metastases. The activated tumour specific cytotoxic T cells have the ability to recognize and destroy the cancer-cells all over the body. The NK cells, as the front-line defensive fighters, are intensified also by the general enhancing of the immune surveillance. Some cytokines, like IFN-gamma and TNF, could make a decisional addition to the tumour-destructive processes, and in this sense the old kind of anthracyclines [410] and/or electrodynamic therapy like mEHT could boost the immune cells and could create ICD by cytokine response to the treatment. The homeostatic balance is again clear with regard to the DAMP action, which may ignite the tumour-attack but on the other hand may trigger chronic inflammation, promoting tumour-growth [411] [412].

Enhancing the temperature of tumour-cells could increase their sensitivity to immune cell recognition and killing [413]. The naturally developed intracellular heat-shock proteins (HSPs) protect the cancer cells against any attacks, but the expression of them on the outside cellular membrane may activate the NK cells to attack the cell, promoting NK-cell cytotoxicity. When HSP70 is liberated to the extracellular electrolyte, it could tumour-specifically carry genetic information and prepare an orchestrated adaptive immune action against the tumour. In general, an induced immune-effect is observed in mild hyperthermia [414], even in preoperative application too [415]. The cytotoxic activity of NK-cells sharply reduces when the temperature growth is to over 41˚C [416] [417], and the general immune activity also drops at over 40˚C [418]. Due to the "only local" blocking of immune activity in high-temperature heating, it is neglected in local/regional hyperthermia (LRH) due to an assumption that new immune cells from the non-heated areas will be delivered and substitute for the blocked activity. This effect, however, does not help to form in-situ, real time immune actions. The time delay in presenting active immune-cells in the treated area could

be crucial, as genetic information needs to be available promptly for the possibility to mature the dendritic cells to form antigen presentation for a tumour-specific immune effect.

After the precise selection of the clusters, the transmembrane proteins (rafts) on the membranes of the cancer cells absorb the energy [368]. The malignant cells have relatively high raft density compared to their non-malignant neighbours [419], helping the selection by this additional factor and the energy-absorption heats the membrane to at least 3˚C higher than its surrounding extracellular electrolyte. The full process from the temperature point of view shows the growing temperature to the raft, representing the gradient responsible for mEHT's action [420].

There are a lot of natural compounds, herbal immunostimulants that support the immune system, enhancing its effects [140]. Evidence indicates that several anticancer drugs stimulate the immune system [399]. Antioxidants and phytomedical compounds, enzymes, etc., are all good candidates for the complex improvement of the immune actions against cancer development. However, again and again we have to emphasize that the homeostatic, healthy complexity needs a balancing equilibrium, that the interconnected feedback mechanisms can be counterproductive, and that a lack of expected benefits or even serious adverse effects can be observed. The complexity could be controlled by dosing (quantity of the taken compounds) and, in the same regard, by their relative applications in dose and time, considering their strong interconnections. One lucky situation is that phytomedical processes (nourishment) involving the taking of herbal and other effectors are usually harmless, because the quantity of the active drugs in the food is generally lower than dangerous levels. High quantity consumption of such nourishments tends to be limited by the stomach's capacity and by healthy lifestyle. However, even natural nourishments are not completely without side effects, especially since interactions between agents can cause side effects, though again, the healthy body will often avoid such problems by quick elimination (usually by the vomiting of drastically interacting contents). The real challenge, which could be dangerous with high dosing of compounds extracted from natural products, is not only quantitative, but deeply qualitative; the homeostatic dynamism is complex in time, and the SOC mechanisms and the fractal interactions redress imbalances in relatively narrow time bands. The observed fractal noise (1/f noise) is the fingerprint of the balance, and its dynamic support could have the same benefit as the variants of herbal or other immunostimulants. This is what is recognized by mEHT, and it applies electromagnetic fluctuations to stimulate the healthy dynamism of the complex interactions. The applied electric field, which transports information to the cellular level, induces chemical changes, but when the energy-absorption is not lethal for the cells by necrosis, it will not cause notable side effects.

The well applied electromagnetic effects are not too strong, causing necrosis by their absorbed energy, and not too weak to cause signal pathway excitations.

Of course, it is frequency dependent, so there is no excitation limit for the zeroth component of fluctuations [421]. The electric field could be associated with injury currents, which orients cellular migration and wound healing in general, as was discussed above. In reactions to injury, immune actions have a pivotal role. Injuries produce a higher population of immune cells. Modifying the injury currents could act as a healing factor by physical effects, helping the natural biological processes, which has a probable role in the effect of mEHT too. A continuous injury current, which stimulates cell-proliferation (intending to heal the wound) and promotes the tumour-infiltration of immune-cells, promotes the malignant proliferation [422]. However, the fluctuating current intensity of mEHT and its directional constraint blocks the negative effects of injury currents, blocking the proliferation stimuli.

The primary goal of the local therapies like radiation and local-regional hyperthermia is to eliminate the tumour, measured by the local response of the therapy. Cancer patients with multiple distant metastatic lesions have multiple local therapies as macroscopic tumours are observed. However, most metastases, at least in their early stages, are microscopic, and there is no fine enough resolution of imaging diagnosis to recognize them. A change of paradigm away from these local treatments looks mandatory to solve the consequence of the spreading of malignancy. Intensive research is targeting the challenge to treat distant metastatic lesions even in their microscopic state. The expected appropriate tool to meet these requirements would be a local effect far away from the treatment's actual application location. Radiation generates "danger" signals, transmitting from irradiated to non-irradiated cells, which could lead to off-target effects.

The explanation of radiotherapy by traditional radiobiology has focused on DNA damage to avoid the repair of the targeted tissue. This effect is clearly localized on the irradiated area. The first published observation on a systemic effect of local radiotherapy was made by R. H. Mole, who proposed the term "abscopal effect" in 1953 [423]. The word abscopal is derived from the Latin ab, meaning "positioned away from", and scopos, meaning "a target for shooting at". The abscopal effect is defined as a systemic action of radiation therapy observed in apparently untreated tumour locations distant from the site of irradiation field. These distal effects were neglected for a long time after their first detection; they were "rediscovered" [424] outside the treated field of ionizing radiation [425], but were generally under-recognized in clinical practice [424]. Similar, but certainly much shorter in their effective distance, are bystander effects, which are communicated from an irradiated cell to a non-irradiated bystander cell via cell-to-cell gap junctions [426] or by the secretion or shedding of soluble factors [427] [428]. Important information was provided by case reports showing that despite the radiosensitivity of hypoxic lesion being suppressed, when targeting the hypoxic centre of the tumour the non-targeted bystander area is also affected [429]. The precise nature of factors that mediate the bystander effect is unknown, but reactive oxygen and nitrogen species and various cytokines have

been implicated. The short distance bystander information transfer has been ascribed to redox mechanisms, which may produce transmission of ROS, various cytokines, and reactive nitrogen species (RNS), making the off-target response similar to inflammation [430]. The propagation of bystander effects among cancer cells additionally to inflammatory mechanisms involves cellular communication under irradiation with non-uniform dose distribution nearby, and probably immune action in far-away localizations [431].

Radiation-induced long-distance abscopal effects have been extensively documented in several recent reviews [432] [433], which have described both detrimental (e.g., DNA strand cleavage, chromosomal damage, and cytotoxicity [434]) and potentially beneficial abscopal effects. The explanation of abscopal effects has well distinguished it from the bystander effects in the traditional sense [435], having no direct short communication pathway between the treated and untreated cells. Much of the observed physiological abscopal effect has been associated with splenic irradiation [436], but intensive development in using it for solid tumours had been started. In the early period of applications, the explanation of the effect related to the immune response mediated by cytokines, but the mechanism remained unclear because this phenomenon was so rare and poorly understood in clinical practice, also giving rise to many controversies [433]; and sometimes being used complementary to other types of local therapies including surgery, hyperthermia, and immunotherapy.

Evidence is piling up that radiotherapy in the appropriate dose stimulates the immune system. In consequence, the abscopal effect has recently been revised, receiving attention as a new therapeutic facility [437]. Intensive application in the clinical setting has been started in a variety of malignancies including lymphoma [438], papillary adenocarcinoma [439], melanoma [440], adenocarcinoma [441] [442], chronic lymphocytic leukaemia [443] [444], lung malignancies [445] [446], and hepatocellular carcinoma [447] [448]. Low-dose radiation delivers clinical benefits by abscopal effect [449]. The application of emerging immunotherapies by check-point inhibitors combined with radiotherapy has also been tried [450] [451]. This complementary application did not give clear clinical evidence for the benefit of this combination [452] not delivering stable results [453], but the positive promise remains [454]. Despite the incomplete understanding and sometimes controversial results, the present results show clearly the trend of cancer therapy development: cytotoxic drugs used for systemic therapies will be replaced by more complex combined therapies involving the immune-system, providing systemic, abscopal facility [455].

The abscopal effect is probably of the same complex as other living phenomena, tumour-specific mechanisms being seen which are defined by the type of the tumour, and there also being observed general immune responses which could be connected to the distant effects [456]. The role of non-uniform dose could be essential to take account of the mechanism of the distant actions, because it opens a wide spectrum of doses, among which the optimal value need be found

from the "offered" quasi-linearly changing dose-spectrum. This is probably the reason why the definitely necrotic ablation technology has observable off-target effects [457] showing a broad range of electromagnetic interactions, from the necrotic to the weak, negligible effect in the far distance, which may include the necessary optimum for abscopal applications. Probably the same could happen with local high temperature heating too [458]. However, in account of the complexity it is important that the critical homeostatic regulator, the immune system, has a pivotal role in the new paradigm of oncology.

One possible part of the complex approach could be the electrical field, which has no direct macroscopic physiological effects. In in vivo experiments to clarify abscopal effects in rats in combination with radiotherapy, a pulsed electrical field was successfully investigated [459]. These experiments support the idea of trying the mEHT method in the same way, giving reason to expect positive results from the abscopal application of mEHT. The immune-stimulation approach in hyperthermia was well demonstrated earlier [460], and so it is high time to try it with mEHT too. We have to consider also that the old challenge of the homogeneous heating paradigm of conventional hyperthermia, described above, has appeared again using an updated combination of methods: a complex protocol of radiotherapy check-point inhibitors and nanoparticle hyperthermia were applied in a mice model with controversies observed: there was no increase of survival time, and metastatic dissemination to the lung of the model animal was observed [461].

mEHT is immunogenic [462]. Our main idea was based directly on the immune effects of mEHT, which induces ICD by DAMP, as we have shown above. It was however obvious that for a tumour-specific immune action we need APC, which needs a proper immune system, where un-matured DCs are available. An immuno-boosting, as others have used with radiation [463], could be the solution. We report a case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. We learned earlier that a cytokine that activates dendritic cells, the granuloceyte-macrophage colony stimulating factor (GM-CSF) as immune-boost, was earlier used with hyperthermia for inoperable pancreatic tumours with success [460]. The boosting of radiation therapy for abscopal effect used this method too [464] [465] [466]. Following this line, the patient was treated with fractional radiotherapy, modulated electro-hyperthermia (oncothermia), and GM-CSF. The success was significant, and the distant metastases disappeared while the treated primary lung lesion had good shrinking [467].

Our direct goal remained the simple tumour-specific immune attack, as was described above: to develop T-cells to perform action against the malignant cells all over the body, irrespective of their distance from the treated primary lesion [468]. One of the effective methods of inducing abscopal effect starts with ICD [469]. This was clearly demonstrated in murine model in vivo, when the abscopal effect appeared far away from the locally, mEHT treated tumour lesion, all the

DAMP molecules of the pattern—CRT, HMGB1, HSP70, and ATP—being measured, and being liberated into the extracellular electrolyte [470]. The model was tried in the situation where the originally available immune system is too weak to produce enough APC. The experiments in vivo showed the excellence of the injection of general un-matured DC-cells to produce clear abscopal effect [471]. Note, the injection of DC cells alone did not show abscopal effect without mEHT application. The immune action works like vaccination, and the re-challenging by the same tumour was ineffective [472]. The vaccination idea was patented [473].

The general abscopal effect by mEHT could be induced not only by DC [471] [472] or GM-CSF immune stimuli [467], as was shown above, but a general treatment complexity including diet and life-style change could work well with mEHT too [474]. Other complex immune-stimuli can be effectively produced by virus application [475] [476], there being excellent case-reports showing the results [477] [478], as well as there being statistically evaluable significance with the serious glioblastoma multiform showing the excellence of the virus-supported mEHT method [479], engineering the bacterial "Trojan horse" [480] to carry out a viral trick. Low-dose check-point inhibition with IL-2 support in combination with mEHT is also successful [481].

A Phase III clinical trial was performed for advanced cervical cancer treated with radio-chemotherapy with and without mEHT [464]. The abscopal effect was also evaluated beside the evaluation of the primary and secondary endpoints [482]; a significant abscopal effect was shown to be induced by mEHT compared to in the control arm. Positron emission tomography-controlled results show clearance of the metastases in the not directly treated pelvic area in more than 25% of the patients, while complete, all disease resolved results were observed in 24% of the cases on the active, mEHT treated arm, compared to just 5.6% in the radio-chemotherapy only control. The result is remarkable, because no extra immune-support was used to obtain these results in such advanced stages.

Elongated survival time, together with the improved quality of life, has been measured with mEHT in many Phase II trials with secondary endpoints of the local response. The joint positive result of the response and survival [362] [479] [483]-[489], even in cases when no conventional complementary treatment was applicable and mEHT monotherapy was performed [490], indirectly justifies the abscopal effect by the method, which was missing in conventional hyperthermia in many cases.

The best SC and PT depend on many and complex factors. The most important factors to consider:

1) First is the patient's characteristics:

a) the dosing of the treatment drugs, considering the patient's sensitivity to SC/PT;

b) general immune status;

c) kind of disease (morbidity);

d) stage and severity of disease;

e) without medical aid, home applied SC/PT.

2) Interactions with conventional, standard treatments:

a) pharmacological properties of the concomitantly applied standard treatments;

b) previously applied conventional, standard treatments;

c) comorbidities, or adverse effects of the applied standard treatments;

d) biological or physiological reasons for limiting or blocking the standard treatments.

3) Availability of SC/PT in the therapy process:

a) availability of optimal palliative and supportive drugs;

b) preparedness and SC/PT knowledge of the medical staff;

c) sufficient and accepted confidence of the patient in the physician and the therapies prescribed;

d) availability and intensity of follow-up.

For example, the IV application of high dose vitamin C with mEHT for non-small cell lung cancer was safe [206] had provided significant improvements in a well-selected and controlled cohort of the patients [372]. One of the controlled studies of the best SC for glioblastoma and astrocytoma [486] and pancreas carcinomas [362] shows the necessity of mEHT for significant results [486].

3. Conclusions

The war against cancer [491] is not over yet. There have been many good results and year-by-year new chemotherapies show improvements, but we are far from a final solution. Probably we need a change of paradigm from tumour-oriented therapy strategies to patient-oriented ones and also from product targeted to process targeted treatments, from static distortion to dynamic blockade. The focus of therapy must be reoriented from the products of the tumour (hallmarks, which appear, and are chosen to target) to the process which produces the malignancy [398]. Due to the complexity of the living object the blocking of one product or of a group of them helps only temporarily, because the complex bodily regulation mechanisms soon substitute the absent means for the tumour to develop. We know very well that a single finger as a barrier to overflowing water cannot stop the process itself; we must act at the source of the flow

We have to stop concentrating on the tumour alone and instead focus on the integrity of the patient. Integrative thinking is necessary with regard to the complex structure of life-processes. We believe that, as mathematics has no "alternative mathematics", medicine also has no alternative medicine. When we see the limits of current medical approaches, we have to change the paradigm to meet the challenges. Treatments, and not just medicine, could have alternatives, forcing us in the same direction: towards regarding the patient as a whole, integrative unity.

We propose three goals as a result of this "prospective review":

1) An early palliative therapy should support the conventional therapies, increasing their effects together with decreasing their adverse effects. This has to be a part of the CTA, using early palliation and vigilant supportive care. This point must be measured according to the elongation of survival time with improved quality of life.

2) Care should be taken to restart and replenish the hampered immune system, which is below its normal capability due to cytostatic effects and disease burden resulting in overloaded immune functions. This refers not only to the possibility of inducing the desired abscopal effect, but to general surveillance too, avoiding comorbidities and new challenges generally in the life-quality of the patient.

3) Complete the revitalization of the immune-system and the whole body in the follow-up period. This goal contains physiological, psychological, and social components too, helping to form a new and convenient lifestyle for the patient.

The key to the new paradigm is the helping of natural complex processes to solve the challenges, and not forcing upon the system something which explodes the homeostatic dynamic balance and which causes the body's regulatory mechanisms to fight against the applied treatment. There are some desired rules on how to discuss the problems of herb–drug interactions with cancer patients [492]:

- Clarify what type of herbs the patient takes regularly, counting that some herbs are considered as food or spices, and the possible similar ingredients in these that could have a commutative effect;
- The health professional has to have an open mind, not refusing immediately those herbs which have no proven useful effect. Concentrate on the explanation of proven negative effects. Despite few herbs having evidence of usefulness in treating malignancies, some of them may help relieve symptoms, and many eases the psychological pressure on the patient;
- When the herb has proven disadvantages, explain for the patients why it is so (for example, it reduces the effectivity of the applied therapy or increases the side-effects, or interacts with other useful herbs in a negative way). It is of great help when a similar herb without contraindications can be proposed;
- Educate the patient on the general pros and cons of supplementary drugs;
- Monitor the adverse effects of the herbs which you have agreed to their taking during the therapy and follow-up period;
- When there is no choice of herbal supplements, other therapies like meditation, yoga, or acupuncture could be suggested to improve the quality of life of the patient;
- It would be fine to refer to a specialist who could make a professional balancing of the risks/benefits of the supplemental therapies, and who could offer herbal therapy in the specific circumstances, properly considering the cancer therapy.

All preventive steps have to concentrate on a healthy lifestyle, including a well-balanced diet, care for acid-alkaline balance with intensive liquid consumption, regular daily exercises, and low chronic stress. Nevertheless, the acute daily stresses could be helpful [493] [494]. The hypothalamus-pituitary gland-adrenal-glands (HPA axis) has a complex homeostatic dependence [495]. Its primary function involves the body's reaction to stress involving the sympathetic nervous system and could involve the psychological self-suggestion [496]. The healthy circadian rhythm also affects the HPA axis [497]. Consequently, physiological and psychological health is strongly connected and has an essential role in preventing cancer. No further preventive action is required in the case of a well-working immune system and balanced psychologic status. The homeostatic surveillance actively regulates.

We may follow how the change in paradigms has been mirrored in the adjudgment of oncological hyperthermia:

1) First cames the conclusion regarding unsolved challenges in early applications: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment" [498].

2) "The biological effects are impressive, but physically the heat delivery is problematic" stated an editorial of the European Journal of Cancer in 2001 [499]. They invoked a shortage of technical knowledge: "The biology is with us, the physics are against us".

3) Later, when no significant development was possible in technical solutions, physiology became the target: "The biology and the physics are with us, but the physiology is against us" [500].

4) In a recent physical analysis of mEHT [347] it was well formulated, as emphasized in two conferences as well, that "physics is our friend, but we have not noticed it" [501] [502].

We have to conclude that the new paradigm is the way back to complexity, using biology, physics, and physiology in their interconnection. Nature takes no consideration that we have divided the phenomena into categories and disciplines, and natural processes involve all aspects, which we are not able to consider in such complexity as is the reality. Cancer as a phenomenon does not distinguish between the human-created disciplines. It is as complex as all the nature around us. We may surmount the gap of the missing complexity by modulated electrohyperthermia (mEHT), answering the question as to "where medicine went wrong" [35]. Thinking on the hyperthermia paradigm has to be complex like the malignancies it aims to treat. The mEHT treatment has shown a wide range of applications from in the laboratory to the clinic [361]. A clinical review was recently published [363] showing excellent results in advanced diseases, mostly in cases where the conventional protocols offer palliation only.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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