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**SPIRITUALITY AND CANCER DISEASE: A STUDY ON
THE EFFICACY OF ANTITUMOR THERAPIES WITH
NATURAL ANTICANCER AGENTS IN RELATION TO
THE SPIRITUAL PROFILE**

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1. ABSTRACT

Spirituality is more about constant questioning than about providing fixed or final answers. Cancer patients do not expect spiritual solutions from oncology team members, but they wish to feel comfortable enough to raise spiritual issues and not be met with fear, judgmental attitudes, or dismissive comments. Spiritual needs may not be explicit in all illness phases, yet spirituality is not only confined to the areas of palliative or end-of-life care. Sensitive and effective methods to assess and address spiritual needs of cancer patients are being developed and qualitative research on the topic is underway. In addition, formal education and training in communication about cancer patients' spiritual issues and in how to assess and address them in the clinical context is being increasingly provided. Spirituality can be a major resource for both patients and physicians, yet it can never be imposed but only shared. Those oncology professionals who are familiar with their own spirituality will be better at recognizing, understanding and attending to their patients' spiritual needs and concerns.

The recent discoveries of the existence of natural anticancer agents either from plants, such as Aloe, Myrrh and Magnolia, or from the human body, namely the pineal hormones, allowed the possibility to elaborate new therapeutic natural combinations as a link between the commonly used palliative and curative cancer therapies, which would have not considered in a separate manner. The present study was carried out to evaluate the influence of the spiritual status on the efficacy of a natural anticancer combination containing pineal anticancer hormones in association with Aloe, Myrrh and Magnolia extracts in a group of 70 untreatable metastatic solid tumor patients with life expectancy less than 1 year. The spiritual sensitivity was evaluated by an appropriate faith test for patients affected by an untreatable disease. The percentages of both objective tumor regressions and disease control obtained in patients with high faith score were significantly higher with respect to those found in patients with low faith score. On the same way, the 3- year percent of survival achieved in patients with high faith score was significantly longer than that found in the other group. This study would suggest the efficacy of an antitumor therapeutic strategies with natural anticancer agents also in metastatic cancer patients from whom no other standard antitumor treatment was available, with a greater efficacy in the presence of a real status of spiritual faith.

2. INTRODUCTION

Why should oncology professionals be expected to know about their patients' spirituality? Patients confronted with a life-threatening illness tend to disclose many aspects of their spirituality, offering to their physicians the unique opportunity to serve as non-judgmental mirrors of their spoken or silent feelings of fear, despair and hope. Nonetheless, to draw nearer to the realm of patient spirituality, physicians should first become familiar with the language of their own spirituality [1]. What is spirituality? Philosophers and some physicians have long searched for a broad understanding of spirituality, beyond reductive or dogmatic paradigms [2]. Yet, there is no agreement on an established definition of spirituality that could guide research and clinical practice in oncology. The term "spiritual" has multiple meanings and applications, and too often the spiritual and religious dimensions are conflated, engendering the risk of superficial or doctrinaire approaches to spirituality. In this article we try to dispel common sources of confusion that may hinder our ability to provide respectful holistic care for cancer patients and survivors and we offer our perspective on sharing, rather than imposing or forcing, spirituality in oncology practice.

Reflecting on spirituality is similar to reflecting on "self-identity." Being engaged in a constant spiritual quest is the core of our existence, and it goes beyond usual psychological or social variables, such as gender, age, education, jobs and activities, positions and roles in society. In the process of self-development, accomplished persons or persons still in search for their identity, going through phases of relative calm or through dramatic events in their lives, may all ask similar spiritual questions and draw strength from spiritual sources, often kept private and hidden from others. Spirituality is a common terrain for humanity, irrespective of sources of authority and paths of faith or worship [3]. It concerns each person's "naked self", authenticity, dignity and hope. It refers to transcendent questions, to questions of meaning and of values, and to those interpersonal relationships that form the tapestry of our lives within the human community [3,4]. Spirituality challenges our notions of inner- and outer-self, making us confront and overcome boundaries between our-selves and other persons or nature or transcendent divinity. Through spirituality, we connect with something located both within and beyond us—we create a bridge between us and the surrounding universe [1, 5, 6].

3. THE PSYCHONEUROEDOCRINOIMMUNOLOGY (PNEI)

Psychoneuroendocrinology is the most recent medical discipline studying the neuroimmunochemistry of emotions and states of consciousness and their effect on the state of health or disease through a central psychoneuroendocrine regulation of the immune system.

Emotions are an expression of the psychological dimension of the soul, while the state of consciousness is related to the spiritual dimension of the person, bearing in mind that spiritual is not synonymous with mental or moral conscience, but only with self-consciousness. Spiritual is nothing but self-consciousness, and true self-consciousness is only founded on love, meant as the perception of the other as another self.

Chemical psychoneuroendocrinology is applying psychoneuroendocrinology knowledge to clinical medicine at aetio-pathogenic, diagnostic, therapeutic, and preventive levels. Unlike scientifically obsolete psychosomatics, which attributed the mediating role of psychic influence on the function of the organs only to the neurovegetative central and peripheral system, psychoneuroendocrinology determines in the lymphatic immune system the main means of the relation between psycho-spiritual experience and state of health.

In other words, the nervous system is the vehicle of mental life, whereas the immune system is the vehicle of spiritual consciousness in the functionality of the biological body. While changes in the nerve neurovegetative functionality originate persistent but marginal chronic functional disorders, despite worsening life conditions, the immune system responds with death or life in the two antithetic conditions of a lacking or amplified reaction, in reference to tumours or autoimmune diseases, in fact decreeing recovery or death [1].

Psychoneuroendocrinology does not replace or thwart any of the previous medical branches; conversely, it integrates them according to a holistic vision of the human being, finally getting past the mechanistic and separating notion of the various functionalities of living organisms. Psychoneuroendocrinology in itself is the integration of three medical branches: 1) endocrinology, relevant to the endocrine and neuroendocrine functionality; 2) immunology, relevant to the psychoneurochemical functionality; 3) neurology-psychiatry relevant to the psychoneurochemical functionality. Compared to psychoneuroendocrinology, meant first of all as experimental science, clinical psychoneuroendocrinology requires the knowledge of a fourth medical branch, internal medicine, to turn the scientific knowledge originating from psychoneuroendocrinology into a new understanding of the aetio-pathogenic physiopathology of the main human diseases. A new competence typical of psychoneuroendocrinology, the physiopathology of the pineal gland must be added to all this. Although being one of the 7 endocrine glands, the pineal gland is not included in the competence of endocrinology. Likewise, psychoneuroendocrinology includes the study of the biological effects of the various proteins produced by the immunological cells, the cytokines, that the old immunology, founded on the simple transformation in vivo of what had been observed in vitro at immunological level – therefore without considering the neuro-endocrine modulation of the immune response – still does not seem able to consider the possibility of a new systematic vision of the involvement of the immune system in the main human pathologies [7].

1) nervous and endocrine cells have receptors for the cytokines of the immune system, therefore are influenced by them, and in turn produce endocrine and neuro-active molecules able to influence the functionality of the immune cells, stimulating or inhibiting them.

2) immune cells, lymphocytes and macrophages have receptors for hormones and neuro-active molecules, therefore their functionality is under a neuro-endocrine central control; in turn, through the production of cytokines, they can influence not only the other immune cells, but also the neuro-endocrine system, and consequently the hormonal and neurologic state of a person. Therefore, psychoneuroendocrinology requires a general reassessment of the entire medical and medical-psychological science.

4. THE SPIRITUALITY

The notion of spirituality, while grasped by each one of us in daily life, is extremely difficult to define because its many dimensions are intangible even more so when a person is confronted with a life-threatening illness [2]. Oncologists practice a highly complex and demanding specialty under enormous time and financial pressures, often with no, or limited, training in basic communication skills or in dealing with common feelings of sadness or anxiety in cancer patients. At first glance, it may seem most appropriate to set aside the more impenetrable dimension of spirituality until we have addressed those still missing basic issues of compassion and empathic communication in oncology. However, cancer patients often raise questions of a spiritual nature with their oncology providers, who need to be prepared to respond to their patients, even when they do not wish to act as spiritual advisors. Faced with the ambiguity of the present and the many uncertainties about the future, in fact, many cancer patients rely on their spiritual beliefs as a source of strength, rebellion or uncharted hope. They do not expect spiritual answers or solutions from oncologists or other team members, but they wish to feel comfortable enough to raise spiritual issues and not be met with fear, judgmental attitudes, or dismissive comments. Spiritual needs may not be made explicit by cancer patients in all of their illness phases, yet spirituality is not solely confined to the areas of palliative or end-of-life care. Spirituality is one dimension by which cancer patients can fight feelings of fear and alienation during the entire course of their illness, and some patients rank faith as a significant factor in decision making, and consider spiritual well-being important for a better quality-of-life during and after their cancer treatment [9–12]. Similarly, many oncologists are personally engaged in a spiritual path and they should not be impeded in sharing a spiritual search with their patients by a technocratic culture, which emphasizes the more easily quantifiable aspects of medicine at the expense of the ineffable humane dimensions of healing [13]. At times of economic, social, political and moral uncertainties in rapidly evolving western societies, why not

appeal to the existing range of spirituality, no matter how much in disguise, in those who have chosen a profession that brings them so close to human pain, suffering and dying? Thus, while oncologists and other oncology professionals should not be forced to engage in spiritual or religious discussions with their patients, if they do not feel comfortable about taking upon themselves a role of spiritual advisors that is not within their field of expertise or training, nurturing a spiritual dimension in oncology practices is a legitimate educational goal. Learning how spirituality might help cancer patients cope with physical and existential suffering may, in fact, also strengthen cancer specialists' own meaning. The American College of Physicians and the American Academy of Family Physicians affirm the importance for health professionals to recognize and assess cultural, psychosocial, existential, spiritual and religious aspects of patients' suffering, and learn how to address them as part of their caring for individual patients [14–16].

5. SPIRITUALITY, CULTURE AND RELIGION: INTERACTION AND INTEGRATION

5.1. DEFINITIONS

Spirituality, culture and religion are interconnected, yet each has defined and separate spheres of influence and action. Religion is about the congregational aspects and formal ways to express one's beliefs, while spirituality is about personal authenticity. Spirituality involves broad humanistic issues and developmental aspects of a person's life, which are based on values and on individual, community and society needs [4]. A typical view of spirituality refers to a personal experience increasingly independent of organized forms of worship [17].

Religion comes from the Latin *religare*, which means “to bind together.” Religion organizes the collective spiritual experiences of a group of people into a system of beliefs and practices. Religious involvement, or religiosity, refers to the degree of participation in, or adherence to, the beliefs and practices of an organized religion [19]. Spirituality, by contrast, is a broader concept than religion. It is primarily a dynamic, personal and experiential process. The term derives from the Latin *spiritualitas* meaning “to breathe, inspire or respire”, which, in turn, derives from the Hebrew word *Bereishit* meaning “in the beginning” when God “breathed” life into Adam and Eve. Interestingly, this idea reverberates in modern Jewish law, where death is declared only when breathing stops and not when the brain stem ceases to function [20]. The Qur'an and the teachings of Muhammad constitute the foundations for the inseparable religious and cultural lives of Muslims throughout the world. According to these authoritative sources, there is no spirituality without religious belief and practice, and the Islamic religion plays an integral role in Muslim cultural perspectives concerning illness [21]. A study of Islamic-based religious devotion showed speedier recovery from anxiety and depression among practicing than non-practicing Muslims [22].

5.2. ROLE OF SPIRITUALITY AND RELIGION IN CLINICAL CARE

Spirituality relates to both culture and religion, and all three domains influence our perceptions of health and illness [23–26]. Throughout history, health and disease have often been directly related to a variety of religious beliefs and practices, and specific prescriptions concerning the body, physical activities, quiet reflection and prayer are contained in contemporary religious creeds [23]. An overview of 35 studies of the relationship between religiosity and health related physiological processes found that adherence to both Judeo-Christian and Eastern religious practices was associated with reduced blood pressure and improved immune function [24]. Zen, yoga and meditation practices correlated with lower levels of stress hormone and cholesterol, and better overall health outcomes among patients [27]. The positive association between religious beliefs or practices and health outcomes, reported in many studies and overviews of several hundred publications, makes a compelling argument that physicians should have basic knowledge of published studies and ongoing research in this field [28–33]. Despite research showing that patients who have a religious faith may benefit from prayers or other religious practices, emphasizing the link between religion and health can be especially dangerous when dealing with vulnerable cancer patients. By contrast, denying that a positive link may exist for some patients, would amount to taking a dogmatic stance on a subject extremely difficult to quantify in scientific terms [34–36]. In the clinical setting, we should focus on broader understandings of the notion of spirituality and avoid confusing spiritual with religious dimensions, even though religion remains the primary locus for the expression of many cancer patients' spirituality and religiosity may affect their coping with physical and existential pain [29, 37, 38]. Studies in the United States show that a great majority of the general population, including physicians, believe in God and most American adults believe that spiritual faith can help people recover from illness, injury or disease [37, 39–41]. Even persons defining themselves as non-religious would like medical providers to discuss the spiritual aspects of their illness [39]. Although most physicians agree about questioning their patients approaching death concerning spiritual and religious beliefs and practices, only few raise spiritual or religious issues in their clinical practice [41, 42, 43]. Several studies show that most clinicians are uncomfortable with the prospect of praying with their patients, and, although few may do it upon patients' requests, it is advisable not to encourage the use of prayer by oncology professionals as part of their professional duties [44]. As contemporary medicine has adopted the post-modern presumption that scientific discourse is “public”, while spiritual or theological discourse is “private”, common perspectives on the role of spirituality in the healing process range from cynical scepticism to supportive advocacy [36, 45]. Many oncologists think that more rigorous empirical evidence, based on well-controlled studies, is needed to support spiritual claims in regard to clinical

outcomes. While oncologists have started acknowledging the need to acquire specific communication skills to improve the delivery of sensitive and culturally competent cancer care, the importance of addressing their patients' spiritual or religious issues in the clinical context has not yet been widely recognized [7, 17, 46]. As not all cancer patients are reported to suffer physically and psychologically, some oncologists may believe that only a minority of patients would require spiritual help for their existential suffering, while others are concerned about imposing on patients their own views in matters of spirituality or religion [47, 48]. Yet, regardless of individual oncology professionals' attitudes toward engaging in spirituality with their cancer patients, the principle of patient autonomy requires that physicians respect the decisions of competent patients, which are often based on religious and spiritual beliefs [12, 49–51]. In addition, patients often spontaneously raise spiritual issues and concerns with their physicians that are unrelated, or not directly related, to decision making. For all these reasons, it is almost impossible for physicians to ignore or avoid recognizing that there is a spiritual component at the core of the patient–doctor relationship and this is magnified when the illness is cancer [8, 9, 52–56].

6. MEASURING SPRITUALITY: ASSESSMENT IN CANCER PATIENTS

6.1. VALIDATED ASSESSMENT TOOLS

Defining and measuring spirituality as distinct from religion, but also from psychological well-being, is a difficult task, yet recent literature offers various suggestions and guidelines on how to gather a “spiritual history” in cancer patients [56,57]. A few instruments that measure multidimensional indicators of religion and spirituality have demonstrated good psychometric properties, including self-ratings used to predict a range of social attitudes and health behaviours [16, 57, 58]. The SPIRIT scale is based on an assessment of spiritual beliefs, personal spirituality, integration with a spiritual community, and ritualized practices and restrictions, with implications for use in medical care and terminal events planning [59]. The Systems of Belief Inventory (SBI-15R), a brief self-report inventory designed for use in quality-of-life and psychosocial adjustment to cancer illness, measures religious and spiritual beliefs and the social support derived from a community sharing those beliefs [60, 61]. The HOPE questions and the spiritual involvement and belief scale are validated tools developed for family physicians [62, 63]. The FICA scale is based on assessment of faith and beliefs, importance of spirituality, spiritual community support, and how patients address immediate spiritual needs [64]. A measure of spiritual well-being distinguishes spiritually related elements among both religiously diverse populations and persons who consider themselves spiritual but not religious [65]. Qualitative research is being increasingly applied to

appraise the more intangible aspects of the spiritual dimensions of life that are not easily quantifiable by standard scientific criteria, yet play a key role for many cancer patients [66–68].

6.2. BEST CLINICAL PRACTICES AND EDUCATION

Emerging best practices in regard to spirituality in clinical care have also been implemented. The US Joint Commission for the Accreditation of Healthcare Organizations mandates that a basic spiritual assessment be completed for each patient admitted to an acute care facility or nursing home, or seen by a home health agency, and documented in the patient's medical record. Examples of elements that the JCAHO recommends to include in a basic spiritual assessment are sources of strength and hope for the individual patient, practice of prayer and possible role in a religious community, ways to express his or her spirituality, type of desired spiritual or religious support, meaning of suffering and dying [69]. A typical spiritual history adds only a few minutes to the medical encounter, yet, if taken with sensitivity, it may already serve as an initial intervention to reassure patients and to open a channel of future communication between them and oncology professionals. However, while both the American College of Physician and the American Association of Family Physicians recommend the inclusion of spiritual assessment and support within the scope of medical care, a discrepancy between professional guidelines and actual clinical practice exists, and still few oncology professionals follow established guidelines regarding spirituality [16–18, 70–72]. Ideally, the spiritual needs of patients are best met within the context of an established relationship, through progressive steps: establishing an empathic connection with the patient or the patient's family, engaging the patient and/or family in significant spiritual sharing, moving to specific questions of meaning, value and relationships only when appropriate, and referring and introducing interested patients to other members of the spiritual team [9]. An increasing number of medical schools worldwide offer courses on spirituality to foster clinicians' knowledge and skills, or are in the process of developing such educational area [73]. A growing number of cancer centers and clinics in western countries are establishing interdisciplinary teams to meet the spiritual needs of cancer patients, a particular challenge in those multicultural settings, where patients and oncology staff often do not share the same language, values, religion or modalities of spiritual search [15, 17, 46]. Oncology professionals may be involved in such spiritual teams and take part in designing and evaluating research projects on spiritual interventions. However, following a general trend to keep professional roles separate in industrialized societies, spiritual advisors are hospital chaplains, along with cancer survivors, members of the clergy and volunteers. In the US, hospital chaplains receive specialized education and training in how to elicit spiritual and existential histories, while avoiding religious biases, and have thus become valuable skilled professionals who can interact with cancer patients and their families in effective and

sensitive ways [5, 50, 72–77]. Oncology professionals who may feel comfortable responding to their patients' spiritual needs or requests, need to recognize that they also would benefit from formal education and training to be spiritual advisors [78]. The integration of spiritual assessment and basic communication in cancer care may therefore occur at different levels, ranging from asking patients to respond to basic questions about their spiritual beliefs and needs, to engaging at a personal level with patients who try to involve their oncologists in the spiritual dimension of their care, to intervening as part of a spiritual team. In all different circumstances, discussions about spiritual issues may benefit from being carried on in “healing spaces”, whether special rooms or special times, dedicated to patients' spiritual issues [8].

7. SHARING, NOT IMPOSING, SPIRITUALITY IN ONCOLOGY

Illness is both a biomedical reality and a socio-cultural construct. Illness affects a person's body, mind and soul and, when severe, inexorably raises questions of a transcendent nature about meaning, value and relationships. These are spiritual questions [3, 4, 73]. How we answer them for ourselves will affect whether and how we can help our patients' spiritual search. As the patient–doctor relationship is based on asymmetry, physicians, holding more authority and power, may easily impose, or attempt to impose, their own views in matters related to spirituality [79, 80]. Spiritual beliefs and timing, however, cannot be imposed [4]. They can only be shared, for there is no right or wrong time or way to experience, feel, suffer or face death. Patients, health professionals and caregivers bring to the clinical encounter and the therapeutic relationship their personal history of experiences, values, beliefs and prejudices involving the spiritual domain. Whether or not a person's spirituality is lived through a religious lens, the strong and often passionate beliefs that relate to the spiritual dimension of one's life are difficult to set aside, even within the context of a professional relationship of help. The risks of enforcing, rather than sharing, spirituality in the relationship between oncology professionals and their patients are multiple and complex. Patients may not wish to discuss spiritual issues, and permission to do so is always needed [4, 34, 50, 51]. By contrast, some patients may try to express their own spiritual preferences and needs, and may feel, or in effect are, silenced. Narratives are a common, powerful, way for patients to find a spiritual thread that connects their lives before and with cancer, and to communicate their spirituality in the clinical context [81]. In the presence of cross-cultural differences between patients and oncology professionals, patients may have to readapt their illness narratives to be understood [46]. Any imposition of dominant models of narratives that are disrespectful of patients' cultures hinders patients' ability to express their spirituality, and it may even result in attempts to proselytize patients at times of particular vulnerability [4, 50, 51, 73]. Physicians, psychologists and other

oncology professionals can, however, find effective ways to share in their patients' spiritual searches and be tuned to their needs. Communication at a spiritual level in the patient–doctor relationship requires openness to true dialogue and to the possibility that the resulting discourse will bewilder, disconcert and, perhaps, change the involved partners in their beliefs and behaviours. Rather than imposing a professional ideology that may progressively isolate patients and their caregivers, oncology professionals can demonstrate their utmost respect for their patients' spiritual searches by showing their patients—through physical, mental and spiritual availability—that they also are engaged in a spiritual path. Knowing that doctors, nurses and other team members are immersed in the spiritual dimensions of living establishes an atmosphere of reassurance and trust for those cancer patients who choose to confide in them.

Some authors have suggested that it may be appropriate at times to ask the patient directly: “What is the relationship between you and your personal God? Do you speak with Him?” [8] Conversations of such depth are rare in the clinical context, yet they may happen at times of special connections in the patient–doctor relationship [82]. Most often, cancer patients initiate dialogue about spirituality and religiosity with their physicians, wishing that oncology professionals not only would show respect for their spiritual needs and points of view, but would also engage with them in private reflections on issues of meaning, faith and hope. Some patients may desire to pray with their oncologists, others simply to be heard or given the opportunity to speak about their spiritual beliefs and needs. Others may prefer to discuss spiritual issues with someone other than a medical professional. Each person has a different threshold for intimacy; and how to share one's spirituality is a very personal matter for both patients and health professionals. Consequently, spirituality and religiosity should not be imposed in the clinical setting and spiritual or religious practices should not become a routine part of cancer care. Many oncologists may feel privileged to be involved in the spiritual dimension of healing and caring. Others may believe that spirituality is the domain of chaplaincy and wonder why add spirituality to their work load. Some may ask why would it not suffice for them to acquire broad communication skills and cultural competence to address each patient with sensitivity. In view of our reappraisal of medical humanities and of growing attention being paid to cancer patients' and survivors' quality-of-life, however, we should consider oncologists' education complete once they also learn how to examine and weigh claims based on spiritual, religious and cultural grounds, and how to uncover adaptive and less adaptive coping mechanisms that may require oncologists to refer their patients for proper evaluation and interventions. In the end, however, the ability to provide optimal oncology care is mostly based on knowing how to share, rather than simply to address, the many dimensions of patients' experience of cancer, including spiritual ones. This is only possible if oncology professionals are allowed and encouraged to develop a strong sense of their own intimate path of spirituality, along with scientific

knowledge and technical and communication skills, starting from the years of medical or nursing school and training. Oncology professionals may then be able to build stronger bonds with their patients during a journey that inevitably involves a quest for spiritual meaning, up to the time when the transcendent boundaries between life and death are met.

8. ROLE OF PINEAL GLAND IN SPIRITUALITY DIMENSION

After all, under a clinical-practical perspective, what distinguishes clinical psychoneuroendocrinology from any previous medical discipline is the acknowledgement of the importance of a clinical assessment of the functionality of the pineal gland in all human pathologies, but most of all in those that as of today are still incurable, because we have not understood them completely in their pathogenesis: we are speaking of cancer, autoimmune diseases, neurodegenerative diseases, and psychotic pathologies. Therefore, there is no such thing as a real clinical psychoneuroendocrinology of holistic medicine without a clinical assessment of pineal functionality, since the pineal gland is the one mainly responsible for the integration between endocrine, nervous and immuno-haemato-poietic systems, both in connection with the endogenous state of the organism, and the universal bio-energetic conditions: the light-darkness rhythm and magnetic fields, separation from which causes a state of disease, as proved by chrono-biological medical science. Unless we have a correct pineal functionality, there cannot be chronobiology.

In practice, the clinical assessment of the pineal gland becomes the most significant investigation of psychoneuroendocrinology, both because theoretically the pineal gland is at the basis of psychoneuroendocrinology, in other words the anatomic structure that allows the very existence of psychoneuroendocrinology. And because in practice, no medical specialization deals with the pineal gland. Endocrinology does not deal with it, despite the pineal being one of the seven endocrine glands; neurology doesn't either, despite the crucial role of the pineal in the modulation of all the neurotransmissions and the neurotrophic properties of its indole hormones; psychiatry doesn't either, despite the proved involvement of the pineal in several psychiatric pathologies, such as depression, schizophrenia and autism; or medical oncology, notwithstanding the fact that for over 50 years the anticancer properties of the pineal have been known; or cardiology, in spite of the cardiostrophic and the sympathetic-inhibitor role of the pineal hormone, melatonin; or pediatrics, although the role of the pineal gland has been proven at the beginning of puberty; lastly, geriatrics, despite the fact that the progressive decrease in the pineal endocrinal activity is one of the most precocious and typical sign of ageing.

The first prejudice we need to overcome is the wrong association between the pineal gland and melatonin (MLT), while MLT is simply the most common and researched pineal hormone, not necessarily the most important at a psycho-biological level, together with other indole and peptide

hormones. Anatomically, the pineal gland is located under the splenius of the corpus callosum, representing the union between the white substances of the two brain hemispheres, therefore the nerve communication between the right and left encephalon. It is named after its pine shape, and it has a diameter of about 1 cm. It is a medial exiguous organ, within the encephalon, where everything tends to come in pairs.

The pineal gland is within the encephalon but does not belong to it; rather, it's the bottom part of the neurovegetative sympathetic system, since its innervation is due to the post ganglionic fibre deriving from the upper cervical ganglion of the sympathetic chain. Anatomically, and functionally, the pineal gland represents the real connection between neurovegetative and conscious lives in human beings. The conscious and unconscious, in short, light and darkness. The pineal gland has the structure of an endocrine gland, since it releases directly into the blood the molecules it produces, and also represents the most vascularized organ in the human body. Histologically, it shows two kinds of cells: pinealocytes, originating from the retinal light receptors and with endocrine activity; and glial cells, of macrophagic origin.

The pineal gland produces about twenty hormones, whose knowledge will bring about a complete revolution in medicine, finally creating the grounds for an actual medicine of the spirit, a statement legitimated by the fact that the research carried out on MLT has torn down the fragile theoretical and mechanistic structure of the old medicine. These hormones may be subdivided into four fundamental groups:

- 1) indole hormones: melatonin (MLT), 5-methoxytryptamine (5-MTT), 5-methoxytryptophol (5-MTP), 5-methoxy-indole-acetic (5-MIA);
- 2) peptide hormones: the pineal gland produces at least two specific peptide hormones, arginine-vasotocin (AVT) and epithalamin, both of tripeptide nature;
- 3) carboline hormones: several beta-carbolines are produced, and it is still difficult to say which may be considered hormones or catabolites. The most typical pineal beta-carboline is pinoline;
- 4) hypothalamus neuro-hormones and endogenous opioid peptides.

The pineal gland has receptors both for opioids and cannabinoids, therefore it carries out within itself the harmonic relation between the opioid system and cerebral cannabinergic system, respectively in symbolic and functional relation with unconscious and conscious life.

All the research on the pineal gland refers in fact to the study of the physiology of MLT on which the clinical and investigational research in the pineal field has been developing. We still do not know much about the circadian aspect of the secretion of the four pineal indoles; the four indoles may be secreted more in one of the four essential moments of the photoperiod, that is, 5-MIA at dawn, 5-MTP at midday, 5-MTT in the afternoon and MLT at night: this has been proven only for MLT and MTP, having their peaks respectively at midday and midnight. The main stimulus triggering the

liberation of MLT occurs in the dark that is in the absence of light that in turn inhibits the secretion of MLT. Light information reaches the pineal gland not directly from the retina through the encephalic nerve pathways, but from the mesencephalon to the sympathetic system, that is, to the upper cervical ganglion, and from this it goes back to the pineal through the post-ganglion fibres that use noradrenaline as neurotransmitter. Light inhibits the secretion of noradrenaline from the post-ganglion sympathetic fibre, which is instead liberated during dark, acting on a beta-adrenergic receptor at pinealocyte level. Unlike the other endocrine glands, the pineal is subject to a main stimulating control that is nervous and not endocrine: therefore, the pineal gland should be regarded as a neuro-endocrine organ. Since it is subject to a beta-adrenergic stimulus control, the secretion of MLT will be inhibited by beta-blockers. The pineal cell expresses also alpha-adrenergic receptors with stimulating effect by the alpha-1-agonists, and inhibiting effects by the alpha-2-agonists. Like the other indoles, MLT is produced from tryptophan first by the action of n-acetyl-transferase (NAT), turning serotonin into N-acetyl-serotonin, and then by the action of hydroxyindole o-methyltransferase (HIOMT), turning n-acetyl-serotonin into n-acetyl-5-methoxy-tryptamine (or MLT). The specific enzyme of the synthesis of MLT is HIOMT, but NAT is the limiting enzyme, whose activity is inhibited by lights. If 5-MTT were produced or administered in darkness, when NAT is active, the latter would automatically turn it into MLT.

Magnetic fields are another energetic feature, besides light, influencing the pineal functionality. Due to their receptors, pineal cells are sensitive to endless neuro-active substances. Major stimulants of the release of MLT are cannabinoids agonists. The liberation of MLT is stimulated also by mu- and delta-opioid agonists, by VIP and the heart hormone atrial natriuretic peptide (ANP), while it is inhibited by substance p and high concentrations of suprarenal or gonadal steroids. The role of the serotonergic, dopaminergic e cholinergic neurotransmission systems would be mildly modulatory of the pineal activity. The pineal gland has receptors for the cytokines, therefore performing the integration between neuroendocrine and immune systems. Most of the inflammatory cytokines inhibit the secretion of MLT, in particular IL-6, IL-1, and IL-12. Low SC doses of IL-2 or TNF-alpha seem to have stimulating effects on the secretion of MLT. The latter acts on two kinds of specific membrane receptors called MT1 and MT2. There is also a nuclear receptor for MLT, directly involved in the control of the expression of DNA. Finally, MLT can act directly, without any receptor modulation as antioxidant, that is, as a molecule able to remove free radicals (scavenger action). MLT's ability to control even the expression of DNA explains its endless therapeutic biological effects that have contributed to the creation the myth of MLT as universal panacea for any human pathology, in part true, since the synchronization of the biological systems is in fact a basic condition of any real process of physical, psychic and spiritual healing. The following is a synthesis of the main activities of MLT:

- anti-tumour activity: MLT inhibits neoplastic growth because it is able to carry out any kind of antitumor action, that is: 1) anti-proliferative activity, particularly evident in the event of neoplasia expressing the receptors for MLT, whose activation inhibits malignant cell proliferation; 2) inhibition of the activation of some receptors for the growth factors of tumours, such as the receptor for epidermal growth factor (EGF-R); 3) immunostimulating activity, basically the stimulus of the production of IL-2 and IL-12, respectively of the T lymphocytes and dendritic cells, while antibody production is not influenced much by MLT, therefore the B lymphocytic functionality; 4) anti-angiogenetic action due to the inhibition of the production of VEGF 5) cyto-differentiating action, in particular the stimulus of the expression of the estrogenic receptor in negative-estrogen mammary neoplasia;
- anti-oxidant activity: MLT is one of the most powerful natural anti-oxidant agents, about 30 times that of vitamin e and glutathione;
- thrombopoietic activity: MLT stimulates the production of platelets causing the fragmentation of the megakaryocytes and perhaps interacting with the cytokines involved in the production of platelets;
- neuro-trophic and cardio-trophic action, resulting in the possible use of MLT in the event of heart of brain ischemia;
- anxiolytic effect, slight anti-depressive action and hypnotic activity, with stimulus of the rem phase in sleep compared to benzodiazepines, instead suppressing it;
- anti-cachectic action due to the inhibition of the production of TNF-alpha, one of the main cytokines responsible for the induction of cachectic states.

Our knowledge of the effect of the other pineal indoles is really poor. The 5-MTP may have the ability of increasing concentration and decreasing the effect of alcohol on the state of consciousness. In vitro 5-MTT has proved to have an anti-tumour anti-proliferating activity that is more powerful than actual MLT. The 5-MTT also have a thrombopoietic effect, and as far as immunomodulating effects are concerned, also the 5-MTT may stimulate the anti-tumour immunity through a block of the immunosuppressive action carried out by the macrophage [83].

9. THE STUDY: RESEARCH FOCUS

Being cancer a biological war between a human host and an apparently unconscious tumor mass, it is obvious that the prognosis of the neoplastic diseases may depend on both tumor characteristics and the psychobiological identity of cancer patients. Tumor characteristics regard histology, disease extension, biological grading and eventual genetic mutations of cancer cells. At the other side, the

individual identity of the single cancer patients involves their consciousness status, psychological behaviour, life style, but also and mainly their endocrine, neuroendocrine and immune status in addition to their clinical conditions [83]. Until some years ago, the human diseases were considered to be due to organicistic or psychosomatic reasons. On the contrary, with the progressive advances in the area of Psychoneuroendocrinology (PNEI), it was understood that the psychospiritual status of patients may influence the biological body not only through the nervous system, but also through complex nervous, neuroendocrine and endocrine interactions with the immune cells, which after their activation may interact with the endocrine and nervous systems by releasing immunomodulating proteins, the so-called cytokines, which are also able to exert neuroendocrine effects by realising complex feed-back circuits between neuroendocrine and immune systems [84].

As far as the psychological and spiritual point of view is concerned, must be remarked that until few years ago and yet up to now by most researchers, the spirituality has been simply considered only as a part of the psychological status of humans, and only recently some preliminary clinical investigations have suggested that the spirituality is a different condition from both psychology and religion [85]. As far as the relation between psychology and spirituality is concerned, it is possible to affirm that the Psychology represents the analysis of the emotional life, which has its energetic matrix in the sexuality, whereas the Spirituality regards the reality of the different consciousness states. At the other side, the relation between Religion and Spirituality, according to a definition previously reported in the literature [86], the Spirituality is the research of the ultimate meaning of life, while Religion is only a set of beliefs and ritual practices within a well defined religious institution, then it would simply represents one of the possible ways to realize own self spirituality, even though more widely followed with respect to an individual manner to live and feel the spiritual dimension. Then, the individual spirituality may be realized through the same religion or other mystical experiences, and it is not a simple set of emotions, but it constitutes a status of consciousness. Moreover, in agreement with PNEI discoveries [87], both emotions and consciousness states require a well defined psychoneuroendocrine mediation. Then, from a clinical point of view, the two major problems concern the identification of adequate methods to clinically investigate not only the religious profile of patients, but also their spiritual sensitivity, as well as of possible eventual blood biochemical parameters able to reflect the psychological and spiritual status of patients and its influence on the clinical course of the neoplastic disease. However, most studies carried out up to now have been generally limited to the investigation of the influence of the personal religion rather than the real status of cancer patients. In any case, even though limited to the investigation of the influence of religion on the prognosis of cancer, preliminary clinical results seem to suggest that the religious support may allow an increase in the survival time of advanced cancer patients and to improve their clinical status, even though through still unknown mechanisms

[86, 87]. The recent advances in PNEI knowledgements, by demonstrating that the immune responses in vivo are physiologically under a psychoneuroendocrine modulatory control [88, 89], which represents the biochemical mediation of the spiritual and psychological status of the patients, may allow the hypothesis that the spiritual status may influence the clinical course of the neoplastic disease and the efficacy of the different antitumor therapies by stimulating the immune system and piloting it in an antitumor way through the activation of well-defined psychoneuroendocrine circuits [89]. Moreover, it has to be considered that until about 20 year ago, almost all scientific investigations in the oncological area were limited to the identification of possible carcinogens in the nature, either endogenous molecules, such as estrogens and androgens, or exogenous substances, capable of inducing the malignant transformation. On the contrary, more recent researches have demonstrated the existence of several antitumor plants containing well characterized anticancer molecules, in particular aloe hemodin from Aloe [90], guggulsterone from Myrrh [91] and honokiol from Magnolia [92], as well as more surprisingly the evidence of anticancer endogenous molecules, which would be responsible for the natural immunobiological resistance against cancer onset and growth, in particular some indole hormones released by the pineal gland, namely melatonin (MLT) [93] and 5-methoxytryptamine (5-MTT) [94], and the great group of beta-carbolines [95], which are mainly produced by pineal gland itself. All those natural anticancer agents has no important toxicity. Therefore, the existence of both endogenous and exogenous anticancer agents with a complete lack of biological toxicity but with well known antitumor properties, would justify their employment in the medical Oncology in an attempt to realize a link between the simple palliative and the curative therapies of cancer, since several anticancer natural agents, according to the PNEI knowledgements, may deserve both palliative and antitumor effects on cancer progression at least in terms of survival time. The present study was performed to investigate the influence of the spiritual status of consciousness on the antitumor efficacy of a psychoneuroendocrine regimen with antitumor pineal hormones in association with the most investigated anticancer plants in a group of metastatic solid tumor patients, for whom there is no other standard effective therapy of their tumor, by evaluating the spiritual status through a previously described clinical test to explore the spiritual faith in patients affected by an untreatable disease [96].

9.1 MATERIALS AND METHODS

Sample recruitmet and inclusion criteria

The study included 70 untreatable metastatic solid tumor patients.

Eligibility criteria were, as follows: histologically proven metastatic solid neoplasm, measurable lesions, no availability of standard antitumor therapies because of progression on previous chemotherapies, low performance status (PS), and life expectancy less than 1 year. Patients affected by metastatic breast cancer or prostate carcinoma were excluded from the study, because of the availability for those tumors of well tolerated hormonal therapies also by the standard medical Oncology.

Measures

The faith test for patients affected by an untreatable disease employed in the study was performed by the observation of the clinicians in an attempt to exclude possible unconscious mental manipulations in their answers by the patients, and it consisted of the analysis of five major criteria [17], by assigning 20 points to each single criterion, with a maximum score of 100 points and by defining the presence of a real status of spiritual faith for a minimal score of at least 60 points or more. Therefore the test scores can only be of this type: 20, 40, 60, 80 or 100. The “cut-off” value of 60 was established by the therapists who developed the test, based on a previous published study [18].

The five criteria were, as follows: 1) complete self-consciousness by the patients of the severity of their diagnosis and prognosis in terms of life expectancy: the absence of an adequate knowledge of the severe prognosis would transform the faith in a simple illusion; 2) lack of excessive anxiety: the anxiety would represent the opposite mental condition with respect to a real spiritual faith; 3) lack of an exaggerated attribution of value by the patients to the professional capacities of the single clinicians, being their disease as considered as untreatable on the basis of the standard medical therapies; 4) lack of an excessive analytic tendency by the patients to understand the chemical mechanisms involved in the efficacy of treatments instead of their significance in terms of reactivation of an effective biological natural anticancer resistance; 5) perception of own neoplastic disease not only as a personal problem, despite pain and other intolerable symptoms, but also as an individual manifestation of a general universal suffering involving all humans.

The clinical characteristics of patients are reported in Table 1. Lung cancer, pancreatic adenocarcinoma and colorectal cancer were the neoplasms most frequent in our patients.

Treatment

The PNEI strategy of cancer cure consisted of the oral administration of the two most investigated anticancer pineal hormones, MLT and 5-MTT, in association with a phyto-therapeutic regimen consisting of the administration of extracts of the most investigated antitumor plants, including *Aloe arborescens*, Myrrh and Magnolia. MLT was given at 100 mg/day during the dark period of the day, while 5-MTT was administered at 5 mg in the early afternoon. Magnolia cortex, with a honokiol content of at least 50%, was given at 500 mg twice/day. Finally, Aloe and Myrrh were

given at a dose of 10 ml twice/day of a mixture of 60% Aloe and 40% Myrrh. Patients with brain metastases also received Boswellia at 1000 mg/day in the morning, because of its anti-oedema effect. The clinical response was assessed by the WHO criteria by repeating the radiological examinations at 3-month intervals.

Statistical analyses

Data were statistically analyzed by the chi-square test. The survival curves were calculated by the Kaplan-Meier method and statistically analyzed by the log-rank test.

9.2 RESULTS

The clinical response achieved in our patients is reported in Table 2. A complete response (CR) was obtained in 2/70 (3%) patients, who were affected the former by gastric cancer and the latter by lung adenocarcinoma. A partial response (PR) was achieved in other 9 patients (colon cancer: 2; melanoma: 2; lung cancer:1; pancreatic cancer:1; endometrial adenocarcinoma:1; bladder cancer:1; biliary tract carcinoma: 1). Then, an objective tumor regression was observed in 11/70 (16%) patients. A stable disease (SD) was found in other 41 patients. Therefore, a disease control (CR + PR + SD) was obtained in 52/70 (74%) patients, whereas the remaining 18 patients (26%) had a progressive disease (PD). A faith score of at least 60 points was found in 51/70 (73%) patients. By considering faith score in relation to the other individual variables, no significant differences between males and females was observed in the percent of values of at least 60 points (28/37 (76%) vs 22/33 (67%). On the same way, no difference in the percent of high faith score occurred in relation to the three most frequent neoplasms (lung: 12/18 (67%); colon: 9/13 (69%); pancreas: 9/14 (64%)). Moreover, more surprisingly there was no significant difference in the percent of faith score of at least 60 between patients who followed a specific religion and those who had no religion or no defined religion (22/29 (76%) vs 29/41 (71%). Finally, by considering the clinical response in relation to the faith score, the percent of objective tumor regressions (CR+PR) achieved in patients with faith score of 60 or more was significantly higher with respect to that found in patients with values less than 60(11/51(19%) vs 1/19 (5%), $P<0.05$). On the same way, the percent of DC (CR+PR+SD) achieved in patients with high faith score was significantly higher than that observed in those with low faith score (44/51(86%) vs 8/19 (42%), $P< 0.01$). Table 3 shows the clinical response in relation to the different values of faith score. A progressive increase in the percent of DC occurred concomitantly with the increase in faith score values.

9.3 CONCLUSION

This study, carried out in a considerable number of untreatable metastatic cancer patients, would suggest that a neuroendocrine approach with endogenous anticancer molecules, such as the antitumor pineal hormones, and natural antitumor plants, may counteract cancer growth also in patients, who had been considered as untreatable according to the standard anticancer treatments. Moreover, the study shows that the efficacy of therapy is higher in cancer patients with a true spiritual faith, at least in the untreatable ones, even though it cannot be excluded that the reduced therapeutic efficacy observed in patients with low faith score may be simply due to an interruption or a discontinuation of therapy. In any case, even though we are only at the beginning of the possibility to understand the psychochemical mechanisms responsible for mediating the influence of the spiritual faith on the clinical course of the neoplastic diseases, the recent advances in PNEI knowledgements have demonstrated the possibility to modulate the immune system, including the anticancer immunity, by acting on its psychoneuroendocrine regulation [85, 97]. Then, in agreement with the PNEI discoveries, showing a stimulatory effect of both pleasure and spiritual sensitivity and an inhibitory one of stress and depression on the anticancer immunity, it is probable that the increased efficacy of cancer therapies with natural antitumor agents and the prolonged survival time achieved in patients with evidence of spiritual faith may mainly be due to an improvement in the potency of the immune reaction against cancer dissemination [98-100]. Moreover, the study would show that the presence of a real spiritual faith is relatively independent from the adhesion to a specific well defined religion, then it would represent an individual variable rather than to depend on external behaviours, such as the religious practices, by confirming the observations of previous authors, who had considered religion and spirituality as different human conditions [86, 87]. In more detail, since the anticancer action of the pineal hormones and of most antitumor plants is due to both antiproliferative and immunomodulating effects [101], at present, according to the PNEI discoveries, it is possible at present to identify two major functional psychoneuroendocrine systems involved in the mediation of the influence of emotions and spirituality on the anticancer immunity, consisting of the former brain opioid system-pituitary adrenal gland, which is related to stress, pain, anxiety and depression and which plays an inhibitory effect on the anticancer immunity by stimulating T regulatory (T reg) and inhibiting T helper-1 (TH1) lymphocyte functions [102], and the latter brain cannabinergic-mirror neuron- pineal gland functional axis, which on the contrary is related to both pleasure perception and spiritual sensitivity, and which enhances the anticancer immunity by stimulating TH1 and inhibiting T reg activities [103-105]. In any case, both systems would be essential for the survival of the biological

species, since the opioid system-pituitary-adrenal gland functional axis would play a fundamental role in the adoptive mechanisms to the environmental and social conditions, while at the other side the cannabinergic system-mirror neuron systems-pineal gland axis would be in relation to the both biological and mind evolution , as suggested by the appearance of cannabinoid receptors in a subsequent time with respect to that of the opioid ones [106], as well as by the evidence of the fundamental role of mirror neurons in the processes of imitation, learning, language, memory and selfconsciousness and of the involvement of pineal molecules, such as the beta-carbolines, in mind expansion [107]. If successive studies will confirm the possibility to prolong the survival time and improve the clinical status of metastatic cancer patients, for whom no other standard therapy may be available, by the administration of natural endogenous and exogenous anticancer molecules, the application of the faith score could allow to predict the probability of efficacy of natural treatments themselves, as well as for the commonly used anticancer therapies in relation to the different tumor histotypes and disease extensions.

Limitations

Certainly the identification of an adequate method to evaluate the spirituality sensitivity of the patients represents the most weakness of the research. Future research will have to integrate different perspectives (i.e. multidimensional rating: patients, clinicians, relatives, friends, etc...) with some possible variables in the field of spirituality (spirituality of the physician-raters, their belief and prejudices, degree of knowledge of the patient, duration of the relationship patient-clinician). Moreover, it would also be important to discuss the characteristics of the clinician-raters and some available aspect about their relations with the patients who rated.

Also it must be specified that the whole study was performed by the doctor and the psychologist and the test score was established together to guarantee a minimum of objectivity: all patients were evaluated by the same doctor and by the same psychologist.

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Table 1. Clinical characteristics of 70 untreatable metastatic solid tumor patients

CHARACTERISTICS M/F: Median age Median PS (ECOG)	37 / 33 65 years (range 43 — 92) 1 (0–3)
RELIGIOUS FAITH - Specific religion: - Catholic Christian religion: - Protestant Christian religion: - Oriental Christian religion: - Buddhism: - Islam: - No religion or undefined religion:	29/ 70 (41%) 23 2 1 2 1 41/70 (59%)
TUMOR HISTOTYPE - Lung cancer: - Non-small cell: - Small cell: - Pancreatic adenocarcinoma: - Colorectal cancer: - Gastric adenocarcinoma: - Biliary tract cancer: - Hepatocarcinoma: - Bladder carcinoma: - Gynecologic tumors: - Ovarian cancer: - Endometrial adenocarcinoma: - Melanoma: - Soft tissue sarcoma:	18 15 3 14 13 5 4 3 3 4 3 1 2 4
METASTASIS SITES - Soft tissues: - Bone: - Lung: - Liver: - Liver + lung: - Peritoneum: - Brain: PREVIOUS CHEMOTHERAPY:	18 2 16 18 6 4 6 52/70 (74%)

Table 2. Clinical response (WHO criteria) in 70 untreatable cancer patients in relation to their faith score.

PATIENTS	CLINICAL RESPONSE +						
	n	CR	PR	CR+PR	SD	DC	PD
Overall patients	70	2 (3%)	9	11 (16%)	41	52 (74%)	18 (26%)
Faith score > 60	51	2	8	10 (19%)*	34	44(86%)**	7 (14%)
Faith score < 60	19	0	1	1(5%)	7	8(42%)	11(58%)

+ CR: complete response; PR: partial response; SD: stable disease; DC (CR + PR + SD): disease control; PD: progressive disease

* P< 0.05 vs low faith score; ** P< 0.01 vs low faith score

Table 3. Clinical response (WHO criteria) in 70 untreatable cancer patients in relation to the different Values of faith score.

CLINICAL RESPONSE +							
FAITH SCORE (points)	n	CR	PR	CR+PR	SD	DC	PD
20	5	0	0	0	1	1 (20%)	4 (80%)
40	14	0	2	2(14%)	6	8 (57%)	6 (43%)
60	33	0	3	3(9%)	18	21(64%)	12 (36%)
80	15	1	3	4(27%)	9	13 (87%)	2 (13%)
100	3	1	0	1(33%)	2	3 (100%)	0