The Role of Fasting in Cancer Treatment: Mechanisms, Protocols, Clinical Evidence, and Risks

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***Abstract*—Fasting and fasting-mimicking interventions are emerging as promising adjuncts in oncology, offering metabolic strategies to enhance conventional therapies while potentially reducing treatment-related toxicity. Cancer cells, characterized by high nutrient demands and metabolic inflexibility, appear more vulnerable to nutrient deprivation than normal cells, a phenomenon termed differential stress resistance. Various protocols including intermittent fasting, prolonged water fasting, fasting-mimicking diets, time restricted eating, caloric restriction, and ketogenic diets modulate key pathways such as insulin/IGF-1 signaling , mTOR, AMPK, and autophagy. Preclinical studies consistently demonstrate slowed tumor growth, improved immune responses, and heightened sensitivity to chemotherapy and immunotherapy. Early clinical trials suggest reductions in chemotherapy-induced fatigue, gastrointestinal discomfort, and hematological toxicities, with fasting-mimicking diets showing particular feasibility and safety. However, risks such as malnutrition, cachexia, and electrolyte imbalances limit applicability in vulnerable populations. Current evidence supports short-term, structured fasting protocols under medical supervision, while long-term outcomes and survival benefits remain under investigation. Future research must standardize protocols, refine patient selection, and evaluate integration with immunotherapy to determine the clinical utility of fasting-based strategies in personalized cancer care.**

***Index Terms*—cancer treatment, Insulin, Fasting Type, Clinical Evidence**

I. INTRODUCTION

Research on dietary changes in cancer treatment has become a hot topic in recent years. Scientists are looking closely at how metabolism is involved in tumor development, growth, and resistance to treatments. Among these dietary strategies, fasting includes a range of methods like intermittent fasting (IF), time restricted eating (TRE), prolonged water fasting, caloric restriction (CR), fasting-mimicking diets (FMDs), and metabolic diets such as ketogenic diets. These approaches are gaining interest in both labs and clinics. While traditional cancer treatments like chemotherapy, radiotherapy, targeted therapy, and immunotherapy focus on attacking cancer cells or adjusting immune responses, dietary methods might shift metabolic states to improve the effectiveness of treatments and lessen side effects. This growing area has drawn interest from scientists, clinicians, and patients because of the idea that limiting nutrients can make cancer cells more vulnerable while helping normal cells.

The motivation for looking into fasting for cancer arises from the clear differences in how healthy and cancer cells use energy. Cancer cells often have high energy demands and rely on specific nutrients and signals to multiply quickly. Fasting and fasting-mimicking methods lower the levels of glucose, insulin, insulin-like growth factor 1 (IGF-1), and other signals that promote growth. This may make cancer cells more sensitive to stress from treatments while protecting normal cells through mechanisms known as "differential stress resistance." Studies in cell and animal models have shown that fasting can change key pathways like mTOR, AMPK, and autophagy. These pathways are vital for nutrient sensing, cell survival, and managing metabolism. This understanding has led to early-stage clinical trials that explore how fasting could work alongside chemotherapy or immune therapies.

In clinical studies, fasting-related methods come in many forms, durations, and intensities. Intermittent fasting usually involves set times for reduced or no food intake. This can range from daily periods of eating (time-restricted eating) to fasting every other day. Prolonged fasting, which can last 48 hours or more, is often conducted under medical supervision due to higher metabolic stress and potential risks.

Fasting mimicking diets provide a controlled, low-calorie, plant-based meal plan designed to imitate fasting's metabolic effects while allowing some nutrient intake. Ketogenic diets, though not the same as fasting, aim to shift the body to use ketones instead of glucose, which could be relevant for tumors with abnormal glucose metabolism.

In recent years, more clinical trials, reviews, and expert opinions have aimed to clarify how feasible and potentially beneficial fasting is in cancer treatment. Initial studies suggest that fasting might lessen some side effects of chemotherapy, like fatigue, nausea, and blood-related issues, for certain patients, although the evidence is still in its early stages. Small pilot studies have also looked into metabolic and immune system markers linked to fasting, with mixed results. Importantly, while some patients report feeling better and more tolerant of treatment, this is not enough to make fasting a standard recommendation in cancer care. The diversity of cancer types, treatment methods, and individual dietary needs requires careful assessment and tailored approaches.

Combining fasting with cancer treatment is a complex matter. Possible benefits need to be compared to risks, particularly for people with unintentional weight loss, cachexia, or poor nutritional status conditions common among cancer patients. Malnutrition can lead to worse treatment responses and overall outcomes. Therefore, unsupervised or strict fasting could be harmful. Safe and effective clinical practices must involve guidance from teams of professionals, including oncologists, registered dietitians, and support specialists, to ensure metabolic interventions fit patients' medical situations, treatment plans, and nutritional needs.

- Mechanism of Action

1. Background and Rationale The idea of using dietary interventions in oncology stems from the metabolic differences between normal and cancer cells. Cancer cells rely heavily on glucose and growth signals (e.g., IGF-1, insulin) for proliferation, while fasting reduces these pathways, potentially creating a therapeutic window. Early mechanistic studies in animal models demonstrated that fasting enhances autophagy, stress resistance, and immune modulation, laying the foundation for clinical exploration.
2. Preclinical Evidence Intermittent fasting (IF) and prolonged fasting in mice reduced tumor growth and improved chemotherapy sensitivity. Mechanisms include: ↓ IGF-1 and insulin signaling ↑ Autophagy and DNA repair in normal cells ↑ Immune infiltration (CD8+ T cells) into tumors These findings established the concept of Differential Stress Resistance (DSR), where normal cells adapt to nutrient scarcity but cancer cells remain vulnerable.
3. Clinical Studies and Trials • Intermittent Fasting (IF): Small pilot trials show reduced chemotherapy toxicity (fatigue, GI symptoms, hematological side effects). Biomarker modulation: ↓ insulin, ↓ IGF-1, improved erythrocyte counts. Survival benefits remain inconclusive due to small sample sizes.
4. Prolonged Water Fasting: Limited human evidence; case reports suggest improved tolerance but risks of malnutrition and electrolyte imbalance are high. Most guidelines restrict prolonged fasting to supervised clinical trials.
5. Fasting-Mimicking Diet (FMD): Strongest evidence among fasting protocols. Phase II/III trials show reduced chemotherapy toxicity, improved immune responses, and better tumor depletion. High adherence rates compared to water fasting.
6. Time-Restricted Eating (TRE): Observational studies link nightly fasting >13 hours with lower recurrence risk in breast cancer. Improves metabolic markers and quality of life.
7. Ketogenic Diet: Shares metabolic overlap with fasting (ketosis). Evidence for anti-tumor effects is mixed; adherence challenges and side effects limit widespread use.
8. Consensus and Controversies Consensus: Fasting can reduce chemotherapy toxicity and improve patient-reported outcomes. FMD and TRE are the most feasible and safest protocols. Mechanistic rationale is strong, especially regarding IGF-1 reduction and immune modulation.
9. Future Directions Larger, standardized RCTs are needed to confirm survival outcomes. Integration of fasting with immunotherapy and targeted therapies is a promising frontier. Personalized approaches considering nutritional status, cancer type, and treatment modality will be essential. Biomarker-driven patient selection (IGF-1,

ketone levels, immune profiles) may optimize efficacy.

II. KEY TAKEAWAYS

1. Prolonged or unsupervised fasting, especially water fasting beyond 72 hours, is associated with significant risks malnutrition, electrolyte imbalances, and worse outcomes in at-risk patients mandating expert oversight.
2. Fasting-mimicking diets (FMD) offer a safer, more feasible approach for most cancer patients, with high adherence and a growing evidence base for integration with standard therapies.
3. Current guidelines do not endorse fasting as routine oncology practice outside clinical research; nutrition screening, patient education, and multidisciplinary collaboration are essential for any fasting-related interventions.
4. Future trials must refine fasting regimens, identify best-suited patient subsets, clarify impacts on survival, and establish standardized monitoring protocols to safely harness the anti-cancer potential of fasting.

As research proceeds, an individualized, evidence-based approach blending caloric/fasting interventions with state-of-the-art oncology care may soon become part of comprehensive cancer therapy for selected patient groups. Until then, participation in controlled trials, expert guidance, and robust patient monitoring are the cornerstones of safely translating fasting from the laboratory bench to the clinical bedside.

Overview of Fasting Protocols and Their Biological Mechanisms in Cancer

Classification of Fasting Interventions Fasting in oncology encompasses a spectrum of protocols that vary by duration, caloric intake, macronutrient composition, and timing relative to treatment. Major protocols include:

- Intermittent Fasting (IF): Regular cycles of voluntary abst Prolonged Water Fasting: Complete abstinence from calories, generally defined as fasting for three days or more, with only water permitted.
- Fasting-Mimicking Diet (FMD): Plant-based, very low calorie, low-protein dietary regimens (often 3–5 days) engineered to replicate the metabolic effects of fasting while providing some nutrients.
- Time-Restricted Eating (TRE): Restricts food intake to a specific window each day (often 6–10 hours), without necessarily reducing total daily caloric intake.
- Caloric Restriction (CR): Chronic or periodic reduction in total energy intake (often 20–50%) without inducing malnutrition.
- Ketogenic Diet: High fat, modest protein, and very low carbohydrate intake to induce sustained nutritional ketosis, often used as a standalone therapy or in combination with other protocols. Elaboration of this table will occur within each protocol-specific section, drawing attention to the relevant mechanisms and clinical outcomes.

III. INTERMITTENT FASTING (IF) IN CANCER CHEMOTHERAPY

Mechanistic Rationale

Intermittent fasting (IF) exerts multiple biological effects that intersect with known cancer pathways

- Downregulation of Insulin/IGF-1: Fasting periods lead to reductions in circulating insulin and insulin-like growth factor 1 (IGF-1), both implicated in tumorigenesis.
- Activation of Autophagy: Intracellular nutrient sensing triggers heightened autophagic flux, promoting cellular recycling and removal of damaged organelles, with tumor-suppressive implications.
- Differential Stress Resistance (DSR): A central tenet is that nutrient deprivation drives normal cells into a protected, repair-focused state, whereas cancer cells typically hyperproliferative and metabolically inflexible fail to adapt, increasing their vulnerability to chemotherapeutic insults23.Shift to Ketone-based Metabolism: Fasting conditions force a switch from glycolysis to fatty acid/ketone body metabolism, starving glycolytic tumor cells while normal cells adapt.

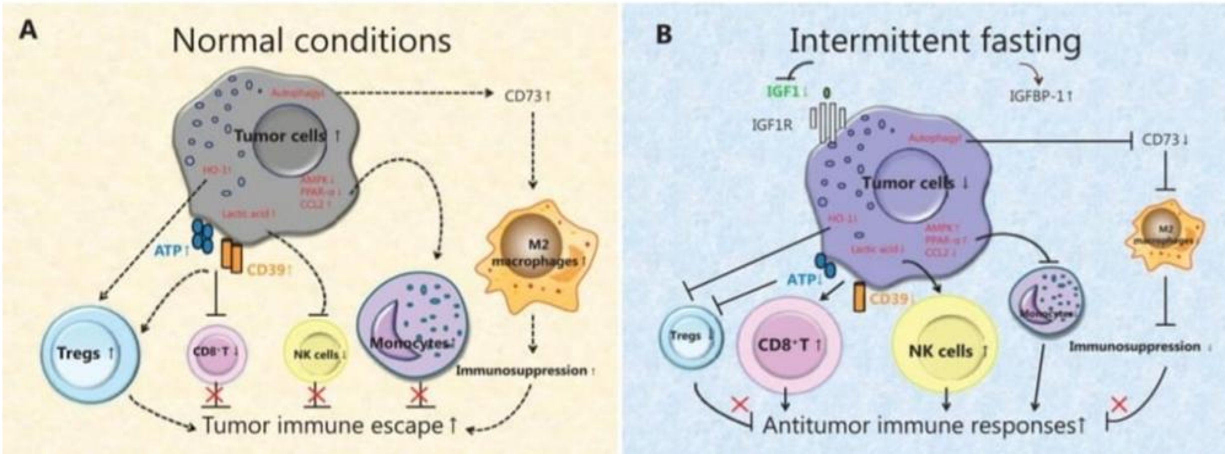

Fig No 01 Preclinical and Clinical Evidence

Preclinical and Clinical Evidence

Preclinical Studies: Mouse models demonstrate that IF can slow tumor growth, enhance survival, and sensitize tumors to chemotherapy. Mechanistically, these effects are linked to decreased growth factor signaling and altered tumor microenvironments, including immune cell infiltration enhancements

Clinical Trials and Meta-Analyses: Recent systematic reviews and meta-analyses summarize several randomized and observational studies evaluating IF protocols (typically 24–72 hours of fasting) in patients undergoing chemotherapy

- Reduction in Treatment Toxicity: Multiple small clinical trials and meta-analyses indicate that IF can significantly reduce side effects of chemotherapy most notably fatigue, gastrointestinal discomfort, and hematological toxicities (e.g., neutropenia, anemia).
- Quality of Life Improvements: Reports of improved well-being and decreased fatigue are frequent among patients practicing IF alongside chemotherapy
- Biomarker Modulation: Fasting is consistently associated with reductions in plasma insulin andIGF-1 and improvements in erythrocyte counts; changes in leukocytes and anthropometric measures appear less consistent

Fasting Type	Mechanism of Action	
Intermittent Fasting	↓ Insulin/IGF-1, ↑ Autophagy, ↓ Inflammation, DSR, metabolic switch	↓ Tumor growth, ↓ Chemotherapy toxicity, ↑ Quality of life
Prolonged Water Fasting	↑ Stress resistance, ↑ Autophagy, immune modulation	↑ Immune activation, ↓ Tumor progression, ↑ Chemosensitivity
Fasting-Mimicking Diet	Mimics fasting effects, lowers glucose/IGF-1, ↑ Immune response	↑ Chemotherapy efficacy, ↓ Side effects, ↑ Antitumor immunity
Time-Restricted Eating	Aligns with circadian rhythm, improves metabolism	Improved metabolic markers, potential ↓ Tumor growth
Caloric Restriction	Sustained energy restriction, hormonal/metabolic changes	↓ Tumor progression, ↑ Treatment responsiveness, mixed sustainability
Ketogenic Diet	↓ Glucose, ↑ Ketone bodies, metabolic reprogramming	Modifies cancer metabolism, variable anti-tumor effects

Summary Table and Considerations

Fasting Type	Mechanism	Clinical Observations
Intermittent Fasting	↓ IGF-1/Insulin; ↑ Autophagy	↓ Chemo toxicity, ↑ Well-being/QoL, Biomarker mod.

Although IF is regarded as safe and feasible for selected, well-nourished cancer patients, heterogeneity in protocols and study populations, as well as differences in cancer type and concurrent therapies, limit generalizability. Adherence rates may vary and patient selection is critical. Importantly, IF must be undertaken under expert supervision to mitigate the risk of malnutrition particularly in frail, elderly, or already underweight patients.

Prolonged Water Fasting and Tumor Progression
Rationale and Preclinical Evidence Prolonged water fasting, generally defined as abstention from all caloric intake (except noncaloric fluids) for 3–7 days, is hypothesized to exert more pronounced metabolic stress on both host and tumor cells, with vital effects including:

- Profound Drop in Insulin/IGF-1 and Glucose: Leading to deep metabolic changes unachievable by shorter fasts.

- Enhanced Autophagy: Prolonged fasts further drive macroautophagy and chaperone-mediated autophagy, stretch tissue tolerance, and fully switch the body into fat-derived energy utilization

Human Evidence, Case Reports, and Cautions

- Pilot Clinical Trials: Early studies using 48–72 hour pre-chemotherapy fasting found decreased chemotherapy side effects and improved DSR markers, but no direct evidence of increased remission or survival.

- Case Series and Anecdotal Reports: Instances of 7-day water fasts in clinical settings, coupled with conventional therapy, sometimes resulted in better tolerance, smaller tumors, and improved well being. However, these are insufficient for clinical recommendations.

- Risks of Prolonged Water Fasting: Significant concerns include malnutrition, dehydration, electrolyte imbalances, and refeeding syndrome. Cancer patients, especially those exhibiting weight loss or cachexia, are at high risk of harm if such protocols are attempted unsupervised

IV. FASTING-MIMICKING DIETS (FMD): SAFETY AND EFFICACY

Concept and Mechanism

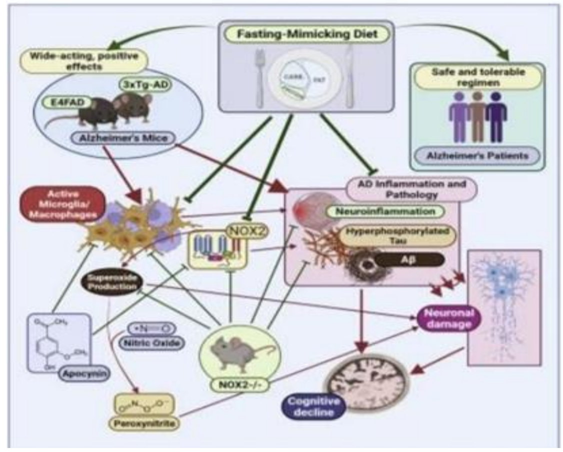

Fig No 2 Fasting-Mimicking Diets (FMD): Safety and Efficacy

The Fasting-Mimicking Diet (FMD) is a plant-based, low-protein, low-calorie regimen (approximately 300 800 kcal/day, mainly from complex carbohydrates and fats, for 3–5 days) designed to trigger physiological fasting-like responses e.g., reduction of insulin, glucose, and IGF-1 without total nutrient deprivation. FMD aims to combine the metabolic benefits of fasting with improved safety and practicality, particularly for cancer patients.

Recent Clinical Trials and Observed Benefits
Phase II and III Trials (e.g., DIRECT, NCT03340935):

- Feasibility and Safety:
  Cyclic 5-day FMD regimens, coordinated with standard chemotherapy or immunotherapy, proved highly feasible and safe. Overall compliance was over 90% in large multicenter studies, though adherence dropped with increasing cycles, often due to patient preference rather than toxicity.
- Reductions in Chemotherapy Toxicity:
  Randomized controlled trials in breast cancer showed significant reductions in grade III vomiting and neutropenia, as well as improvements in immune parameters, with no major increases in adverse events.
- Metabolic Improvements:
  FMD cycles consistently decrease blood glucose, insulin, and IGF-1 levels, while promoting

nutritional ketosis. These changes occur across tumor types and independently of other clinical variables.

- Biological Evidence of Antitumor Effects: Integrated analyses reveal that FMD cycles reduce myeloid-derived suppressor cells and regulatory T cells, while enhancing the infiltration of cytotoxic CD8+ T cells in the tumor. These immune shifts are associated with better clinical outcomes and are similar to those observed in animal models.
- Tumor Response: Imaging and pathological assessments show more frequent complete or partial responses and deeper tumor cell depletion in FMD arms compared to controls in neoadjuvant chemotherapy settings.

Immunotherapy Synergy: Emerging data suggest that FMD augments the efficacy of checkpoint inhibitor immunotherapies by remodeling the tumor microenvironment, reducing cardiotoxicity, and mitigating immune-related adverse events (e.g., colitis)

Limitations and Unresolved Questions

Although FMD demonstrates robust metabolic and immunological effects, the absolute magnitude of improvement in clinical endpoints (e.g., overall survival, progression-free survival) awaits confirmation in more extensive and longer-term studies. Discontinuation rates rise with cycle number due to acceptability issues for subsets of patients

Table of Key Outcomes:

Fasting Type	Mechanism	Outcomes
Fasting-Mimicking Diet	↓ Glucose/IGF-1; ↓ Treg/MDSC; ↑ CD8+ T	↓ Chemo toxicity, ↑ Immunity, ↑ Tumor response

Time-Restricted Eating (TRE) in Oncology Physiological and Metabolic Effects TRE protocols restrict food intake to a daily window (commonly 8–10 hours), aligning nutrient cycles with circadian rhythms without explicit caloric restriction. Key mechanisms include:

- Circadian Entrainment: Synchronization of feeding with the body's biological clock may optimize metabolic health and reduce cancer-promoting signals.
- Glucose and Insulin Modulation: TRE protocols consistently reduce fasting glucose and insulin levels, improving insulin sensitivity and reducing inflammatory markers—some of which are relevant to cancer risk and progression.
- Activation of Autophagy: Even overnight fasting (13–16 hours) may trigger autophagy pathways associated with cell maintenance and repair

Clinical Research Findings

- Cancer Risk Factor Modification: Observational and interventional studies demonstrate that nightly fasting periods >13 hours improve metabolic parameters and are associated with lower cancer recurrence risk, particularly in breast cancer.
- Feasibility and Adherence: Adherence to TRE is high (75–98% in various studies), and patient reported outcomes often show improved quality of life and reduced fatigue

Quality of Life: In trials involving breast and endometrial cancer patients, TRE interventions alleviated cancer-related fatigue and, in some cases, improved mood, physical functioning, and glycemic control.

Safety and Limitations

TRE is considered the most sustainable and least invasive fasting protocol. The main risk is that those with already inadequate caloric intake or at risk of malnutrition may further compromise their nutritional status if the eating window is too short or protein intake is insufficient

Ketogenic Diet Versus Fasting Protocols

Mechanistic Comparison

Both ketogenic diets and fasting share the endpoint of ketosis, producing ketone bodies as alternative fuels. However, differences exist:

- Ketogenic Diet: Sustained high fat, moderate protein, and very low carbohydrate intake. Induces stable ketosis over weeks to months. Proposed mechanisms include inhibition of glycolysis dependent tumors, reduction of insulin and IGF-1 signaling, and anti-inflammatory effects.

- Fasting Protocols: Achieve ketosis acutely via energy deprivation, also promote autophagy and marked hormonal changes not always matched by ketogenic diets.

Evidence Synthesis

Meta-Analyses and RCTs:

- Studies suggest that ketogenic diets can reduce insulin and glucose, promote weight loss, and improve fatigue and quality-of-life metrics in cancer patients, but the direct anti-tumor effects in human trials remain less consistent compared to fasting or FMD
- Preclinical work indicates that ketogenic diets may sensitize tumors to chemotherapy and immunotherapy, but there is limited high-level evidence for superiority over combined fasting-based strategies. Some evidence suggests caloric restriction's tumor-protective effects may not be entirely mimicked by ketogenic diets, especially where lipid availability and use are critical.

Clinical Limitations:

- Adherence to strict ketogenic protocols is challenging for many patients, especially during therapy. Some patients experience adverse events, including gastrointestinal symptoms and micronutrient deficiencies, which must be considered in risk assessment

Caloric Restriction and Cancer Progression

Mechanisms and Animal Data

Chronic caloric restriction (typically 20–40% reduced intake) is one of the most robust non-pharmacological interventions to delay tumor growth in laboratory animals. Mechanisms include:

- Suppression of Growth Factors/Hormones: Persistent reduction in IGF-1, insulin, and leptin, attenuating cancer-promoting pathways.
- Downregulation of Oncogenic Signaling: Reduced activation of mTOR, PI3K/AKT, and other pro proliferative pathways.
- Anti-inflammatory and Epigenetic Effects: Induction of metabolic and genetic adaptations countering oxidative stress and inflammation.

Human Evidence and Feasibility

Sustained caloric restriction is difficult to implement in humans, especially in cancer patients at risk for or actively experiencing weight loss. Trials show that only marked caloric and protein restriction reduces IGF-1 in humans; isocaloric restriction alone is insufficient. Patient groups with stable weight and good reserves may tolerate moderate CR efforts, but routine use in individuals with advanced cancer, weight loss, or nutritional risk is contraindicated due to exacerbation of malnutrition and cachexia

Mechanisms of Fasting-

Induced Stress Resistance The conceptual pillar underpinning the use of fasting in oncology is differential stress resistance (DSR) and sensitization (DSS).

- Normal Cells:

Enter a quiescent state, activate maintenance genes, repair DNA, and increase resistance to oxidative and genotoxic stress via suppression of proliferation and mTOR signaling.

- Cancer Cells:

Often have mutations disabling stress response pathways and remain in a vulnerable proliferative state, making them selectively sensitive to chemotherapy, radiation, and immune attack during fasting states.

Fasting Combined with Immunotherapy

Rationale and Preclinical Evidence

Preclinical models demonstrate that fasting or FMD (especially combined with chemotherapy or PD-1/PD L1 blockade) enhances anti-tumor immunity by:

- Enhancing T Cell Priming and Infiltration: Fasting decreases regulatory T cells and myeloid derived suppressor cells, increases antigen-presenting CD16+ dendritic cells, and boosts tumor infiltrating cytotoxic lymphocytes.
- Protection Against Immune-Related Adverse Events (irAEs): FMD cycles reduce immune mediated tissue damage, including colitis and cardiac toxicity, in preclinical and early clinical settings.

Ongoing Human Studies

Trials such as NCT06671613 are evaluating the effect of combining FMD with immune checkpoint inhibitors in advanced lung cancer, with a focus on toxicity reduction, response rates, and quality of life.

- Meta-Analyses and Systematic Reviews Recent meta-analyses consolidate findings across cancer types and fasting protocols:
  - Insulin/IGF-1/Glucose Reduction: Fasting reliably lowers these pathways, crucial in metabolic cancer promotion.
  - Fatigue and Well-Being: Systematic reviews consistently show reductions in fatigue and improvements in subjective quality of life.
  - Chemotherapy-Related Toxicity: Meta-analyses suggest a reduction in grade III/IV toxicities with fasting interventions, especially FMD and short-term IF, with neutral or beneficial effects on other side effects.
  - Glycemic Control: Lower fasting glucose, insulin, and improved glycemic excursion parameters observed broadly across studies.

- Biomarker Changes During Fasting Several reproducible changes have emerged as fasting signatures in cancer studies:

✓ ↓ Circulating IGF-1 and Insulin: Key anti-tumor pathways suppressed with almost all fasting protocols; however, significant IGF-1 reduction in humans often requires both calorie and protein restriction

✓ ↑ Ketone Bodies: Enhanced with FMD, ketogenic diets, and longer IF; provides alternative fuel for normal cells, potentially starves glycolytic cancer cells105. • ↓ Inflammatory Markers (e.g., hs-CRP, IL-6): Fasting and FMD interventions consistently decrease markers of systemic inflammation, linked to tumor promotion

✓ Immune Cell Subsets: Reductions in Treg and myeloid-derived suppressor cells, with increases in activated cytotoxic T lymphocytes and NK cells, are common post-FMD or after longer fasting episodes.

Risks and Contraindications of Fasting During Cancer Treatment Main Risks

Despite potential benefits, fasting in cancer presents significant hazards for certain populations:

❖ Malnutrition and Sarcopenia: Especially in patients with advanced disease, GI cancers, or preexisting weight loss/cachexia. Prolonged or inappropriate fasting can worsen nutritional deficits, leading to immune compromise, poor wound healing, delayed recovery, and even increased mortality.

❖ Electrolyte Imbalances and Refeeding Syndrome: Particularly with water-only fasts or in patients with depleted stores.

❖ Worsening Chemotherapy Tolerance: For those with borderline nutritional reserves, fasting can exacerbate toxicity and delay treatment.

❖ Contraindicated Populations: Pregnant women, those with active eating disorders, BMI < 18.5, severe hepatic dysfunction, uncontrolled diabetes, or recent significant weight loss should not fast during treatment without strict medical supervision

V. PROFESSIONAL GUIDELINES

Major guidelines (e.g., ESPEN, ASCO, MD Anderson, and others) recommend against unsupervised caloric restriction or fasting in patients with or at risk for malnutrition, and do not endorse fasting as a standard adjunct to active cancer therapy outside clinical trials .

Prudent approaches must ensure:

- Screening for nutritional risk before starting fasting protocols.
- Ongoing monitoring for signs of malnutrition or adverse effects.
- Medical and nutritional supervision, especially if trials or longer protocols are attempted.

Patient Adherence and Feasibility

❖ Adherence Rates: Higher with FMD and TRE due to less severe restrictions and structured protocols; many patients complete 3+ cycles in trials when given adequate support.

❖ Barriers to Adherence:

Hunger, fatigue, taste fatigue, and emotional challenges are main obstacles. Social and medical support can improve feasibility but some patients discontinue due to lack of acceptability over repeated cycles.

Patient-Reported Outcomes: Many reports feeling that fasting gives them control, reduces side effects, and improves QOL under proper supervision

Expert Guidelines and Opinions Expert groups advocate for continued, careful research in the fasting-oncology interface, highlighting several key points:

- Personalization Is Critical: Fasting should not be "one-size-fits-all." Individual patient factors disease status, nutritional reserve, comorbidities, personal preference determine suitability.
- Integration With Oncology Teams: Supervision, education, and ongoing monitoring by medical and nutritional professionals are non-negotiable.
- Standardization Needed: Large, well-controlled studies using standardized protocols and uniform outcome measures are urgently needed to define optimal fasting regimens, patient selection criteria, and long-term benefits and risks.
- Most Promise in Protocolized, Short-Term Approaches: Current evidence supports structured FMD as adjunct for selected patients, particularly with breast, ovarian, and prostate cancers, and time-restricted feeding for prevention and survivorship

Summary Table: Fasting Types, Mechanisms, and Observed Outcomes

Fasting Type		
Intermittent Fasting	↓ Insulin/IGF-1; ↑ Autophagy; DSR	↓ Chemo toxicity, ↑ Fatigue relief, ↑ Quality of life, biomarker modulation
Prolonged Water Fasting	Marked metabolic/immune stress, ↑ Autophagy	Enhanced chemo sensitivity, immune activation; risk of malnutrition
Fasting Mimicking Diet	Mimics fasting biochemistry, ↑ immune effectors	↓ Chemo toxicity, ↑ Tumor response, ↑ CD8+ T cells, improved tolerance
Time-Restricted Eating	Circadian/timing-dependent metabolic effects	Improved metabolic parameters, possible ↓ tumor progression, high adherence
Caloric Restriction	Sustained energy restriction, hormones/signal paths	↓ Tumor growth, anti-inflammatory, limited by feasibility in humans

Advantages of Fasting in Cancer Treatment

1. Reduced Chemotherapy Toxicity
 o Lower fatigue, nausea, vomiting, and hematological side effects (e.g., neutropenia, anemia).
2. Differential Stress Resistance (DSR)
 o Normal cells enter a protective state, while cancer cells remain vulnerable to treatment.
3. Immune Modulation
 o Increased CD8+ T-cell infiltration, reduced immunosuppressive cells (Tregs, MDSCs).
4. Metabolic Benefits
 o ↓ Insulin, ↓ IGF-1, improved glucose metabolism, enhanced autophagy
5. Improved Patient Quality of Life
 o Reports of better tolerance to treatment and reduced fatigue.
6. Feasibility of Fasting-Mimicking Diets (FMD)
 o Safer than water fasting, high adherence rates, and strong evidence for reducing chemo toxicity.
7. Potential Synergy with Immunotherapy
 o Remodeling of tumor microenvironment may enhance checkpoint inhibitor efficacy.

Disadvantages / Risks

a) Malnutrition & Cachexia
 o Cancer patients often have weight loss; fasting can worsen nutritional status.
b) Electrolyte Imbalances & Refeeding Syndrome
 o Especially with prolonged water fasting (>72 hours).
c) Protocol Heterogeneity
 o Different fasting durations and intensities make results hard to compare.
d) Limited Survival Evidence
 o No large-scale RCTs proving overall survival benefit yet
e) . Patient Selection Challenges
 o Benefits mainly in well-nourished patients; frail or underweight patients at risk.
f) Adherence Issues
 o Long-term fasting or ketogenic diets are difficult to sustain.
g) Contraindications
 o Unsafe for pregnant women, uncontrolled diabetics, or those with severe liver disease.

VI. CONCLUSION

Fasting and fasting-mimicking interventions represent a rapidly evolving area in oncology, bridging metabolic science with clinical practice. Evidence from preclinical models and early clinical trials consistently highlights their potential to reduce treatment toxicity, enhance immune responses, and sensitize tumors to conventional therapies. Among the various approaches, structured and short-term protocols such as fasting-mimicking diets and time-restricted eating appear most feasible and safest, offering metabolic benefits without severe nutritional compromise.

At the same time, risks such as malnutrition, cachexia, and electrolyte imbalance underscore the need for careful patient selection and strict medical supervision. Current data do not yet justify fasting as a universal adjunct to cancer therapy; rather, it should be considered a personalized strategy within well-defined clinical contexts.Future research must focus on standardizing protocols, clarifying long-term survival outcomes, and exploring synergies with immunotherapy and targeted treatments. Ultimately, fasting-based interventions hold promise as part of integrative, patient-centered cancer care, but their adoption must remain evidence-driven, cautious, and individualized.

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