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Commentary: Resonance-Induced Therapeutic Technique for Skin Cancer Cells

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Introduction

Basal cell carcinoma (BCC) has the highest occurrence among Non-Melanoma Skin Cancers (NMSC), representing a substantial clinical and economic burden, particularly in regions such as the Southern Hemisphere, where annual treatment costs alone are projected to reach USD 950 million[1]. An estimated 90,000 non-melanoma and 7000 melanoma skin cancers are diagnosed each year in New Zealand alone, resulting in almost 500 deaths per year[2, 3]. It poses persistent treatment challenges due to its potential for local invasion and recurrence. Current treatment techniques are either invasive, such as surgery, or they are non-invasive, like gamma radiation, with significant side effects, which include thermal ablation, long recovery periods, and even a breeding ground for second cancer[4].

For the past few decades, focused ultrasound has been investigated and has proved its viability as a non-invasive cancer treatment technique[5, 6]. However, the current modalities of focused ultrasound use high intensities, which accumulate high energy at the target zone in a very short time, causing thermal injury and pain. This becomes an even greater challenge in regions like skin, which has the highest concentration of sensory receptors. Based on patients ‘ feedback, we summarized clinical trial results of focused ultrasound for various dermal applications[7] It was found that in almost all cases, patients reported suffering from medium to severe pain and the formation of thermal injury zones. Hence, there is a need for a safer therapeutic technique for the skin. This commentary

In recent years, some researchers have attempted to analytically determine the dynamic behavior of hepatocellular carcinoma and healthy cells using linear elastic and hyper-elastic models. However, no numerical or experimental work had been done, and the viability of this hypothesis for skin cancers had yet to be explored. In this commentary, we provide insight into our work, which explores the viability of the selective skin cancer treatment hypothesis based on the difference in the dynamic response of healthy and cancer cells to ultrasonic excitation.

Key Findings

In our recently published article[8], we employed viscoelastic models based on fluid-solid Interactions to study the difference between the dynamic behavior of healthy and cancer cells. We demonstrated that the difference in the mechanical and physical properties of healthy skin and cancer cells can be exploited to determine frequencies that will precisely excite cancer cells only. The difference in Stiffness and the size of the cellular structure between healthy skin and cancer cells were used to determine the resonant frequencies. The stiffness of skin cells at various stages of cancer progression, as published in experimental studies, was employed[9]. The healthy skin cell stiffness of 34 kPa was considered, whereas the calculations were performed for healthy cell nucleus radii of 1.5 µm, 2.5 µm, and 3.5 µm. By utilizing the well-known nucleus-to-cytoplasmic ratio (n: c), we predicted changes in physical and mechanical properties at different stages of cancer progression, i.e., a higher (n: c) ratio indicates a higher degree of neoplastic transformation.

In the analytical model, the nucleus was assumed to be a rigid spherical body inside the cytoplasm. The cytoplasm represented the combined viscoelastic properties of all subcellular structures within a cell except the nucleus. It was assumed that the vibration of the nucleus would be resisted by the viscoelastic nature of the cytoplasm, as shown in Fig. 1. The relative displacement between the nucleus and the cytoplasm at various excitation frequencies was studied, and the frequencies with the maximum relative displacement were identified.

The analytical calculations were performed using MATLAB 2024b, and the results revealed a significant difference of 50-100 kHz in the resonant frequency between healthy and cancerous skin cells, as shown in Table 1. This was further verified using a numerical simulation performed in Ansys Mechanical 2024.

In some cases, fundamental resonant frequencies of cancer cells were very close to the nth harmonic of healthy cells. To verify the hypothesis in such conditions, the transient response was also evaluated to determine the difference in excitation amplitude between healthy and cancer cells when both are excited at the resonant frequency of the cancer cells. For a healthy nucleus radius of 3.5 µm in a healthy cell radius of 35 µm, Cancer cells have undergone substantially higher vibration amplitudes, consistent with model predictions, as shown in Fig. 2.

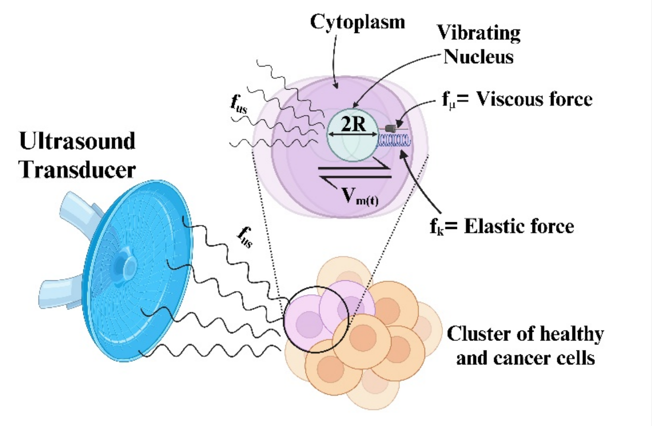

Figure 1. A Spherical rigid body, i.e., the nucleus, is surrounded by viscoelastic cytoplasm (This image was created using Biorender.com).

In the present model, the cell nucleus is mechanically stiffer, embedded within a softer viscoelastic cytoplasm. Under resonant ultrasonic excitation, the nucleus exhibits amplified oscillatory motion relative to the surrounding intracellular matrix. Rather than adopting a static stress-based rupture criterion, failure is defined in terms of relative displacement, reflecting the dynamic nature of intracellular damage mechanisms such as cytoskeletal rupture, organelle–membrane interactions, and loss of intracellular cohesion. Specifically, when the relative vibration amplitude of the nucleus approaches approximately half of the cell radius, the resulting oscillatory deformation is assumed to exceed the structural tolerance of subcellular components, indicating functional cell failure. This displacement-based criterion provides a physically motivated basis for estimating the minimum pulse duration required for resonant excitation to accumulate sufficient dynamic amplitude, consistent with resonance-driven lysis mechanisms proposed in oncotripsy literature. Fig. 2 shows that the relative nuclear displacement reaches approximately 17–18 µm within a 200 µs excitation pulse, corresponding to a length scale comparable to the cellular radius (~17.5 µm for a 35 µm radius cell). At this displacement scale, the nucleus undergoes oscillatory excursions spanning a substantial fraction of the intracellular space, a regime in which irreversible subcellular damage and functional cell failure are expected to occur.

Experimental validation using cell-mimicking hydrogels and ex vivo human skin tissue has been completed and forms part of an active patent application. To protect intellectual property, raw data and images are not disclosed here.

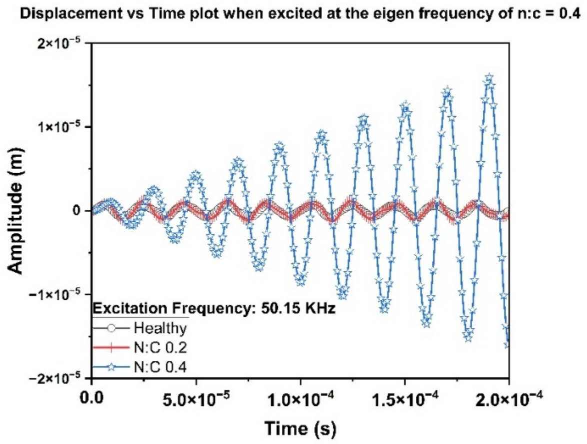

Figure 2. Growth in vibration amplitude when cells are excited at the natural frequencies of n:c = 0.4 using Ansys Transient. (a) at the Eigen frequency of n:c = 0.4, i.e., 50.15 kHz[8].

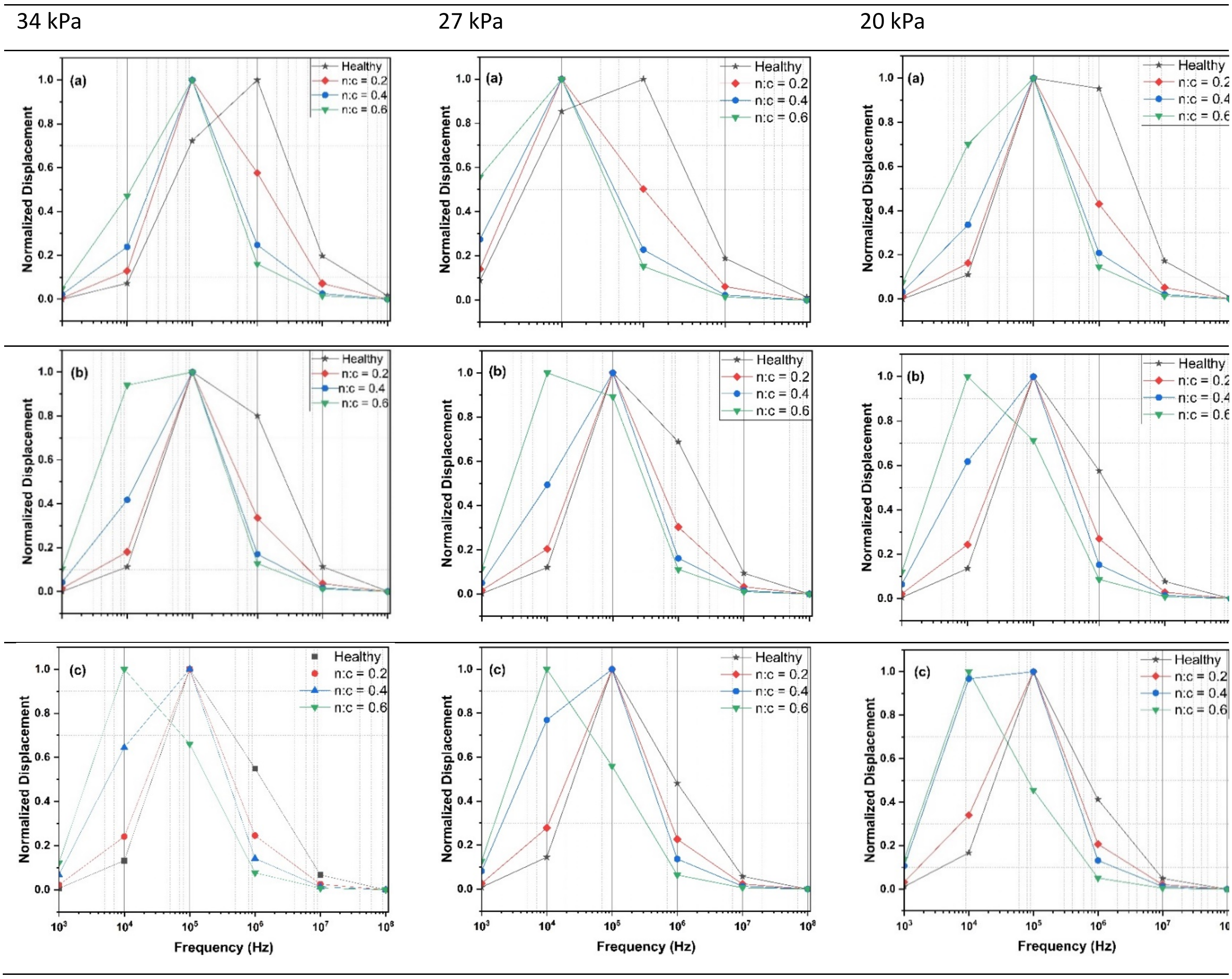

Table 1: Summary of the relative displacements of cellular constituents for stiffness 34, 27, 20 kPa in a healthy state with cancer progression and nucleus of radius (a) R=1.5 µm, (b) R=2.5 µm, and (c)R=3.5 µm[8].

Clinical Implications

Conventional therapies such as surgical excision and chemotherapy come with side effects and, in some cases, may nucleate a second cancer, such as gamma radiation[10]. Moreover, the current non-invasive focused ultrasound techniques are primarily based on thermal ablation, which is unsuitable for regions such as the skin, which has the highest concentration of sensory receptors. The authors reviewed this, where clinical outcomes of focused ultrasound treatment for various dermatological conditions were evaluated, with particular emphasis on patient-reported satisfaction and pain levels[7]. It was found that in almost all clinical studies, patients reported mild to severe pain. Moreover, it took several weeks for the thermal injury zone to heal completely.

By leveraging the concept of mechanical resonance, this method proposes a therapeutic strategy that could disrupt skin cancer cells without affecting surrounding healthy skin. Such a selective mechanism has significant clinical appeal, particularly in dermatological oncology, where it could minimize scarring, preserve cosmetic integrity, and avoid systemic side effects, which are critical.

Building on these findings, our ongoing work (Part of an active patent application) investigates the application of selective targeting using ex vivo human skin tissue samples with histologically confirmed BCC; these preliminary insights further support the clinical promise of our ex vivo findings.

If validated in vivo and translated into clinical practice, this technique may complement or even reduce the need for surgical excision, especially for superficial lesions such as basal cell carcinoma or squamous cell carcinoma. Furthermore, the method's non-chemical and non-thermal nature suggests a potential for fewer complications, faster healing, and enhanced patient compliance. Ultimately, this biomechanically driven modality could pave the way for a new class of personalized, low-risk cancer treatments grounded in the physical properties of diseased tissue.

Limitations and Challenges

Basal cells rest on the basement membrane between the epidermis and dermis, and there is a need to incorporate the effects of the mechanical properties of the basement membrane in the dynamical model to enhance the predictability of desired frequencies.

Although low-frequency ultrasound exhibits greater penetration compared with high-frequency diagnostic ultrasound but attenuation and mechanical damping in skin, subcutaneous fat, and connective tissue limit effective energy transmission to deeper targets. Owing to this, the proposed resonance-based approach is most suitable for superficial and near-surface lesions, such as basal cell carcinoma and early-stage squamous cell carcinoma, where the target depth typically lies within a few millimeters of the skin surface.

Moreover, cancers are highly heterogeneous; hence, it is unlikely to eliminate the whole cancer using a single set of frequencies. Therefore, there is a need to investigate the synergetic effect of selective targeting and immune response. Mechanical stress induced by focused ultrasound can trigger immunogenic cell death, resulting in the increased secretion of damage-associated molecular patterns (DAMPs), including HMGB1, calreticulin, and heat shock proteins. These DAMPs function as danger signals, activating antigen-presenting cells and pro-inflammatory pathways, which in turn lead to dendritic cell activation and subsequent adaptive immune responses[11]. Moreover, studies on ultrasound-mediated cavitation and microbubble techniques demonstrate that mechanical interactions can enhance the release of tumor antigens and DAMPs, thereby increasing immune effector cell infiltration into the tumor microenvironment[12].

Many of these approaches rely on the fabrication and injection of microbubbles to generate mechanical stress, but we aim to use a beat frequency technique (two transducers producing localized low-frequency beating pressure) to generate sufficient mechanical stress to release DAMPs and stimulate dendritic cell activity, without requiring exogenous agents.

The theoretical calculations suggest a very short pulse duration for selective disruption. An investigation into hepatocellular carcinoma revealed that a pulse duration of 70 µs is required to achieve cell lysis[13]. In contrast, we[8] found that a pulse duration of 200 µs is necessary to produce substantial vibration within the cell, leading to cellular disruption. However, a higher pulse duration will be required for real skin due to higher viscoelastic damping and mechanical coupling with surrounding tissues.

In our latest study (part of a patent application), the viability of this technique was evaluated using an ex vivo test on human skin tissue with cancer, yielding an encouraging outcome. However, there is a need for extensive pre-clinical ex vivo trials on skin tissues with cancer, as well as the observation of changes at cellular levels using various analytical techniques, such as fluorescence microscopy, to confirm the viability of this technique.

Conclusion

This work lays the foundation for developing a customized and targeted therapeutic approach for skin cancers. Extensive study is still required in ex vivo and in vivo conditions. With ongoing technological advancements, focused ultrasound-based therapies may emerge as a safe, effective, and targeted alternative to traditional cancer treatments, potentially reducing reliance on surgical procedures and limiting harm to surrounding healthy tissue. The insights gained from this study provide a solid foundation for future research and clinical innovation in therapeutic biomedical ultrasound.

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