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Time-Restricted Eating as an Adjunct to Radiotherapy and Androgen Deprivation Therapy in Prostate Cancer

Clinical Evidence Brief
Current state of evidence — preclinical, clinical, and investigational
Prepared March 2026

Proposed mechanisms

The biological rationale for combining dietary restriction with radiotherapy centers on the **differential stress response**.[1] Under conditions of nutrient deprivation, normal cells activate conserved protective pathways — reducing metabolic activity, upregulating stress resistance, and entering a quiescent state. Cancer cells, whose oncogenic mutations constitutively activate RAS, AKT, and mTOR signaling, are largely unable to make this shift; they remain metabolically active and, as a consequence, more vulnerable to radiation-induced damage. Concurrently, normal tissue is relatively protected — a divergence that forms the basis for combining fasting with radiotherapy.

The interaction between dietary restriction and androgen deprivation therapy (ADT) works through different mechanisms that depend on the class of ADT used, as described below. Separately, dietary restriction may also help counteract the metabolic side effects of ADT itself.

Time-restricted eating (TRE) — typically a 16:8 fasting-to-eating window — is among the more clinically feasible implementations of dietary restriction during active treatment, avoiding the weight loss and nutritional risk associated with sustained caloric restriction.[2] Transitioning from typical Western eating patterns to a sustained 16:8 window requires deliberate on-ramping; the author has written separately on a structured approach to this transition.[3]

TRE and radiotherapy

A 2020 systematic review in *Advances in Nutrition* (Icard et al.) evaluated 26 studies — 17 preclinical, 9 clinical — on the interaction between dietary restriction and radiotherapy across tumor types.[4] Short-term pre-irradiation fasting increased tumor radiosensitivity across multiple preclinical models. Concurrently, normal cells demonstrated relative radioprotection under fasting conditions, consistent with the differential stress response hypothesis.

Of specific relevance to pelvic field irradiation: a 2015 study in *PNAS* (Tinkum et al.) demonstrated that 24-hour fasting protected small intestinal epithelial stem cells from lethal DNA damage in mice, reducing gastrointestinal toxicity without diminishing antitumor effect.[5] The DNA-damaging agent in that study was etoposide, not ionizing radiation, but both act primarily through double-strand breaks — the mechanism central to the differential stress response.

A 2017 review in *BMC Medicine* (O'Flanagan et al.) concluded that intermittent fasting enhances cytotoxic treatment efficacy — both chemotherapy and RT — through the differential stress mechanism, and identified intermittent fasting as a more feasible alternative to chronic caloric restriction for patients in active treatment.[2-1]

Limitation: The strongest mechanistic data in this area uses 24–48-hour fasting windows. The 16:8 TRE window shares the proposed mechanism but has a substantially thinner direct evidence base.

Window alignment during RT (author inference): The differential stress response hypothesis requires that cells be in a fasted — and therefore differentially stressed — state at the time of irradiation. This has a practical implication for scheduling: the fasting window should encompass each treatment fraction, with the eating window opening after the day's session rather than before it. Patients established on 16:8 TRE should shift their window in the days prior to commencing RT so that the fast-breaking meal follows their scheduled treatment time. Note: this scheduling recommendation is a logical inference from the differential stress mechanism[1-1] and has not been tested directly in clinical studies.

TRE and androgen deprivation therapy — prostate-specific evidence

Androgen receptor antagonists

ADT administered via androgen receptor (AR) antagonists — including enzalutamide, apalutamide, and darolutamide — acts directly at the receptor level, competing with androgens for AR binding and blocking downstream signaling.

In August 2025, Pili et al. (University at Buffalo, Jacobs School of Medicine) published evidence that intermittent fasting enhances the efficacy of AR antagonist therapy in prostate cancer models.[6] Using alternate-day fasting across multiple murine prostate cancer lines, the investigators found that fasting reduced AR expression and downstream signaling within tumor tissue. The proposed mechanism is nutrient deprivation-driven suppression of global protein synthesis, reducing available AR and rendering tumors more sensitive to enzalutamide. The effect was replicated across multiple model lines. The same group is currently conducting a pilot feasibility study (NCT06172283) examining 16:8 TRE specifically in prostate cancer patients receiving ADT — notably, not limited to AR antagonists, suggesting the investigators see potential benefit across ADT classes.

GnRH agonists and antagonists — castration-level testosterone suppression

The majority of ADT courses in the post-prostatectomy setting use GnRH agonists (e.g., leuprolide, goserelin) or GnRH antagonists (e.g., degarelix, relugolix), which suppress testosterone production at the hypothalamic-pituitary axis rather than acting at the androgen receptor. The Pili et al. mechanistic findings — reduced AR expression potentiating direct receptor blockade — do not directly translate to this class. No published preclinical or clinical evidence currently demonstrates that TRE enhances the cancer-control effect of castration-level testosterone suppression specifically.

Evidence does exist, however, for dietary restriction as a way to counteract the metabolic side effects of testosterone suppression, which apply regardless of the mechanism by which castration is achieved. A

2022 pilot study in *Prostate Cancer and Prostatic Diseases* (Fay-Watt et al.) tested a periodic fasting mimicking diet (four consecutive low-calorie days monthly) in prostate cancer patients with current or prior ADT exposure.[7] Patients demonstrated statistically significant reductions in weight (−3.79 kg, p=0.0002), abdominal circumference (−4.57 cm, p=0.0003), and blood pressure (systolic −9.52 mmHg, p=0.007; diastolic −4.48 mmHg, p=0.03). Fasting glucose and lipid parameters were also measured; results for those markers are reported in the full text but were not available in abstract form for independent verification. Cedars-Sinai (Freedland et al.) is currently conducting a Phase II RCT (NCT05832086) examining a 5-day/month fasting mimicking diet with intensified ADT in metastatic hormone-sensitive prostate cancer, with cancer control and metabolic toxicity as co-endpoints.

References

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