Supplementary Materials

Table S1. Effect of time of day on radiation treatments for non-breast cancers. Any overall conclusions about a preferred radiation time are indicated in bold in the findings. See Table 3 for studies on the effect of time of day on radiation treatments for breast cancer. SRS = stereotactic radiosurgery, PBT = proton beam therapy.

Time of Radiotherapy for Other Cancers				
Cancer Site and Study	**Type**	**Timing**	**Radiation**	**Endpoints and Findings**
Head and neck Oral mucositis in morning vs. evening irradiated patients: a randomized prospective study	Prospective randomized (n = 212)	8:00–11:00 vs. 15:00–18:00	Daily 2-Gy fractions 5×/week > 60 Gy with Cobalt- 60	Oral mucositis: Trend toward increased grade 3 toxicity of mucositis in the evening group (not significant, p =0.08) (Early preference)
Head and neck Comparison of toxicity associated with early morning versus late afternoon radiotherapy in patients with head-and-neck cancer: a prospective randomized trial of the National Cancer Institute of Canada Clinical Trials Group (HN3)	Prospective randomized (n = 205)	8:00–10:00 vs. 16:00–18:00	66–70 Gy in 3–35 fractions	Grade 3 mucositis: Grade 3 mucositis higher in evening group (62% vs. 53%) for all patients (not significant, p = 0.17) Grade 3 mucositis significantly higher in evening group for smokers receiving >66 Gy (p = 0.024) Less weight loss noted in the morning group (Early preference)
Head and neck The impact of delivery daytime and seasonality of radiotherapy for head and neck cancer on toxicity burden	Retrospective (n = 617)	Seasonality: Median day of radiotherapy falling after March equinox ("light") vs. after September equinox ("dark") Time of day: median radiotherapy time before vs. after 12:00	≥60 Gy, definitive or adjuvant, ±chemotherapy	Acute toxicity, late toxicity: Higher acute toxicity with radiotherapy delivered in the "dark" half of the year (p = 0.0127) Time of day was not associated with toxicities analyzed; trend toward higher acute toxicity in the afternoon (p = 0.0387, did not meet authors' criteria) (Early preference)
Cervical Circadian variation in radiation-induced intestinal mucositis in patients with cervical carcinoma	Prospective randomized (n = 229)	8:00–10:00 vs. 18:00–20:00	50 Gy in 25 fractions using Cobalt- 60	Multiple toxicities: Increased grade 3+ diarrhea in the morning group (p < 0.01) Other toxicities increased in morning group (not significant) (Late preference)
Cervical Research on radiotherapy at different times of the day for inoperable cervical cancer	Prospective randomized (n = 67)	9:00–11:00 vs. 21:00–23:00	50 Gy in 25 fractions external beam and 36–42 Gy in 6–7 fractions brachytherapy	GI toxicity, hematological toxicity, apoptotic potential: Increased grade 3+ GI toxicity in the morning group (75% vs. 58% diarrhea, 13% vs. 6% high-grade toxicity) Worse hematologic toxicity in afternoon group Levels of PER1, PER2, CLOCK correlated with apoptosis (Ambivalent preference)

Prostate Differences in toxicity and outcome associated with circadian variations between patients undergoing daytime and evening radiotherapy for prostate adenocarcinoma	Retrospective (n = 409)	Before vs. after 17:00	High-dose radiotherapy (median dose 78 Gy without elective pelvis treatment)	Toxicity, failure-free survival: Increased grade 2+ late GI toxicity for patients older than 70 in the afternoon group ($p < 0.001$) Poorer 5-year failure-free survival for afternoon group ($p = 0.05$) (Early preference)
Prostate Chronoradiation Therapy for Prostate Cancer: Morning Proton Beam Therapy Ameliorates Worsening Lower Urinary Tract Symptoms	Prospective cohort (n = 168)	08:30–10:30 vs. 10:31–14:30 vs. 14:31–16:30	PBT 78 Gy in 39 fractions or 70 Gy in 28 fractions	Urinary tract symptoms, quality of life: Morning PBT ameliorated quality of life and lower urinary tract symptoms from localized prostate cancer compared to near-noon or late afternoon groups under multiple linear regression ($p < 0.05$) (Early preference)
Rectal Does chronomodulated radiotherapy improve pathological response in locally advanced rectal cancer?	Retrospective (n = 155)	Before vs. after 12:00	25–50.4 Gy neo-adjuvantly	Tumor response, staging: Increased complete pathologic response ($p = 0.035$) and nodal downstaging in afternoon group (Late preference)
Brain (high-grade glioma) Clinical effects of morning and afternoon radiotherapy on high-grade gliomas	Retrospective (n = 109)	Before vs. after 12:00	60 Gy conventional fractionation, hypo fractionation for frail patients	Local control, distant CNS control, progression-free survival, overall survival: No difference in overall survival ($p = 0.76$) or progression free survival ($p = 0.30$) Univariate analysis showed improved overall survival if treated in the morning ($p = 0.05$) (Early preference)
Brain metastases Could time of whole brain radiotherapy delivery impact overall survival in patients with multiple brain metastases?	Retrospective (n = 755)	8:00–11:00 vs. 11:00–14:00 vs. 14:00–17:00	WBRT, 30 Gy in 10 fractions (93%) and 20 Gy in 5 fractions	Overall survival: No difference in overall survival for total group Univariate analysis showed survival difference for elderly women with ≥70% or ≥80% WBRT received in a single time window ($p = 0.02$) (Preference for consistent timing)
Brain metastases from lung (NSCLC) Impact of time of day on outcomes after stereotactic radiosurgery for non-small cell lung cancer brain metastases	Retrospective (n = 437)	9:12–11:40 vs. 11:41–18:02 (determined with receiver operating characteristics analysis)	SRS 18–20 Gy	Overall survival, local control: Univariate analysis showed decreased overall survival ($p = 0.016$) and local control ($p = 0.012$) in the later time group Effect not reproduced on multivariate analysis with confounders (Early preference)
Brain metastases from lung (NSCLC) The effect of treatment time on outcome in non-small cell lung	Retrospective (n = 172)	Before vs. after 12:00	SRS treatment to 1 lesion, median dose 21 Gy	Overall survival, local control: No difference in overall survival or local control seen; linac-based SRS

cancer brain metastases treated with stereotactic radiosurgery				can be effectively delivered in the morning or afternoon (No preference)
Brain metastases from lung (NSCLC) Gamma knife radiosurgery for brain metastasis of non-small cell lung cancer: is there a difference in outcome between morning and afternoon treatment?	Retrospective (n = 97)	10:00–12:30 vs. 12:30–15:00	SRS with GammaKnife, mean dose 18.6 Gy	Survival, CNS vs. systemic cause of death: Improved local control and overall survival for morning group (p = 0.014, 0.025) (Early preference)
Bone metastases Effects of circadian rhythms and treatment times on the response of radiotherapy for painful bone metastases	Retrospective (n = 194)	8:00–11:00 vs. 11:00–14:00 vs. 14:00–17:00	8 Gy, 20 Gy, 30 Gy	Pain palliation: Improved pain control (clinical response) if treated 11:00 to 14:00 group, detected for females only (p = 0.02) (Midday preference)
Nasopharyngeal, Esophageal, Lung, Cervical The clinical effect study on malignant tumors with chronoradiotherapy	Prospective randomized (n = 121)	9:00 vs. 21:00	Radiotherapy regimens varied by disease	Toxicity, short-term tumor shrinkage: Evening radiation gave significantly lower toxicity for all cancers Evening radiation significantly increased tumor shrinkage for esophageal, cervical; similar nonsignificant trend for lung, nasopharyngeal (Late preference)

Table S2. Zeitgeber-driven chronoradiotherapy. Hypothetical individualized regimen that synergizes light, clock-acting medication, and diet to improve breast cancer response to radiation treatment and patient outcome.

Hypothetical Cancer with Optimal Radiation Therapeutic Index at 12:00h; Patient's Fractionated Radiation Treatments Scheduled for 09:00h Daily		
Light–Dark	**Chronopharmaceutical**	**Dietary**
30 min blue light before bedtime (until DLMO shifts to 03:00h)	20 mg tasimelteon every morning (until DLMO shifts to 3:00h)	Timed feeding such that midday falls at 15:00h
Avoid bright light in the morning	Fix 24-h period with KL001	Intermittent fasting between meals
Confirm patient's circadian phase with biomarkers (e.g., clock gene expression) at 09:00h each session just before radiation		