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An integrated psycho-oncology approach using real-time ultrasonography to transform inescapable stress into escapable stress and enhance anti-tumor immunity

Abstract

Cancer diagnosis, especially in stage IV, constitutes a classic example of inescapable stress that suppresses anti-tumor immunity and worsens prognosis. Building on the 1982 Visintainer–Seligman experiment demonstrating superior tumor rejection under escapable versus inescapable stress, I propose an integrated psycho-oncology approach that transforms perceived lack of control into objective mastery. In patients with ultrasonographically visible solid tumors, real-time color-Doppler ultrasonography is combined with injection of macrophage-activating agents (*e.g.* sargramostim/GM-CSF or mifamurtide). Activated macrophages produce nitric oxide, inducing measurable peri-tumoral vasodilation visible within 24–96 hours. Patients observe this immune activation directly on a large screen while the operator explains the images, creating a powerful, multisensory biofeedback experience. Pre- and post-treatment videos become a personal "switch" that patients recall during moments of stress, reinforcing the shift from inescapable to escapable stress. The method rests on three decades of research on CSF-1/c-fms signaling and transcranial/soft-tissue ultrasonography. By linking psychological control to a tangible physiologic event, this low-cost, non-invasive strategy simultaneously reduces cancer-related distress and potentiates anti-tumor immunity. Formal prospective trials are warranted to validate its clinical impact.

Keywords: psycho-oncology, real-time ultrasonography, macrophage activation, escapable stress, guided imagery, biofeedback, anti-tumor immunity

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A diagnosis of cancer, particularly stage IV disease, represents a profound and inescapable stressor for the vast majority of patients. Chronic uncontrollable stress is well documented to suppress immune function, impair anti-tumor surveillance, and worsen clinical outcomes through sustained activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. However, classic experimental evidence demonstrates that stress can be rendered controllable and thereby transformed from an immunosuppressive factor into an immunopotentiating ally. In 1982, Visintainer, Volpicelli, and Seligman published a seminal study in *Science* showing that rats implanted with an aggressive Walker 256 sarcoma and subjected to escapable electric shock rejected their tumors at a significantly higher rate (63 %) than those exposed to inescapable shock (27 %) or no shock at all (54 %).[1] Perceived control, rather than the mere absence of stress, activated stronger protective immune mechanisms. This finding laid the foundation for the present approach, which provides cancer patients with a tangible, objective "switch" to regain control over the stress of diagnosis and simultaneously stimulate innate anti-tumor immunity.

The method integrates real-time ultrasonography with targeted macrophage-stimulating immunotherapy in patients with solid tumors that are ultrasonographically visible. A high-quality ultrasound scanner is connected to a large screen visible to both the patient and the operator. Under oncologic supervision, an approved macrophage-activating agent—*e.g.* sargramostim (recombinant human GM-CSF) or mifamurtide—is administered by injection at a dose appropriate to the patient's pathology or used off-label when clinically justified. Both agents in this example are already established in conventional anti-tumor therapy and have a well-established capacity to induce proliferation, chemotaxis, and functional activation of monocytes/macrophages while preferentially driving macrophage polarization toward the cytotoxic M1 phenotype, rather than supporting the immunosuppressive tumor-associated macrophage (TAM) M2-like state.

The biological rationale for choosing these molecules rests on more than three decades of research into CSF-1/c-fms signaling. In 1990, Pierce and colleagues, including the present author, demonstrated in the *Proceedings of the National Academy of Sciences* that transfection of the human c-fms/CSF-1 receptor into IL-3-dependent 32D myeloid progenitor cells conferred CSF-1 responsiveness, resulting in proliferation, chemotaxis, reversible monocytic differentiation, and enhanced phagocytic activity.[2] Subsequent studies confirmed that CSF-1-activated macrophages produce nitric oxide (NO) via inducible NO synthase, leading to local vasodilation and increased blood flow that is readily quantifiable by color-Doppler ultrasonography. Within 24–48 hours after injection (peak effect 24–96 hours), real-time echo-color-Doppler imaging demonstrates a measurable increase in peri-tumoral blood flow, providing the patient with immediate visual evidence of immune activation.

This objective feedback converts the session into an advanced form of guided imagery. The pressure of the probe on the skin, the simultaneous appearance of color-Doppler signals on the screen, and the radiologist's real-time explanation create a multisensory, concrete experience far more powerful than traditional imagery techniques. Pre- and post-treatment images are compared and video-recorded so that the patient can review them independently whenever the stress of

diagnosis recurs. Each review reactivates the perception of control, reinforcing the psychological shift from inescapable to escapable stress and sustaining the immunologic benefit.

The scientific plausibility of the approach is supported by the author's long-standing work in both macrophage biology and ultrasonography. The 1990 PNAS study established that a single growth-factor receptor (c-fms) can couple to multiple intracellular pathways regulating proliferation, differentiation, and migration—precisely the mechanisms exploited here.[2] Parallel expertise in transcranial and soft-tissue ultrasonography further underpins the method. In 2013, Ruggiero and colleagues described a modified transcranial sonography technique that visualizes the meninges, subarachnoid space, and cortical layers of the temporal lobe with sub-millimetric resolution.[3] This technique was subsequently applied to autism spectrum disorders, demonstrating increased extra-axial fluid and cortical dysplasia in affected children.[4] The same methodology was extended to Neuro-COVID-19, where respiratory-synchronous brain movements were quantified and therapeutic ultrasound parameters were optimized.[5] These studies collectively demonstrate the reliability, safety, and versatility of real-time ultrasonography as a biofeedback tool across neurologic and oncologic contexts.[3-7]

Psycho-neuro-immunologic synergy is central to the approach. Guided imagery and biofeedback have been shown in oncology trials to reduce anxiety, improve quality of life, and enhance immune parameters such as natural-killer-cell activity.[9,10] The present method augments these effects by linking psychological control directly to a measurable physiologic event—macrophage-driven vasodilation—thus closing the feedback loop in real time. The 1982 Seligman experiment predicted that perceived control would outperform the absence of stress;[1] the current technique operationalizes that prediction by giving patients visible, repeatable proof of immune engagement.

Implementation requires coordination among oncologist, radiologist, and patient, plus access to a quality ultrasound unit connected to a large monitor. Sessions are typically repeated at intervals aligned with the pharmacokinetics of the chosen macrophage stimulant. Although randomized controlled trials are still needed, preliminary clinical observations indicate consistent reductions in cancer-related distress and objective improvements in peri-tumoral perfusion. The approach does not replace standard oncologic therapies but potentiates them by addressing both the immunologic and psychosocial dimensions of malignancy.

In summary, this integrated psycho-oncology strategy harnesses real-time ultrasonography and macrophage-targeted immunotherapy to convert the diagnosis of cancer from an inescapable threat into a controllable challenge. By providing patients with an objective, repeatable demonstration of their own immune system at work, the method restores a sense of agency that preclinical data and decades of psycho-oncology research suggest can meaningfully enhance anti-tumor immunity. Formal prospective studies—beginning with case series and pilot trials—are warranted to quantify the magnitude of clinical benefit and to refine patient-selection criteria. Such validation would position the approach as a practical, low-cost adjunct within modern integrative oncology (Figure 1 & Appendix A).

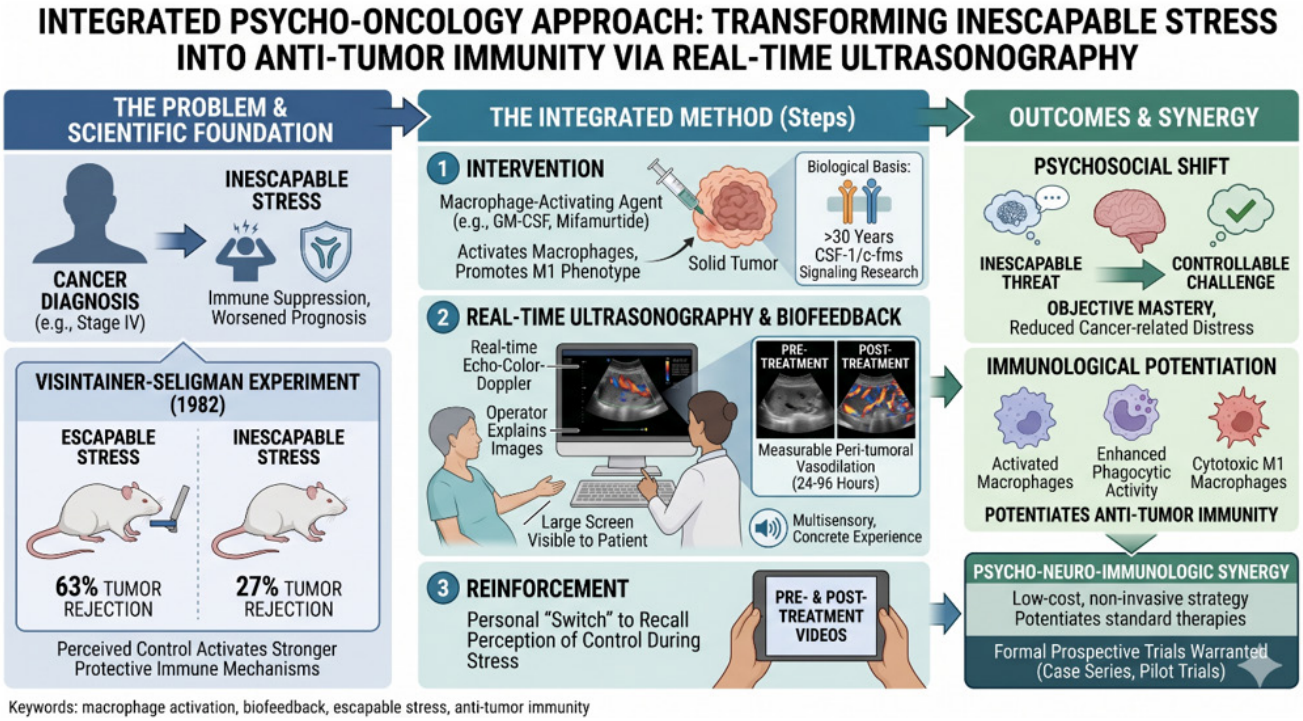

Figure 1 Schematic representation of the integrated psycho-oncology approach aimed at transforming inescapable stress into escapable stress. This infographic illustrates the clinical and conceptual framework designed to overcome the immune suppression resulting from a perceived lack of control, a condition characteristic of advanced-stage cancer diagnoses. The model is based on experimental evidence demonstrating that stress rendered controllable enhances tumor rejection compared to uncontrollable stress. Through the coordinated use of macrophage-activating agents and real-time color-Doppler ultrasonography, the patient directly observes the activation of their own immune system, manifested as measurable peri-tumoral vasodilation within 24–96 hours of the intervention. This multisensory biofeedback experience acts as an objective anchor that reduces distress and promotes psycho-neuro-immunological synergy, providing the patient with a concrete tool to regain agency and actively stimulate anti-tumor defenses.

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Conflicts of interest

The author declares no conflict of interest in regard to the specific topics treated in this study.

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