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Could Fasting-Induced Metabolic and Immune Reprogramming Unlock Novel Pathways in Oral Cancer Treatment and Mechanisms

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a prevalent cancer with significant treatment-related side effects, necessitating innovative adjunct strategies. Short-term fasting (STF), defined as 24–72 hours of caloric abstention, has emerged as a potential complementary approach to enhance cancer therapy outcomes. STF induces systemic metabolic changes, including reduced glucose, insulin, and IGF-1 levels, inhibiting oncogenic pathways like PI3K/AKT/mTOR. This creates a differential stress resistance (DSR) effect, protecting normal cells while sensitizing cancer cells to chemotherapy and radiotherapy. STF also promotes oxidative stress, autophagic cell death, and immune modulation, including reduced regulatory T cells and enhanced cytotoxic T-cell activity, potentially improving immunotherapy efficacy.

STF has shown promise in preclinical studies for enhancing tumor shrinkage, mitigating chemotherapy-induced toxicity, and reducing radiotherapy side effects like mucositis. While it offers significant benefits, careful patient selection and standardized protocols are essential to ensure safety, particularly for those with metabolic disorders or cachexia. Future research should explore biomarkers, optimized fasting protocols, and combinations with targeted therapies. STF represents a transformative strategy in OSCC treatment by integrating metabolic reprogramming, immune enhancement, and tumor sensitivity to optimize therapeutic outcomes.

KEYWORDS

• Oal squamous cell carcinoma • OSCC • Short-term fasting • Chemotherapy radiotherapy • Immunotherapy • Metabolic reprogramming • Oxidative stress • PI3K/AKT/mTOR • Autophagy • Differential stress resistance • Immune modulation

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INTRODUCTION

Oral cancer, primarily squamous cell carcinoma, remains a significant global health challenge. Its treatment often involves a combination of surgery, chemotherapy, and radiotherapy. While effective, these treatments can cause considerable side effects and impact the quality of life of patients. Recently, short-term fasting (STF) has emerged as a promising intervention to enhance cancer treatment efficacy and mitigate side effects. STF refers to voluntary abstention from caloric intake for a period typically ranging from 24 to 72 hours. This practice induces metabolic and cellular changes that may influence cancer cell susceptibility to treatment while protecting normal tissues. This thought explores the mechanisms through which STF impacts oral cancer pathogenesis and treatment outcomes, supported by emerging evidence and clinical implications.

Pathogenesis of Oral Cancer

Oral cancer develops from epithelial cells in the oral cavity, often as a result of prolonged exposure to carcinogens such as tobacco, alcohol, betel nut, and human papillomavirus (HPV). The progression from normal epithelium to invasive carcinoma is a multistep process involving genetic and epigenetic alterations[1,2]. Uncontrolled proliferation is a hallmark of oral cancer, driven by mutations in oncogenes such as EGFR and MYC, and tumor suppressor genes like TP53 and CDKN2A. These mutations result in dysregulated cell cycle progression and unchecked proliferation[3].

Tumor cells evade programmed cell death through alterations in apoptotic pathways. Overexpression of anti-apoptotic proteins like Bcl-2 and loss of pro-apoptotic factors like Bax are frequently observed. Another characteristic feature is metabolic reprogramming, where cancer cells exhibit the Warburg effect, relying on glycolysis for energy production even in the presence of oxygen. This metabolic shift supports rapid growth and survival under nutrient-deprived conditions[4].

Additionally, tumors create an immunosuppressive microenvironment by recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). They also express immune checkpoint molecules such as PD-L1, which allow them to evade immune surveillance. These mechanisms collectively drive tumor initiation, growth, and resistance to treatment, posing significant challenges in managing oral cancer[5].

Mechanisms of Short-Term Fasting in Cancer Treatment

Short-term fasting exerts its effects through a variety of systemic and cellular mechanisms that are particularly relevant to cancer biology. One of the primary effects of STF is the induction of metabolic stress. During fasting, glucose and insulin levels decrease, depriving cancer cells of their primary energy source. Tumors dependent on glycolysis for energy production are particularly vulnerable under these conditions. Reduced insulin and insulin-like growth factor 1 (IGF-1) signaling under fasting conditions inhibits oncogenic pathways such as PI3K/AKT/mTOR, which are critical for cancer cell proliferation and survival[6].

Another critical mechanism is differential stress resistance (DSR). Normal cells enter a protective state during fasting, characterized by reduced metabolic activity and activation of stress resistance pathways. Cancer cells, however, due to their high metabolic demands and inability to adapt to nutrient scarcity, become more susceptible to treatment-induced damage. Fasting also induces autophagy, a cellular process that clears damaged organelles and proteins, enhancing the resilience of normal cells. In cancer cells, however, excessive autophagy under fasting conditions may lead to autophagic cell death, further sensitizing them to therapy.

Fasting increases oxidative stress in cancer cells by impairing their antioxidant defenses, making them more vulnerable to treatments like chemotherapy and radiotherapy that rely on reactive oxygen species (ROS) to kill tumor cells. Additionally, STF boosts immune surveillance by increasing the activity of cytotoxic T cells and natural killer (NK) cells. It also reduces the immunosuppressive tumor microenvironment by decreasing the levels of Tregs and MDSCs, potentially enhancing the efficacy of immunotherapy[6].

Treatment Outcomes of Short-Term Fasting

Short-term fasting enhances the efficacy of chemotherapy, a cornerstone of oral cancer treatment. Chemotherapy often targets rapidly dividing cells, and STF enhances this efficacy by inducing metabolic and oxidative stress in cancer cells. By downregulating pathways like PI3K/AKT/mTOR, fasting may overcome resistance mechanisms in oral cancer cells. Preclinical studies have shown that fasting combined with chemotherapy leads to greater tumor shrinkage compared to chemotherapy alone.

Radiotherapy relies on ROS generation to induce DNA damage and kill tumor cells. STF enhances radiotherapy outcomes by increasing ROS levels and impairing the antioxidant capacity of cancer cells, amplifying the effects of radiation-induced oxidative damage. Normal cells in a fasting state are less prone to radiation-induced toxicity, reducing side effects such as mucositis and xerostomia.

STF has profound effects on the immune system that can enhance the efficacy of immunotherapy. Fasting reduces tumor expression of immune checkpoint molecules like PD-L1, improving the response to checkpoint inhibitors. Increased infiltration of cytotoxic T cells and NK cells into the tumor microenvironment under fasting conditions can boost anti-tumor immunity[7].

One of the most significant benefits of STF is its potential to reduce the side effects of cancer treatment. Fasting reduces gastrointestinal and hematological toxicity by protecting normal cells[8]. It may also mitigate radiation-induced damage to oral tissues, improving patient quality of life. By reducing treatment-related side effects, STF may improve patient adherence to therapy, leading to better overall outcomes.

Considerations and Challenges

While STF offers promising benefits, its implementation in clinical practice requires careful consideration. Not all patients are suitable candidates for fasting. Those with malnutrition, cachexia, diabetes, or other metabolic disorders may face risks. Individualized assessment is crucial to ensure safety and efficacy. STF protocols must be tailored to align with the timing and type of cancer treatments. For example, fasting periods should be synchronized with chemotherapy or radiotherapy sessions to maximize benefits.

Prolonged fasting or inappropriate fasting practices can lead to adverse effects such as electrolyte imbalances, hypoglycemia, and excessive weight loss. While preclinical studies and early-phase clinical trials are promising, large-scale randomized controlled trials are necessary to establish standardized fasting protocols and confirm efficacy.

FUTURE DIRECTIONS

Research into STF as an adjunct to oral cancer treatment is still in its early stages. Future studies should focus on elucidating

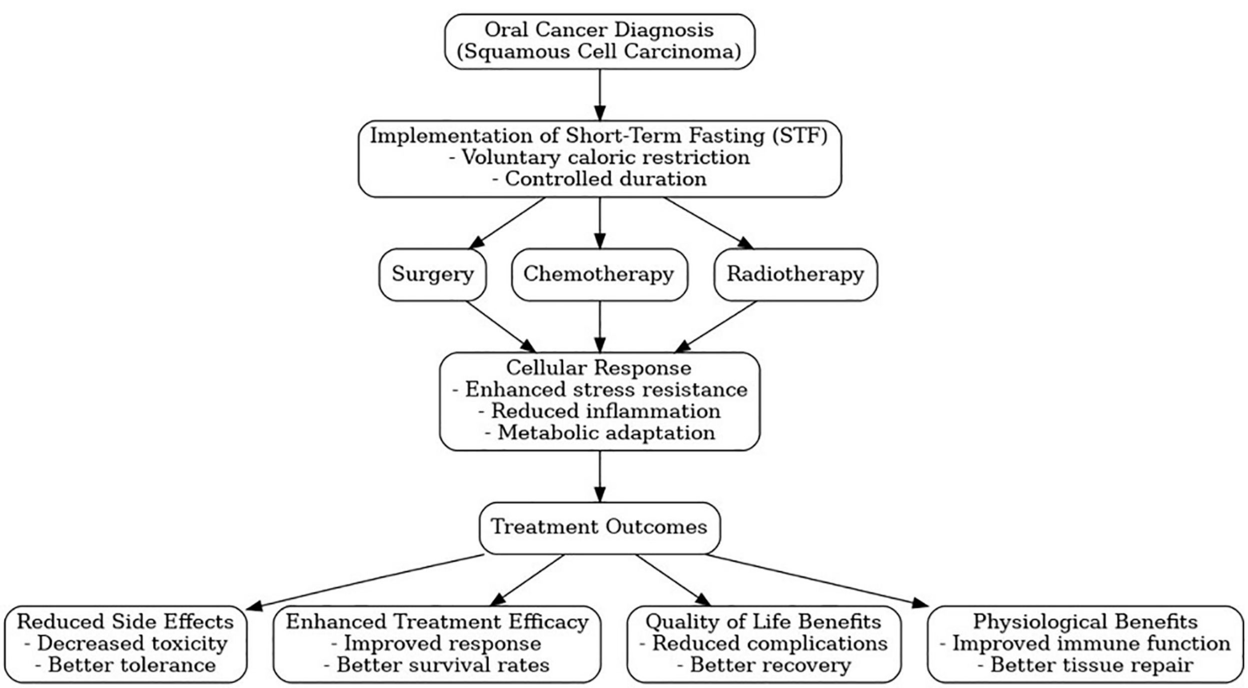

Figure 1: Short term fasting in OSCC treatment outcomes

the molecular pathways through which fasting impacts cancer cells and the tumor microenvironment. Identifying biomarkers to predict which patients are most likely to benefit from STF will also be critical. Exploring combinations of STF with novel therapies, such as targeted therapies and CAR-T cell therapy, could maximize treatment efficacy. Developing patient-friendly fasting protocols that are safe, effective, and easy to adhere to will enhance clinical adoption.

CONCLUSION

Short-term fasting holds significant potential as a complementary strategy for oral cancer treatment. By leveraging metabolic reprogramming, immune modulation, and differential stress resistance, STF can enhance the efficacy of chemotherapy, radiotherapy, and immunotherapy while reducing treatment-related side effects. However, its clinical application requires careful patient selection, standardized protocols, and further research to fully understand its benefits and limitations. With continued investigation, STF could become a valuable addition to the multidisciplinary approach to oral cancer management.

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