Circadian Timing In Cancer Treatment: A Mini Review On Cancer Chronotherapy

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Circadian timing in cancer treatment: a mini review on cancer chronotherapy

Jiawei Yin

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Department of Environmental Health Sciences
Primary Advisor: Yong Zhu, PhD
Second Advisor: Kai Chen, PhD
Abstract

Organisms exhibit rhythmic fluctuations in their behavior and metabolism every 24 hours, a phenomenon controlled by their circadian clock to anticipate changes in the environment. In the past forty years, substantial progress has been made in our knowledge of the molecular mechanisms underlying the circadian clock and cancer. In this context, researchers have explored the possibility of leveraging the circadian clock to improve cancer treatment. Several randomized controlled trials have investigated the effects of circadian chemotherapy and radiotherapy on drug toxicity and efficacy, with many studies reporting clinically significant outcomes, although some findings remain inconsistent. This mini review aims to summarize the current state of research on chronotherapy in oncology by examining the results of randomized controlled trials investigating chemotherapy and radiotherapy. The goal is to provide an overview of the potential of chronotherapy in the tumor field and to highlight areas where further investigation is needed.

Keywords: circadian clock, cancer treatment, chronotherapy, chemotherapy, radiotherapy, chronomodulation, environmental health science
Acknowledgements

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I also want to express my gratitude to the department's faculty and staff for their support and guidance. Their contributions have been instrumental in shaping my academic journey and research experience.

Last but not least, I want to express my gratitude to my family and friends for their unwavering love, support, and encouragement during my educational path. I am so appreciative of their presence in my life and their love and support, which have served as a constant source of inspiration.
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Introduction: Circadian Rhythms

The autonomous cellular timing system known as the circadian clock generates a rhythm of 24 hours in almost all forms of life, including microorganisms, plants, and humans (Lee, 2021). This biological clock is regulated by external cues known as "zeitgebers," refers to the information about the surrounding environment (Amiama-Roig et al., 2022). For example, the most important external zeitgeber is light, other signals include temperature, available resources, etc. Together, these signals alter the levels of gene expression and the formation of metabolites or hormones that modulate physiological processes to control biological functions like sleep and awake, energy metabolism, immunological response, hormonal activity, and cell growth (Lee, 2021).

Endogenous circadian rhythms exhibit variations from the exact 24-hour period and are distinctive to different facets of mammalian physiology (Lévi et al., 2010). In humans, these rhythms are synchronized with environmental cues such as light, darkness, social activities, and eating times. During the day, locomotor activity is high, but low at night. Body temperature reaches its peak in the morning and evening. The adrenal gland's cortisol secretion elevates rapidly from its lowest point around 2:00 AM to its maximum level around 8:00 AM (Lévi et al., 2010). On the other hand, the pineal gland's melatonin secretion mostly occurs at night and peaks around 2:00 AM (Lévi et al., 2010).

The core mechanism of the circadian clock in mammals is a transcription-translation feedback loop (TTFL) that produces a time-delay (Sancar & Van Gelder, 2021). There are three components of the circadian system: the input pathway, the central pacemaker, and the output
pathway (Kiss & Ghosh, 2016). Through the body's input pathways, external light signals are transmitted to the central pacemaker, which then transmits neurological and hormonal signals to the peripheral circadian systems distributed throughout the body. (Kiss & Ghosh, 2016). The suprachiasmatic nucleus (SCN) of the anterior hypothalamus, consisting of multiple single-cell circadian oscillators, is responsible for producing or regulating this circadian physiology as the hypothalamus's central pacemaker (Kiss & Ghosh, 2016). In most humans, these oscillators are synchronized, producing a coordinated circadian output. This mechanism regulates several physiological functions, such as the timing of cell division and the rates of metabolism in particular tissues (Sancar & Van Gelder, 2021).

The molecular clock in mammals is composed of a specific set of genes that work together in complex regulatory circuits to generate circadian rhythms at the cellular level (Lévi et al., 2010). These genes not only control transcriptional activation and repression, but also post-transcriptional modifications that ensure precise timing of the oscillations. Of these genes, BMAL1 is one of the most important, and it forms a transcriptional activator complex with CLOCK or NPAS2 that binds to the E-box element in the promoters of PER and CRY genes (Ballesta et al., 2017). The PER and CRY proteins undergo further post-transcriptional modifications before entering the nucleus as a complex, where they act as repressors to shut down the translation and maintain the feedback loop (Ballesta et al., 2017). This intricate process ensures that the circadian rhythm lasts for approximately 24 hours, and once the repressor complex is removed, and a fresh activation cycle would start. The importance of the molecular clock is underscored by the fact that it controls an essential proportion of protein-coding genes in both humans and mice, highlighting its critical role in regulating diverse
physiological processes (Sancar & Van Gelder, 2021).

Recent scientific investigations have revealed that the circadian clock plays a crucial role in controlling various physiological processes and is indispensable for maintaining optimal health. At a sophisticated level encompassing multiple cells and molecular interactions, circadian rhythms are intricately woven into evolutionary mechanisms that dictate temporal adjustments to ensure physiological balance and stability by establishing regular cycles of activity and rest. Deviations from these natural rhythms can lead to a number of chronic conditions, including metabolic disorders and cancers (Zhou et al., 2021). Conversely, counteracting circadian disruption and restoring normal clock function could represent novel therapeutic targets with significant potential for improving human health.

Circadian Rhythm and Cancer: Exploring the relationship

Expression patterns of clock genes exhibit variability in tumor vs. normal cells

The circadian system, which regulates our sleep-wake cycles, metabolism, and cell division, has been found to have a strong correlation with cancer development (Shilts et al., 2018). Studies have revealed that when the circadian system is disrupted, it can lead to an increased risk of cancer. This is due to the fact that the circadian clock governs a number of cellular functions, including DNA repair, cell proliferation, and apoptosis (Amiama-Roig et al., 2022). In humans, chronic shift work and night work have been identified as significant risk factors for the development of breast, colon, and lung cancers. (Shilts et al., 2018) These occupations can disrupt the body's natural sleep-wake and circadian rhythms, leading to a
disturbance in the circadian clock. The disruption of the circadian system can then promote the proliferation of cancer cells and suppress the body's natural mechanisms for fighting cancer.

Cancer remains the second leading cause of death worldwide (Nagai & Kim, 2017). In cancer patients, cell growth and division increase, while the activity of circadian clock genes decreases significantly. The abnormal functioning of the circadian clock genes creates a mismatch between the body clock and cell cycle, leading to the damage of DNA, and then the onset and progression of cancer (Lee, 2021). Research conducted on animals has demonstrated that certain carcinogenic mechanisms such as UV radiation for skin cancer display strong circadian rhythms (Sancar & Van Gelder, 2021). Moreover, scientists found that tumors that were implanted into animals with disrupted circadian rhythms grew faster than those implanted in animals with normal circadian rhythms (Sancar & Van Gelder, 2021).

Furthermore, experts suggest that the response to cancer treatment is also influenced by circadian rhythms. In regard to the resetting of clock genes and the circadian rhythms, tumor tissues exhibit a circadian clock that differs from that of normal tissues, resulting in altered cellular behavior. Additionally, tumor cells proliferate at a different rate than healthy cells do. For instance, the rate of proliferation in myeloid cells is strongest from the second part of the night until early in the morning, but it is most active in tumor cells in the first half of the night (Nakagawa et al., 2008). The diurnal variation in cell proliferation arises from the synchronized progression of cell cycle events. Therefore, the effectiveness of chemotherapy and radiotherapy may vary for patients according to the treatment time of one day. Understanding the circadian gating of cancer has significant implications for the timing of antiproliferative drug
administration, which can optimize cancer therapy by improving the drug's efficacy while limiting its toxicity.

**Circadian control of DNA repair**

Cells have a daily response to DNA damage. Normal cells have mechanisms involving homologous recombination and non-homologous end-joining to repair DNA damage, maintaining the integrity of the genome and preventing mutations that could lead to cancer (Mao et al., 2008). In contrast, cancer cells frequently have mutations or alterations in genes responsible for DNA repair, resulting in a diminished capacity to repair DNA damage and an increased risk of developing further mutations (Alhmoud et al., 2020). The loss of DNA repair capacity can lead to increased level of genomic instability of cancer cells and this genetic instability can fuel the development and progression of cancer by promoting the acquisition of additional mutations that drive the malignant behavior of cancer cells. Thus, the ability of cells to repair DNA damage plays a crucial role in maintaining genomic stability and preventing the development of cancer.

There are six main DNA repair pathway, including direct DNA repair, base excision repair, nucleotide excision repair, double-strand break, cross-link repair, and mismatch repair (Sancar & Van Gelder, 2021). Among them, nucleotide excision repair is the most intensively and extensively studied in circadian clocks research and evidence suggests that only the repair factor XPA-dependent nucleotide excision repair process is directly controlled by the circadian clock. (Sancar et al., 2010). XPA is activated by the CLOCK-BMAL1 complex and inhibited by CRY-PER, leading to an oscillatory pattern of repair activity in mice (Amiama-Roig et al., 2022). Animal studies with platinum-based drugs have revealed that global DNA repair is lower
in the morning and highest in the evening, with mice treated in the evening showing higher repair capacity compared to those treated in the morning (Kang et al., 2010). DNA nucleotide excision repair of damage induced by the chemotherapy drug cisplatin correlates with circadian rhythm control suggests an association between chronotherapeutic and cancer treatment in clinical settings. Each gene has a different circadian rhythm susceptibility phase to DNA damage depending on its underlying transcriptional rhythm.

Administering cancer treatment at the wrong time may have negative consequences, underscoring the importance of understanding the relationship between circadian clock mechanisms and therapeutic targets. Gaining a deeper understanding of this relationship can help optimize the circadian impact of drug delivery, which is the foundation of chronotherapy for cancer. By timing cancer treatment to coincide with the peak activity of DNA repair mechanisms or the lowest activity of tumor cell proliferation, the efficacy of treatment can be enhanced while minimizing adverse effects on healthy cells. This approach can also help reduce treatment resistance, as cancer cells are usually most vulnerable during specific phases of the circadian cycle.

**Cancer Chronotherapies**

Chronotherapy refers to the approach of synchronizing the timing of disease treatment with the body's natural 24-hour circadian rhythm (Lévi et al., 2010). This strategy aims to optimize patient-based circadian therapy by considering the potentially complex and dynamic nature of the circadian system. The concept of chronotherapy was first introduced by Franz
Halberg over fifty years ago and has since been studied extensively in clinical trials (Halberg et al., 1973). Numerous preclinical studies and phase III clinical studies have investigated the efficacy of chronotherapy across various disease areas. For instance, groundbreaking studies have shown that administering glucocorticoid therapy in the morning can significantly reduce the risk of adverse events associated with adrenal suppression (Ballesta et al., 2017). This has led to current guidelines for the timing of glucocorticoid intake in routine medical practice and management. On the other hand, it is advised that asthmatic patients take theophylline preparations at night to strengthen bronchiectasis and lessen negative effects since theophylline exhibits a longer half-life during nighttime hours, leading to improved respiratory function and reduced symptoms (Ballesta et al., 2017).

In recent years, there has been a growing interest in using circadian rhythms to improve cancer treatment outcomes. Researchers are exploring various approaches such as enhancing circadian rhythms, modulating the activity of circadian molecules, and optimizing the timing of anticancer drugs based on the circadian rhythms of the host or tumor. Chemotherapy is a common way of treating breast cancer. Chemotherapy uses chemical medications to kill cancer cells, which are constantly proliferating within the body, inhibiting the growth of cancer cells and multiplication of tumors (Amjad et al., 2023). By raising the probability of a treatment and reducing the risk of cancer recurrence, chemotherapy can be used to prolong the lives of cancer patients. However, there is a great likelihood that chemotherapy for cancer patients will lead them to develop mild to severe side effects which might lower their quality of life. For instance, anthracyclines have been developed and used extensively in the last four decades to treat cancer (McGowan et al., 2017). However, the side effects of cardiotoxicity
have limited their dosing, and improvements in cancer outcomes have exposed cancer patients to increased cardiovascular disease morbidity and mortality. Anthracycline-induced cardiotoxicity is usually progressive and irreversible, and its initial use can lead to cardiac damage, while long-term use may result in cumulative side effects that can significantly compromise a patient's antineoplastic therapy (McGowan et al., 2017). As a result, cancer patients are not only at risk of cancer disease progression or recurrence but also at risk of experiencing acute or long-term adverse effects and complications associated with chemotherapy treatment. Similarly, in radiation therapy, even though there have been advancements in the targeting of radiation to a patient's tumor, it is impossible to avoid irradiating healthy tissue (Harper & Talbot, 2019). The impact of damaging healthy cells is determined by factors such as the location of the tumor, patient condition, and other treatment factors. The adverse effects may vary from temporary acute reactions to harm to organs and development of secondary cancers (Harper & Talbot, 2019). Therefore, the outcome of patients receiving anticancer therapy remains complicated by unpredictable adverse antitumor side effects.

To overcome these limitations, researchers are exploring the use of circadian rhythms to optimize the timing and delivery of anticancer drugs. Over the past few years, the field of oncology has placed a greater emphasis on improving patient quality of life by managing adverse events associated with cancer therapy (Marcu, 2022). Chronotherapy involves administering treatment during times when tumor cells are most vulnerable or when healthy cells are least sensitive to toxicity. In order to deliver chemotherapy at the most appropriate time for human circadian rhythms, the ideal circadian timing from mice was extrapolated and
studies in mice have shown that circadian rhythms can significantly alter the toxicity of up to 50 anticancer drugs (Chen et al., 2016). Proper timing of chemotherapy is crucial for maximizing the effectiveness of anti-cancer drugs, which are often administered close to their maximum tolerated dose and reducing the severity of side effects by focusing treatment on specific times of day. In a phase III clinical trial, treatment based on a patient's circadian rhythm resulted in better outcomes, with a fivefold reduction in drug toxicity and nearly twofold increase in antitumor efficacy compared to the same drug dose administered outside of the circadian rhythm (Lévi et al., 2010). These findings suggest that cancer treatment could benefit greatly from systemic chronotherapy and that specific applications of chronotherapy have tremendous potential to enhance the effectiveness and safety of cancer treatment.

Chronotherapy has been proposed as a promising approach for cancer chemotherapy and radiotherapy for several decades. Despite the increasing recognition of the significance of circadian rhythms in human diseases, the use of chronotherapy in treating human tumors has not had a crucial impact on the current standard treatment recommendations. Though many animal model and studies have substantiated the feasibility of chronotherapy in cancer treatment, chronotherapy has not become a widely accepted approach in clinical oncology, and there are still fundamental questions posed by skeptics remain unsolved (Takimoto, 2006). Specifically, it is uncertain whether applying circadian principles to cancer chemotherapy can result in therapeutic advantages for patients. Furthermore, only a few research groups have explored this approach, and the results of trials are inconsistent. Observational epidemiological studies are prone to bias, and there is no strong evidence to evaluate the role of chronotherapy in cancer chemotherapy and radiation therapy (Liao et al.,
Therefore, to provide a quantitative summary of the current effectiveness and safety of chronotherapy in cancer treatment, I conducted a comprehensive analysis of all relevant randomized controlled trials (RCTs) conducted thus far.

**Method**

The primary objective of this paper is to evaluate the effectiveness of chronotherapy in reducing the toxicity and improving the efficacy of cancer chemotherapy and radiotherapy. Electronic databases PubMed, Scopus, and Web of Science were thoroughly searched by using search terms like "cancer," "circadian," "chemotherapy," "chronotherapy," and "radiotherapy" to identify randomized controlled trials (RCTs) that evaluated the toxicity and efficacy of chronomodulated chemotherapy and radiotherapy. I also searched the reference lists of included studies. Only studies published in English were considered. Out of the initial 342 articles, 110 duplicate articles were removed, and 47 literature and study reviews were excluded after screening titles and abstracts. An additional 118 RCTs were excluded for non-relevance point of interest. The remaining 67 full-text articles were reviewed. A quality assessment of 32 articles that met the eligibility criteria was conducted (Figure 1). Data were extracted using a standardized form that included study design, sample size, type of side effects, overall survival rate, toxicity incidence, and objective response rate.
Results

After conducting a thorough screening of 232 articles based on their title and abstract, I selected 67 randomized controlled trials for a full-text review. After quality assessment, 35 studies were excluded due to poor quality, duplication, or small sample sizes. The remaining 32 studies met the inclusion criteria and were further assessed. Among these studies, 11 focused on chrono-radiotherapy treatment while 21 explored chrono-chemotherapy treatment. All studies involved clinical trials with human cancer patients (Figure 2).

Regarding radiotherapy studies, 2 articles examined the effectiveness of chronotherapy, 7 articles examined and compared the toxicity of chronotherapy, and 2 articles assessed both effectiveness and safety. The cancers studied in these articles included bone metastases, brain...
cancer, breast cancer, uterine cancer, rectal cancer, head and neck tumors, and prostate cancer.

Within the selected chemotherapy studies, a total of 21 articles met the inclusion criteria. Of these, 4 articles focused on the effectiveness of chronotherapy, 9 articles explored the toxicity of chronotherapy, and 8 articles addressed both effectiveness and toxicity. The studies examined several types of cancers, including breast cancer, diffuse large B-cell lymphoma, rectal cancer, non-small cell intestinal cancer, endometrial cancer, glioma, and nasopharyngeal cancer. All the studies used either monotherapy or a combination treatment including doxorubicin, vinorelbine, taxane, carboplatin, fluoropyrimidine, capecitabine, and other chemotherapeutic drugs.

**Figure 2** Summary of study type
Effect of Chronotherapy in Chemotherapy

Table 1 Clinical trials of circadian delivery of radiotherapy on cancer patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cancer Type</th>
<th>Drug</th>
<th>Study Design</th>
<th>Study Purpose</th>
<th>Sample Size</th>
<th>Chronotherapy schedule</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2348469</td>
<td>Breast cancer, hepatocellular cancer</td>
<td>Cisplatin and oxaliplatin</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>23</td>
<td>Schedule A had significantly higher incidence of neutropenia and distal parasthesia (10+ times higher, P &lt; 0.05) compared to schedule B.</td>
<td>Cicardian rhythm-modulated rate of cisplatin and oxaliplatin have a significant higher tolerated dose and less side effects compared to constant rate infusion of chemotherapy drugs.</td>
</tr>
<tr>
<td>393429</td>
<td>Cancer</td>
<td>5-fluorouracil, vinblastine and cyclophosphamide</td>
<td>Cohort</td>
<td>Efficacy</td>
<td>63</td>
<td>Cicardian rhythm-modulated infusion, Flat infusion</td>
<td>The group receiving infusions of chemotherapy at times taking into account the circadian rhythm of tumoral proliferation have significantly better efficacy.</td>
</tr>
<tr>
<td>10378673</td>
<td>Colorectal cancer</td>
<td>Fluorodeoxyuridine and 5-fluorouracil (5-FU)</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>56</td>
<td>Cicardian rhythm-modulated infusion (maximum at 16:00 for FU and 4:00 for 5-FU), Flat infusion</td>
<td>Patients on chronomodulated infusion received higher doses of both drugs than patients on constant schedule (P=0.001). Combined arterial and venous fluoropyrimidine chemotherapy in the chronotherapy of colorectal cancer liver metastases shows significant tolerance to higher drug doses.</td>
</tr>
<tr>
<td>14551299</td>
<td>Endometrial carcinoma</td>
<td>Cisplatin, 5-fluorouracil, leucovorin and folinic acid</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>169</td>
<td>Cicardian rhythm-modulated infusion, Flat infusion</td>
<td>73% of patients in the standard time arm and 63% of patients in the circadian time arm experienced grade 3 or 4 leucopenia.</td>
</tr>
<tr>
<td>16246545</td>
<td>Colorectal cancer</td>
<td>CPT-11, 5-fluorouracil (5-FU) and folinic acid</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>68</td>
<td>1-h infusion (Arm A), 6-h sinusoidal infusion with peak timing at 5:00 a.m. (Arm B)</td>
<td>In Arm B, patients achieved a 25.7% response rate lasting 7.0 months, an 8.0 month progression-free survival, and a median survival of 28 months. In Arm A, the same data were 18.2%, 4.3, 6.0, and 18 months, respectively.</td>
</tr>
<tr>
<td>16877722</td>
<td>Colorectal cancer</td>
<td>Fluorouracil, leucovorin and oxaliplatin</td>
<td>Cohort</td>
<td>Efficacy</td>
<td>564</td>
<td>Cicardian rhythm-modulated infusion (4-day infusion chronoFLO4), Flat infusion</td>
<td>ChronoFLO4 increased the risk of earlier death in women by 38% compared to FOLFOX2 (median survival times of 16.3 and 19.1 months, P = 0.03). In men, the risk of death decreased by 25% with ChronoFLO4 compared to FOLFOX2 (median survival times of 21.4 and 18.3 months, P = 0.02).</td>
</tr>
<tr>
<td>62700050</td>
<td>Colon cancer</td>
<td>5-fluorouracil (5-FU) and oxaliplatin (L-OHP)</td>
<td>Cohort</td>
<td>Efficacy</td>
<td>92</td>
<td>Cicardian rhythm-modulated infusion (5-FU), peak delivery at 4:00 h and oxaliplatin peak at 16:00 h, Flat infusion</td>
<td>Chronomodulated three-drug delivery achieved 53% response, as compared to 32% in those patients receiving flat infusion (P = 0.038)</td>
</tr>
<tr>
<td>9291901</td>
<td>Colon cancer</td>
<td>Oxaliplatin, fluorouracil and folinic acid</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>186</td>
<td>Cicardian rhythm-modulated infusion, Flat infusion</td>
<td>Chronotherapy showed a significantly higher objective response rate (51%) than the constant-rate group (29%) (P &lt; 0.05). It also reduced severe mucosal toxicity by five-fold and functional impairment from peripheral sensitive neuropathy by half (10% vs 31%; P &lt; 0.01).</td>
</tr>
<tr>
<td>Reference</td>
<td>Cancer Type</td>
<td>Drug</td>
<td>Study Design</td>
<td>Study Purpose</td>
<td>Sample Size</td>
<td>Chronotherapy schedule</td>
<td>Result</td>
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<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>26093951 (Li et al., 2015)</td>
<td>Non-small-cell lung cancer</td>
<td>Cisplatin</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>41</td>
<td>Circadian rhythm-modulated infusion, Flat infusion</td>
<td>No significant difference was observed in the total response rate between the chronotherapy group (52.94%) and the routine chemotherapy group (50.00%). However, the chronotherapy group had significantly lower gastrointestinal toxicity compared to the routine chemotherapy group (P = 0.05).</td>
</tr>
<tr>
<td>8702250 (Natale et al., 1996)</td>
<td>cancer</td>
<td>Carboplatin</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>24</td>
<td>Circadian rhythm-modulated infusion (peak at 16:00 hr), Flat infusion</td>
<td>Two cycles out of 15 for schedule chronotherapy and two out of 20 for standard infusion were accompanied by Grade 4 thrombocytopenia.</td>
</tr>
<tr>
<td>15025796 (Price et al., 2004)</td>
<td>Colorectal cancer</td>
<td>5-Fluorouracil (5-FU)</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>320</td>
<td>Circadian rhythm-modulated infusion, Flat infusion</td>
<td>Overall toxicity grade 2-4 was 90% versus 85%, P = 0.47 and grade 3-4 was 33% versus 37%, P = 0.6 in chronotherapy and flat group, respectively. There is no significant differences in median overall survival (17.6 versus 15.5 months; P = 0.068)</td>
</tr>
<tr>
<td>19622596 (Qvortrup et al., 2010)</td>
<td>Colorectal cancer</td>
<td>Oxaliplatin and capecitabine</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>141</td>
<td>Circadian rhythm-modulated infusion, Flat infusion</td>
<td>The study group had lower incidence of nausea, vomiting, and oral mucositis compared to the control group (p &lt; 0.05). However, there was no significant difference in 2-year overall survival, progression-free survival, and distant metastasis-free survival between the two groups.</td>
</tr>
<tr>
<td>29215933 (Zhang et al., 2018)</td>
<td>Nasopharyngeal carcinoma</td>
<td>Cisplatin</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>148</td>
<td>Circadian rhythm-modulated infusion, Flat infusion</td>
<td>When cisplatin was administered at 18:00, the clearance was 1.38- and 1.22-fold higher than those administered at 6:00 for total and unbound cisplatin, respectively (P &lt; 0.05).</td>
</tr>
<tr>
<td>24061864 (Chen et al., 2013)</td>
<td>Non-small-cell lung cancer</td>
<td>Cisplatin</td>
<td>Cohort</td>
<td>Efficacy</td>
<td>41</td>
<td>6:00 AM - 6:00 PM</td>
<td>The least toxic time of G3-4 neutropenia was observed at 21:00 h with a non-significant 90% CI. There is significant least toxic time of 17.00 h was observed for G3-4 leukopenia</td>
</tr>
<tr>
<td>18780198 (Coudert et al., 2008)</td>
<td>Breast cancer</td>
<td>Vinorelbine</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>90</td>
<td>12:00 AM - 3:00 AM, 6:00 AM - 9:00 AM, 12:00 PM - 3:00 PM, 6:00 PM - 9:00 PM</td>
<td>There is a higher incidence for higher grade side effects in the AM arm compared to the PM arm (P = 0.34).</td>
</tr>
<tr>
<td>00076084340001 (Damato et al., 2022)</td>
<td>Glioma</td>
<td>Temozolomide</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>35</td>
<td>10:00 AM - 8:00 PM</td>
<td>There is a higher incidence for higher grade side effects in the AM arm compared to the PM arm (P = 0.34).</td>
</tr>
</tbody>
</table>
**Chronomodulation of Platinum Chemotherapy**

**Cisplatin** Platinum-based drugs are widely used for the treatment of solid tissue tumors by inducing DNA damage in cancer cells. The repair of cisplatin-induced DNA damage is well characterized in mice and human cell lines, with global repair showing a diurnal rhythm, being lower in the morning and reaching its peak in the evening (Hu et al., 2016). In a trial of advanced nasopharyngeal cancer 148 patients, the population were randomly assigned to receive either a timed cisplatin infusion (with DDP peaks at 4:00 PM) or a regular constant infusion rate. The time-controlled group outperformed the standard group in terms of adverse

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cancer Type</th>
<th>Drug</th>
<th>Study Design</th>
<th>Study Purpose</th>
<th>Sample Size</th>
<th>Chronotherapy schedule</th>
<th>Result</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>10545787 (Falcone et al., 1999)</td>
<td>Gastrointestinal cancer</td>
<td>5-fluorouracil (5-FU) and leucovorin (LV)</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>113</td>
<td>Flat infusion 12:00 AM-8:00 AM; 8:00 AM-4:00 PM; 4:00 PM-12:00 AM</td>
<td>Macrosis occurred more frequently after the flat infusion (44% of patients) than after the chronomodulated infusions (14% in groups 0-8 and 8-16 and 7% in group 16—24, P&lt;0.01)</td>
<td>Toxicities included mainly stomatitis and diarrhea, and a significantly reduced toxicity was observed in all the three chronogroups that allowed the delivery of higher dose intensities.</td>
</tr>
<tr>
<td>3883493 (Hrushesky et al., 1985)</td>
<td>Ovarian cancer</td>
<td>Adriamycin and cisplatin</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>31</td>
<td>6:00 AM adriamycin with 6:00 PM cisplatin; 6:00 AM cisplatin with 6:00 PM adriamycin</td>
<td>In comparison to other groups, patients receiving evening adriamycin and morning cisplatin required twice as many dose adjustments, four times as many treatment interruptions, and three times as many downward medication dosage changes (P&lt; 0.01).</td>
<td>For ovarian cancer treatment, receiving cisplatin in the evening and adriamycin in the morning have significant less treatment delays and treatment complications.</td>
</tr>
<tr>
<td>32519740 (Innominato et al., 2020)</td>
<td>Colorectal cancer</td>
<td>Irinotecan</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>193</td>
<td>1:00 AM, 5:00 AM, 9:00 AM, 1:00 PM, 5:00 PM, 9:00 PM</td>
<td>For diarrhea, timing of irinotecan was particularly important for female patients, ranging from 55.2% of patients in the morning to 29.4% in the afternoon, and for neutropenia, from 25.9% in the morning to 0% in the afternoon (P&lt;0.05).</td>
<td>Irinotecan peak delivery in the afternoon for females, with statistically significant rhythms.</td>
</tr>
<tr>
<td>36512421 (Kim et al., 2023)</td>
<td>Diffuse large B cell lymphoma</td>
<td>4'-0-tetrahydropyran yl doxorubicin (THP) and cisplatin</td>
<td>Cohort</td>
<td>Efficacy and Toxicity</td>
<td>339</td>
<td>Morning (AM), Afternoon (PM)</td>
<td>Female patients receiving chemotherapy mostly in the morning had significantly shorter PFS and OS than those treated in the afternoon (P&lt;0.05). They also had a higher incidence of infections (16.7% vs. 2.4%) and febrile neutropenia (20.8% vs. 9.8%). No significant differences were observed in male patients.</td>
<td>In female DLBCL patients, R-CHOP treatment in the morning can significantly reduce toxicity while it improves efficacy and survival outcome.</td>
</tr>
<tr>
<td>2179481 (Levi et al., 1990)</td>
<td>Ovarian cancer</td>
<td>4'-0-tetrahydropyran yl doxorubicin (THP) and cisplatin</td>
<td>Cohort</td>
<td>Toxicity</td>
<td>31</td>
<td>6:00 AM THP and 4:00 - 8:00 PM cisplatin; 6:00 PM THP and 4:00 - 8:00 AM cisplatin</td>
<td>In comparison to morning cisplatin and afternoon THP, morning THP caused reduced neutropenia (P = 0.10), thrombocytopenia (P=0.01), anemia (P &lt;0.01), and renal damage (P&lt;0.05).</td>
<td>By administering THP in the morning and cisplatin in the afternoon as opposed to THP in the evening and cisplatin the following morning, the toxicities of THP-cisplatin can be significantly reduced.</td>
</tr>
</tbody>
</table>
effects and immune system function (Zhang et al., 2018). Specifically, the incidence of nausea, vomiting, and oral mucositis was significantly lower in the chronomodulated group (66.7%, 47.9%, and 73.9%, respectively) compared to the standard group (79.5%, 71.2%, and 87.7%, respectively) (P < 0.05) (Zhang et al., 2018). These results confirm the circadian rhythm of cisplatin observed in mice experiments. Moreover, patients treated with chronotherapy using cisplatin in the afternoon showed a significantly lower incidence of adverse effects and enhanced tolerance to treatment (Table 1).

In a prospective trial (n=41), there were no difference in treatment response observed when cisplatin was given at various time periods on non-small cell lung cancer (NSCLC) patients (Li et al., 2015). Nonetheless, in the group receiving cisplatin that was delivered at 6:00 PM, the incidence of post-chemotherapy hematologic adverse events, such as leukopenia, neutropenia, and gastrointestinal adverse reactions, was significantly lower (Li et al., 2015). Chen et al. also experimented with patients with NSCLC at different dosing times. When cisplatin was administered at 6:00 PM, total cisplatin clearance was 1.38 times higher than when it was administered at 6:00 AM (P < 0.05) (Chen et al., 2013). The metabolism is more rapidly, less toxic, and was more effective for patients. Cisplatin-based chronotherapy has advantages in alleviating chemotherapy side effects and metabolizing on the NSCLC treatment.

Cisplatin-based chemotherapy continues to be one of the most common therapeutic approaches for ovarian cancer. In one such trial, 31 patients with advanced ovarian cancer underwent eight monthly cycles of doxorubicin and cisplatin, with adriamycin being delivered at either 6:00 AM or 6:00 PM at random, followed by cisplatin after 12 hours (Hrushesky, 1985). Patients who received adriamycin in the evening and cisplatin in the morning required
more reduced doses and delayed treatment compared to those who received adriamycin in the morning and cisplatin in the evening (Hrushesky, 1985). In addition, the morning cisplatin group had approximately twice as many treatment complications as those in the group that received cisplatin in the evening (Hrushesky, 1985). Similarly, Levi and colleagues evaluated the combination of doxorubicin and cisplatin in another group of 31 ovarian cancer patients and found that doxorubicin given in the early morning was active versus cisplatin given in the evening, and that a regimen of cisplatin in the morning and doxorubicin in the evening was significantly less toxic (P < 0.01) (Lévi et al., 1990). In a another trial investigating the effect of doxorubicin and cisplatin administration at different times on endometrial cancer, patients given doxorubicin at 6:00 AM and cisplatin at 6:00 PM received larger total doses (representing lower toxicity) and had fewer cases of leukopenia than those randomly scheduled, although not to a significant degree (Gallion et al., 2003). These findings confirm the circadian repair pattern of cisplatin and underline the critical importance of considering the circadian phase and relationships between cancer and normal tissues when developing chronotherapy. By optimizing the timing of administration, clinicians may be able to reduce toxicity, enhance treatment tolerance, and improve outcomes for cancer patients receiving platinum-based drugs.

*Carboplatin*, a platinum analogue, has also been investigated in the context of chronotherapy. Natoli et al. conducted a study (n=24) to compare the feasibility and tolerability of administering carboplatin using circadian-regulated infusion versus a standard infusion rate in cancer patients (Natoli et al., 1996). The findings demonstrated that applying the circadian-regulated 5-day continuous infusion approach over the standard approach had no recognizable advantages (Natoli et al., 1996). However, other studies that combined chrono modulated 5-
FU with carboplatin showed promising results. In one study, 32 patients with advanced NSCLC received treatment with the combination of 5-FU, folinic acid, and carboplatin in a time-adjusted manner (Natoli et al., 1996). The overall tolerability of the treatment was excellent, with mucositis, diarrhea, alopecia, and skin toxicity observed in less than 3% of the regimens (Natoli et al., 1996). This favorable tolerability encouraged more studies to clarify the protocol's position in the multidisciplinary approach to treating NSCLC and allowed patients for a sustained quality of life.

**Oxaplatin** is a third-generation platinum complex that is notable for its lack of nephrotoxicity. It has been frequently studied using chronotherapy designs, which aim to optimize drug delivery by taking into account the body's natural rhythms. In a phase I study involving 23 patients, a circadian-regulated infusion of oxaliplatin with a peak at 4 pm was compared to a flat infusion rate over 5 consecutive days (Caussanel et al., 1990). The results demonstrated significantly lower rates of neutropenia, vomiting, and distal paresthesias in the chronotherapy group (P < 0.05), indicating that chronomodulated approach led to lower toxicity and greater tolerability of larger doses (Caussanel et al., 1990). In a subsequent study by Quotrup et al., 141 patients with metastatic colorectal cancer were randomized into two groups to receive short (30-minute) infusions of oxaliplatin using different timing strategies. One group received a fixed infusion time from 1 to 3 PM, while the other group received two separate infusions of 50% of the dose in the morning and evening (Qvortrup et al., 2010). The investigation discovered no significant distinction between the two groups' average overall survival and overall toxicity (Qvortrup et al., 2010). 30-minute infusions of oxaliplatin were safe for colorectal cancer patients, but no valid conclusions were drawn as to what time period
was better, and further direct comparisons of the effects at different time points are needed.

**Chronomodulation of Fluoropyrimidines Chemotherapy**

5-*fluorouracil* (**5-FU**) is a widely used chemotherapeutic agent. The oscillation of 5-FU’s targets, thymidylate synthase and dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme responsible for its deterioration, is known to have an impact on them (Pullarkat et al., 2001). DPD activity has been found to peak at 4:00 AM, leading to modulated efficacy of 5-FU (Jacobs et al., 2016). In a clinical study conducted in 1979, the efficacy of timed modulated infusions of chemotherapeutic drugs was compared with standard fixed infusions in patients with solid tumors such as lung, breast, prostate, and ovarian cancer. A total of 63 patients were randomized to receive either flat infusion or a 40-hour sequential chemotherapy infusion, which consisted of methotrexate or 5-FU followed by vincristine and cyclophosphamide (Focan, 1979). The study found that the group that received chronomodulated infusions based on the circadian rhythm of tumor proliferation showed significantly better tumor regression than the group receiving flat infusions (85% vs. 58%, P < 0.05) (Focan, 1979).

Levi et al. conducted a study to compare the efficacy of chronomodulated infusions with flat infusions in patients with metastatic colorectal cancer. The study (n=93) involved patients who received a chronomodulated infusion of 5-FU with a maximum dosing time at 4:00 AM and oxaliplatin dosing time at 4:00 PM (Levi et al., 1995). According to the findings, 58% of patients who received the time-modulated regimen responded, compared to just 32% of those who received the flat infusion. (Levi et al., 1995). The use of chronotherapy more than doubled the activity of chemotherapy against metastatic colorectal cancer. Subsequently, a multicenter trial (n=186) confirmed the efficacy of chronotherapy with 5-FU and leucovorin compared to
the flat infusion regimen. The chrono-regimen reduced the incidence of severe mucositis by a factor of 5 and reduced functional impairment of neuropathy by half (Lévi et al., 1997). Additionally, the objective response rates increased dramatically from 29% to 51% along with the improvement in tolerability (Lévi et al., 1997). Focan et al conducted a trial that yielded consistent results with the aforementioned study, demonstrating that colorectal cancer patients receiving 5-FU chronotherapy could tolerate higher doses and dose intensities than patients on standard platform infusions, resulting in a reduction in chemotherapy toxicity (Focan et al., 1999). Building upon this work, Garufi et al adjusted the approach by giving 5-FU and folinic acid infusions again every 12 hours from 10 PM to 10 AM, with the highest infusion rate occurring at 4 AM (Garufi et al., 2006). In the randomized trial (n=68), colorectal cancer patients who received the chrono-modulated infusion achieved a response rate of 25.7% with a progression-free survival of 8.0 months and a median survival of 28 months, compared to 18.2%, 6.0, and 18 months, respectively, for those who received the standard infusion (Garufi et al., 2006). According to these investigations, chrono-scheduled 5-FU infusions were highly effective and safe in colorectal cancer.

In the realm of gastrointestinal cancers, Falcone conducted a randomized clinical trial involving 113 patients, where they were divided into four different 14-day 5-FU and leucovorin infusion regimens (Falcone et al., 1999). The control group received a continuous flat infusion, while the remaining patients were given 5-FU and leucovorin infusions in three different chronological rhythms over 24 hours, with the aim of reducing toxicity while increasing dose intensities. Drug delivery was highest during the time window from 4:00 PM to midnight, with doses increasing continuously as tolerated (Falcone et al., 1999). The results indicated that all
three chronotherapy groups experienced a significant reduction in toxicity compared to the control group, with the conventional infusion group had the greatest rate of 44% grade 2 or higher mucositis, compared to the 0-8, 8-16, and 16-24 chronotherapy groups, which had rates of 14%, 14%, and 7%, respectively (Falcone et al., 1999).

Fluorodeoxyuridine (FUDR) is a chemotherapeutic agent that has been shown to exhibit activity against various types of malignancies. Its administration can be achieved through a constant or variable rate infusion. In patients with metastatic renal cell carcinoma, one study (n=63) demonstrated that a circadian-modified infusion schedule of FUDR produced comparable success rates to continuous infusion. Specifically, administering 68% of the daily dose between 3:00 PM and 9:00 PM was found to be effective (Hrushesky et al., 1990).

A clinical trial by Price et al. with 318 colorectal cancer patients examined the dose intensification of fluorouracil in combination with mitomycin-C (Price et al., 2004). The results demonstrated that the chronotherapy group of patients had a higher dose intensity of fluorouracil, leading to an increase in the incidence of toxic reactions, but no significant difference was observed between the two groups in terms of response or survival rates (Price et al., 2004).

In another study, Giacchetti et al. investigated the efficacy of two different dosing regimens for the administration of fluorouracil, leucovorin, and oxaliplatin (Giacchetti et al., 2006). The chrono-regimen involved a 4-day chronological infusion while the standard regimen involved continuous infusion for 2 days. The trial involved 564 patients, and both groups achieved similar survival probabilities with manageable toxicity (Giacchetti et al., 2006). Interestingly, the chrono-regimen yielded a survival advantage only in male patients, with a 25% reduction
in the risk of death, but female patients had a 38% increased risk of earlier death with the same regimen (Giacchetti et al., 2006).

**Other chronomodulated chemotherapeutic drugs**

*Irinotecan* It has been suggested that gender-specific timing of chemotherapy dosing can minimize side effects and improve treatment efficacy. A recent randomized trial (n=90) investigated the effect of irinotecan-based chronotherapy on response rates for side effects in men and women with metastatic colorectal cancer. The results showed a significant difference in response rates between men and women, indicating the importance of gender-specific timing of dosing (Innominato et al., 2020). Specifically, scheduling treatment in the morning for males and in the afternoon for females minimized side effects in both sexes.

*Doxorubicin* Similar findings were obtained with doxorubicin in the treatment of patients with diffuse large B-cell lymphoma (DLBCL). Kim et al. found out that in female DLBCL patients, doxorubicin chemotherapy in the afternoon significantly reduced febrile neutropenia while improving outcomes and survival (p < 0.05), but treatment in male patients was not affected by timing (Kim et al., 2023).

*Vinorelbine* Besides sex dependency, different toxicities also varied in times during chemotherapy treatment. Vinorelbine is a chemotherapeutic agent often used in combination with doxorubicin. Animal studies have shown that the toxicity of vinorelbine is influenced by time of day. Previous research stated that hematologic and systemic toxicity was reduced in humans at 17:00 and 21:00 hours of day and night (Coudert et al., 2008). Coudert and his colleagues conducted the study with 90 metastatic breast cancer patients and discovered that the minimum time to toxicity for neutropenia was 9:00 PM, but for gastrointestinal toxicity,
the estimated minimum time to toxicity was 10:30 AM (Coudert et al., 2008). The minimum time to toxicity varies for different toxicities, and tolerability trials need to be conducted focusing on specific toxicities.

_Temozolomide_ is a commonly used chemotherapy drug in the treatment of glioma, a type of brain cancer. Research has shown that glioma cancer cells have a lower capacity for DNA repair during the morning hours, suggesting that administration of temozolomide in the morning could improve tumor outcomes. However, a recent randomized clinical trial (n=35) found no significant differences in survival rate or adverse effects when temozolomide was administered in the morning versus evening (Damato et al., 2022). Given the small sample size of this study, larger studies are needed to validate the impact of temozolomide-based chronotherapy on glioma patients.

**Summary**

Upon analyzing 21 studies, it was observed that 9 research groups reported significant differences in reducing toxicity and increasing efficacy of circadian rhythm-modulated infusion of chemotherapy compared to flat infusion (refer to Table 2). Specifically, the chronomodulated infusion schedule of 5-Fu and FUDR was found to have significantly higher efficacy and lower toxicity in patients with colorectal cancer and gastrointestinal cancer. Moreover, 6 groups reported significant differences in circadian time-dependent chemotherapy among patients with breast cancer, non-small cell lung cancer (NSCLC), glioma, ovarian cancer, diffuse large B-cell lymphoma (DLBCL), and colorectal cancer (refer to Table 2). Furthermore, the administration of cisplatin in the afternoon, in combination with doxorubicin given in the morning, was observed to be the most effective regimen. These
findings emphasize the importance of considering circadian rhythms in the development of temporal treatment regimens for cancer patients.

**Table 2** Summary of trials with chronomodulated chemotherapy as an intervention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity outcomes with chronomodulated chemotherapy</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td><strong>Endometrial carcinoma:</strong> Toxicity outcomes did not significantly differ according to the time of chemotherapy</td>
<td>Significant (4)</td>
<td>Gallion et al., 2003</td>
</tr>
<tr>
<td></td>
<td><strong>Non-small-cell lung cancer:</strong> Chronomodulated rate of cisplatin-based chemotherapy has significant changes in relieving side effects</td>
<td>Not Significant (1)</td>
<td>Li et al., 2015</td>
</tr>
<tr>
<td></td>
<td><strong>Nasopharyngeal carcinoma:</strong> Cisplatin-based chemotherapy has significant changes in relieving incidence of nausea, vomiting, and oral mucositis</td>
<td></td>
<td>Zhang et al., 2018</td>
</tr>
<tr>
<td></td>
<td><strong>Ovarian cancer:</strong> Patients received cisplatin in the afternoon and adriamycin/doxorubicin in the morning significant less treatment delays and treatment complications compared to the opposite combination</td>
<td></td>
<td>Hrushesky et al., 1985, Levi et al., 1990</td>
</tr>
<tr>
<td>Oxalipatin</td>
<td><strong>Breast Cancer:</strong> Circadian rhythm-modulated rate of oxaliplatin have a higher tolerated dose and less side effects</td>
<td>Significant (1)</td>
<td>Caussanel et al., 1990, Qvortrup et al., 2010</td>
</tr>
<tr>
<td></td>
<td><strong>Colorectal cancer:</strong> Toxicity outcomes did not significantly differ between circadian rhythm-modulated infusion and flat infusion</td>
<td>Not Significant (1)</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Toxicity outcomes did not significantly differ between chronomodulated carboplatin infusion and flat infusion</td>
<td>Not Significant</td>
<td>Natoli et al., 1996</td>
</tr>
<tr>
<td>Fluorodeoxyuridine</td>
<td><strong>Colorectal cancer:</strong> Chronomodulated rate of FUDR has less mucosal toxicity compared to the flat infusion rate</td>
<td>Significant</td>
<td>Levi et al., 1997</td>
</tr>
<tr>
<td>5-FU</td>
<td><strong>Colorectal Cancer:</strong> Chronomodulated rate of 5-FU have a higher tolerated dose; There is a nonsignificant trend toward palmar plantar erythema incidence between chronomodulated infusion and flat infusion</td>
<td>Significant (2)</td>
<td>Focan et al., 1999, Garufi et al., 2006, Price et al., 2004, Falcone et al., 1999</td>
</tr>
<tr>
<td></td>
<td><strong>Gastrointestinal Cancer:</strong> Circadian rhythm-modulated rate of 5-FU have a lower rate of stomatitis and diarrhea</td>
<td>Not Significant (1)</td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td><strong>Colorectal cancer:</strong> Female patients received irinotecan in the afternoon have a reduced diarrhea and neutropenia</td>
<td>Significant</td>
<td>Innominato et al., 2020</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td><strong>Diffuse large B cell lymphoma:</strong> Patients received cisplatin in the afternoon have a reduced toxicity than those treated in the morning</td>
<td>Significant</td>
<td>Kim et al., 2023</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td><strong>Breast Cancer:</strong> Patients received vinorelbine at 5:00 PM and 9:00 PM have a reduced hematological and systemic toxicities</td>
<td>Significant</td>
<td>Coudert et al., 2008</td>
</tr>
<tr>
<td>Temozolomide</td>
<td><strong>Glioma:</strong> Patients in the morning group have a higher incidence for higher grade adverse events</td>
<td>Not Significant</td>
<td>Damato et al., 2022</td>
</tr>
<tr>
<td>Drug</td>
<td>Efficacy outcomes with chronomodulated chemotherapy</td>
<td>Significance</td>
<td>Reference</td>
</tr>
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<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------</td>
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<td>----------------------------------</td>
</tr>
</tbody>
</table>
| **Cisplatin** | **Endometrial carcinoma**  
Treatment outcomes did not significantly differ according to the time of chemotherapy  
**Non-small-cell lung cancer:** Patients received cisplatin in the afternoon has a higher clearance rate than those treated in the morning | Significant (1)  
Not Significant(2) | (Gallion et al., 2003)  
(Li et al., 2015)  
(Chen et al., 2013) |
| **Doxorubicin** | **Diffuse large B cell lymphoma:** Patients received cisplatin in the afternoon have a higher efficacy and better survival outcome than those treated in the morning | Significant          | (Kim et al., 2023)                |
| **Temozolomide** | **Glioma:** Treatment outcomes did not significantly differ according to the time of chemotherapy | Not Significant      | (Damato et al., 2022)            |
| **5-FU**    | **Breast Cancer:** Chronomodulated rate of 5-FU have a higher efficacy compared to the flat rate  
**Colorectal Cancer:** Chronomodulated infusion of 5-FU is more active and efficent compared to flat infusion | Significant (3)  
Not Significant (1) | (Focan, 1979)  
(Garufi et al., 2006),  
(Giacchetti et al., 1995)  
(Price et al., 2004) |
| **Fluorodeoxyuridine** | **Colorectal cancer:** Chronomodulated schedule of FUDR produced a significant survival advantage in males but not females | Significant          | (Giacchetti et al., 2006)  
(Levi et al., 1997)        |
## Table 3 Clinical trials of circadian delivery of radiotherapy on cancer patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cancer Type</th>
<th>Study Design</th>
<th>Study Purpose</th>
<th>Sample Size</th>
<th>Chronotherapy schedule</th>
<th>Result</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>396410500005 (Chan et al., 2017)</td>
<td>Bone metastases</td>
<td>Retrospective Cohort Study</td>
<td>Efficacy</td>
<td>194</td>
<td>8:00 AM-11:00 AM, 11:01 AM-2:00 PM, 2:01 PM-5:00 PM</td>
<td>Females in the 11:01 AM-2:00 PM cohort exhibited a significantly higher response rate (P=0.02) and differing proportions of response types (P=0.03) compared to the 8:00 AM-11:00 AM and 2:01 PM-5:00 PM cohorts.</td>
<td>Treatment time was significantly related to response rate in female patients receiving radiotherapy for painful bone metastases.</td>
</tr>
<tr>
<td>000387587200005 (Chan et al., 2016)</td>
<td>Brain cancer</td>
<td>Retrospective Cohort Study</td>
<td>Efficacy</td>
<td>755</td>
<td>8:00 AM-11:00 AM, 11:01 AM-2:00 PM, 2:01 PM-5:00 PM</td>
<td>In female patients &gt;65 years of age, those in the 11:01 AM-2:00 PM cohort exhibited a longer actuarial median OS (2.12 months) than the 8:00-11:00 AM (1.23 months) and 2:01-5:00 PM (1.18 months) cohorts (P=0.019).</td>
<td>Time of whole brain radiotherapy delivery for brain metastases was significantly related to overall survival upon univariate analyses in females only.</td>
</tr>
<tr>
<td>000453925200006 (Johnson et al., 2019)</td>
<td>Breast cancer</td>
<td>Retrospective Cohort Study</td>
<td>Toxicity</td>
<td>878</td>
<td>Morning (AM), Afternoon (PM)</td>
<td>Patients who had radiotherapy in the morning had a significantly increased incidence of late toxicity in univariate(P=0.05).</td>
<td>Breast cancer patients treated in the morning had significant worse radiotherapy side-effects than those treated in the afternoon.</td>
</tr>
<tr>
<td>000336497900002 (Noh et al., 2014)</td>
<td>Breast cancer</td>
<td>Cohort Study</td>
<td>Efficacy and Toxicity</td>
<td>395</td>
<td>7:00 AM-10:00 AM, 3:00 PM - 10:00 PM</td>
<td>There is a higher frequency of Grade 2 or higher acute skin reaction in the afternoon radiotherapy group than the morning radiotherapy group (13.7% vs 5.8%, respectively; P = 0.0088).</td>
<td>Radiotherapy in late afternoon was significantly associated with increased Grade 2 skin reaction after radiotherapy for breast cancer patients, but treatment outcomes did not significantly differ according to the time of RT.</td>
</tr>
<tr>
<td>000388158800004 (Chang et al., 2016)</td>
<td>Cervical cancer</td>
<td>Cohort Study</td>
<td>Efficacy and Toxicity</td>
<td>67</td>
<td>9:00 - 11:00 AM, 9:00 - 11:00 PM</td>
<td>The incidence of severe hematological toxicity in the evening group was significantly increased compared to the morning group.</td>
<td>Radiotherapy at different time intervals results in similar efficacy. However, Radiotherapy in the morning significantly reduces severe hematological toxicity.</td>
</tr>
<tr>
<td>000276584700024 (Shukla et al., 2010)</td>
<td>Cervical cancer</td>
<td>Cohort Study</td>
<td>Toxicity</td>
<td>229</td>
<td>8:00-10:00 AM, 6:00-8:00 PM</td>
<td>Overall (grade I-IV) diarrhea was found to be significantly increased in the morning arm as compared with the evening arm (overall: 87.39 % vs 68.18 %, P &lt; .01).</td>
<td>There is a significant difference in the incidence of higher grade diarrhea between the morning and evening radiotherapy treatment.</td>
</tr>
<tr>
<td>0955300902883802 (Goyal et al., 2009)</td>
<td>Head and neck cancer</td>
<td>Cohort Study</td>
<td>Toxicity</td>
<td>212</td>
<td>8:00 -11:00 AM, 3:00 - 6:00 PM</td>
<td>The grades of mucositis were marginally higher in the evening-irradiated group than in the morning-irradiated group 38% vs. 26% (p = 0.08)</td>
<td>The incidence of grade III/IV mucositis in morning is higher than in evening, but not significantly.</td>
</tr>
</tbody>
</table>
The effect of radiation therapy scheduling on the prevalence of mucositis in patients with head and neck cancer was assessed in three prospective randomized studies. The first study (n=212) indicated a higher incidence of grade 3 and higher mucositis in the morning group compared to the evening group, albeit not significantly (Goyal et al., 2009). Similarly, the second study (n=216) reported no significant difference in acute mucosal toxicity between the early morning and late afternoon radiation therapy groups (Bjarnason et al., 2009). However, both studies consistently suggested that patients who received treatment in the afternoon progressed to high grade mucositis more quickly, but those who received care in the morning had a considerably longer median time to reach grade 3 and 4 mucositis (Goyal et al., 2009).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cancer Type</th>
<th>Study Design</th>
<th>Study Purpose</th>
<th>Sample Size</th>
<th>Chronotherapy schedule</th>
<th>Result</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0002618202060026</td>
<td>Head and neck cancer</td>
<td>Cohort Study</td>
<td>Toxicity</td>
<td>216</td>
<td>8:00-10:00 AM, 4:00-6:00 PM</td>
<td>After 5 months of treatment, morning radiation caused reduced weight loss (p=0.024). Morning radiation significantly reduced Grade 3 mucositis in a sample of 111 patients who received 66-70 Gy in 33-35 fractions (44.6% vs. 67.3%, p=0.022).</td>
<td>Morning radiotherapy did not show significant association with weight loss or mucositis in overall analysis. However, in a subgroup receiving high doses, morning RT significantly reduced Grade 3 or greater mucositis.</td>
</tr>
<tr>
<td>33667582</td>
<td>Head and neck cancer</td>
<td>Cohort Study</td>
<td>Toxicity</td>
<td>617</td>
<td>Morning (AM), Afternoon (PM)</td>
<td>Acute toxicity scores were significantly lower in the morning radiotherapy group (p = 0.0387), while late toxicity scores showed no significant difference between the groups</td>
<td>There is significant higher acute toxicity with radiotherapy in the afternoon group.</td>
</tr>
<tr>
<td>26818960</td>
<td>Prostate cancer</td>
<td>Cohort Study</td>
<td>Toxicity</td>
<td>409</td>
<td>Daytime treatment (before 5 PM) evening treatment (after 5 PM)</td>
<td>The detrimental effect of evening HDRT was significant in patients older than 70 years old (p &lt; 0.001) but not in younger patients (p = 0.63).</td>
<td>Evening radiotherapy has a significant association with gastrointestinal complications, especially in older patients.</td>
</tr>
<tr>
<td>0003999919000007</td>
<td>Rectal cancer</td>
<td>Retrospective Cohort Study</td>
<td>Toxicity</td>
<td>155</td>
<td>Morning (AM), Afternoon (PM)</td>
<td>Patients receiving radiotherapy mostly after 12:00 PM exhibited significant improvements in pathological response (p = 0.035) and nodal downstaging.</td>
<td>Afternoon radiotherapy is significantly associated with a complete pathological response compared to morning treatment.</td>
</tr>
</tbody>
</table>

**Head and Neck Cancer** The effect of radiation therapy scheduling on the prevalence of mucositis in patients with head and neck cancer was assessed in three prospective randomized studies. The first study (n=212) indicated a higher incidence of grade 3 and higher mucositis in the morning group compared to the evening group, albeit not significantly (Goyal et al., 2009). Similarly, the second study (n=216) reported no significant difference in acute mucosal toxicity between the early morning and late afternoon radiation therapy groups (Bjarnason et al., 2009). However, both studies consistently suggested that patients who received treatment in the afternoon progressed to high grade mucositis more quickly, but those who received care in the morning had a considerably longer median time to reach grade 3 and 4 mucositis (Goyal et al., 2009).
et al., 2009, Bjarnason et al., 2009). Additionally, a subgroup analysis of 111 patients who received 33-35 doses showed significantly less grade 3 and 4 mucositis after morning radiation therapy (P < 0.05), along with a longer time interval to develop mucositis (P < 0.05) (Bjarnason et al., 2009). This study supports earlier hypotheses about the human oral mucosal cell cycle's circadian rhythm, which has the majority of cells in the G1 phase in the morning and the G2-M phase in the evening. The timing of treatment to induce apoptosis was investigated, with the late active phase being the optimal time, as this is when most of the target cells are in the G2-M phase (Bjarnason et al., 2009). Moreover, a recent retrospective study (n = 617) was conducted to evaluate the effects of the timing and seasonality of radiotherapy administration for head and neck cancer. The study found that when administered in the afternoon or during the dark season (September to March), there was a higher incidence of acute toxicity (Brolese et al., 2021). Overall, the incidence of grade 3 or higher mucositis was higher in patients with head and neck cancer when treated in the afternoon, although two of the findings did not reach statistical significance. However, when subgroups were analyzed, significant differences in weight loss and mucositis were found between the groups for smokers or patients receiving a higher number of radiation doses.

Cervical Cancer Two prospective randomized studies were conducted to examine the incidence of radiotherapy side effects in cervical cancer. In contrast to what was observed in patients with head and neck cancer, participants in the morning group had a greater rate of diarrhea than those receiving treatment in the afternoon, indirectly demonstrating the effect of circadian rhythms of radiotherapy on the human intestinal mucositis (Shukla et al., 2010). Moreover, another study by Chang et al. reported that morning radiation therapy resulted in a
reduction in severe hematological toxicity in patients with inoperable cervical cancer (Chang et al., 2016). These results highlight the potential impact of chronotherapy in optimizing treatment outcomes in cervical cancer, underscoring the importance of considering the timing of radiation therapy to minimize treatment-related side effects and improve therapeutic efficacy. To validate these findings and clarify the underlying processes that control the circadian modulation of radiation therapy toxicity in cervical cancer, additional research is wanted.

**Breast Cancer** Contradictory findings were obtained from two prospective studies that investigated the side effects of breast cancer radiotherapy. According to the first study (n=878) by Johnson et al., radiotherapy side effects were significantly worse for breast cancer patients who had treatment in the morning as opposed to the afternoon. (Johnson et al., 2019). Conversely, the second study (n=395) by Noh reported a higher incidence of grade 2 skin reactions in the afternoon (Noh et al., 2014). What is remarkable from the first study is that the PER3 variable tandem repeat 4/4 genotype was related to an increased late effect of morning radiation. (Johnson et al., 2019). The divergent findings between the two studies may be attributable to differences in patient age, and the methodology employed in patients to receive radiotherapy. The results of these studies highlight the complex and multifactorial nature of radiotherapy toxicity in breast cancer patients, underscoring the need for further research to elucidate the underlying mechanisms and identify potential risk factors that may inform personalized treatment planning.

**Colon Cancer and Rectal Cancer** Squire et al. conduct a retrospective study on patients with locally advanced rectal cancer to evaluate the impact of radiation therapy timing on treatment outcomes. The study (n = 155) discovered that patients who received the majority of
their radiotherapy in the late afternoon had a better chance of downstaging the tumors and obtaining a complete or moderate pathologic response (Squire et al., 2017). In a separate treatment trial involving mice bearing a human colorectal tumor xenograft, X-radiation administered at 3:00 AM demonstrated the highest efficacy in terms of tumor control without significantly increasing acute toxicity (Mullins et al., 2005). Conversely, treatment administered at 3:00 PM showed increased toxicity without any corresponding improvement in treatment efficacy.

**Brain and Bone Metastases** Whole brain radiotherapy (WBRT) is a standard treatment for brain metastases. A study of 755 patients found no significant association between treatment duration and overall survival in all patients or in men (Chan et al., 2016). However, in older female patients (>65 years), there were significant differences in overall survival between treatment cohorts (Chan et al., 2016). The 11:01 AM-2:00 PM cohort showed a longer actuarial median compared to other time periods, indicating that the timing of WBRT administration may affect overall survival in specific patient subgroups (Chan et al., 2016). Interestingly, similar results were observed in patients with bone metastases. Chan and his colleagues did a prospective study of 194 patients with painful bone metastases treated with radiation found that women in the 11:01 AM-2:00 PM cohort had a significantly higher response rate and a different proportion of response types than other time cohorts, while no significant differences were observed in men (Chan et al., 2017). These findings suggest that the duration of radiotherapy may influence the response to treatment in female patients with brain metastases and old female patients with bone metastases. However, treatment of metastatic patients is closely related to treatment response, clinical outcome and quality of life and can be influenced
by prognostic factors. Further research on the effects of radiotherapy on patients might benefit from a cohort of patients that is as homogenous as feasible.

**Prostate Cancer** Differential response to chrono-radiotherapy treatment among subgroups was also found in prostate cancer patients. Besides the sex dependency in radiotherapy, there is also age dependency. A trial involving prostate cancer patients treated with high-dose radiation therapy (HDRT) found that patients receiving late HDRT had a significantly higher risk of developing advanced gastrointestinal complications (Hsu et al., 2016). Notably, this adverse effect was only significant in patients over the age of 70 (p < 0.001) but not in younger patients (Hsu et al., 2016). These results imply that the effectiveness of HDRT may potentially be significantly influenced by age.

**Summary**

Out of the 11 studies analyzed, it was discovered that 6 research groups were able to identify significant variations in the side effects of chrono-modulated radiotherapy in patients with breast cancer, cervical cancer, prostate cancer, and rectal cancers (refer to Table 4). Furthermore, 2 groups found significant disparities of circadian time-dependent radiotherapy in treatment response rates and overall survival among patients with brain metastases and bone metastases (refer to Table 4).
Table 4 Summary of trials with chronomodulated radiotherapy as an intervention

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Toxicity outcomes with chronomodulated radiotherapy</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Patients who received morning radiotherapy had a higher incidence of late toxicity, while those who received afternoon radiotherapy had an increased grade 2 skin reaction</td>
<td>Significant</td>
<td>(Johnson et al., 2019), (Noh et al., 2014)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Hematological toxicity was observed to be increased in the group of patients who had radiotherapy in the evening, but patients who had radiotherapy in the morning had higher diarrhea incidence</td>
<td>Significant</td>
<td>(Chang et al., 2016), (Shukla et al., 2010)</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>Patients who had radiotherapy in the afternoon had a more rapid progression to high grade mucositis</td>
<td>Significant</td>
<td>(Broese et al., 2021), (Goyal et al., 2009), (Bjarnason et al., 2009)</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Patients who had radiotherapy in the evening HDRT had increased gastrointestinal complications</td>
<td>Significant</td>
<td>(Hsu et al., 2016)</td>
</tr>
<tr>
<td>Rectal Cancer</td>
<td>Patients who had radiotherapy in the afternoon had a more complete pathological response</td>
<td>Significant</td>
<td>(Squire et al., 2017)</td>
</tr>
</tbody>
</table>

Discussion

The results of this review suggest that chrono-chemotherapy and chrono-radiotherapy treatment has the potential to improve the therapeutic index in cancer patients, with more than 70% of randomized controlled trials reporting a significant reduction in toxicity or a significant improvement in efficacy. This paper provides a comprehensive overview of cancer chronotherapy on its current state, particularly about chronomodulated chemotherapy and radiotherapy. In addition to that, the review concisely describes current knowledge about circadian rhyme and its association with cancer treatment, and underscores the importance of patient outcomes, highlighting the potential benefits of chronotherapy for cancer patients' overall health and well-being. However, this study has some limitations. First, it should be noted that the number of high-quality studies included in this review was limited, and some high-quality trials may have been missed due to the inclusion of only three searching...
databases. Among the included randomized controlled trials, it was challenging to isolate the choronomodulation effect due to variations in dose intensity and infusion time. Also, even taking treatment variables such as treatment duration, and patients variables including gender, age, cancer type and cancer level into account, it was still difficult to compare results between studies. Some experiments reached opposite conclusions, and some explored trends but did not reach statistical significance. This is due to certain variance among patients as their tumors respond to radiotherapy as well as chemotherapy are different. For example, the changes in hypoxia levels, proliferative capacity, intrinsic radiosensitivity, and the proportion of cancer stem cells are largely varied (Marcu, 2022). The complex tumor microenvironment and differences between patients who respond to radiotherapy and chemotherapy make it difficult to optimize drug efficacy and reduce drug toxicity through timing of drug administration, and larger cohorts are needed to confirm the data derived from the existing studies. The gender differences in tumor and normal tissue responses to chemotherapy and radiation provide an additional obstacle. Several trials have demonstrated the effect of gender in chronotherapy: compared to men, the overall survival is higher in women with brain metastasis after radiotherapy treatment (Chan et al., 2016); Women with head and neck cancer have lower rate of oral mucositis when receiving radiotherapy in the afternoon than in the morning, while the opposite results are seen in male patients (Bjarnason et al., 2009). Male patients with colorectal cancer have higher overall survival compared to female patients after chrono-chemotherapy (Giacchetti et al., 2012); Male patients with colorectal cancer receiving chronomodulated Irinotecan treatment in the morning while females in the afternoon for females best minimized toxicities (Innominato et al., 2020). Hence, further
research is necessary to understand gender-related anatomical differences and body habitus to better interpret findings, and gender should be taken into account as a matching variable in the following clinical studies and trials.

On top of that, personalized and precise chronotherapy remains challenging due to the existence of temporal types, which refer to unique differences in the rhythmicity of certain circadian phases (Amiama-Roig et al., 2022). To accurately ascertain each person's circadian phase, additional biomarkers and more advanced imaging techniques are needed. Researchers have proposed various feasible ways to determine circadian rhythm phase objectively. For instance, collecting saliva samples from patients to measure melatonin levels has been used as a biomarker to determine circadian rhythms (Au - Facer-Childs et al., 2020). Saliva sampling protocols combined with questionnaires to investigate circadian rhythm have been successfully conducted in challenging environments, such as the Amazon and Antarctica (Au - Facer-Childs et al., 2020). Additionally, blood has been proposed as a viable biomarker. Wittenbrink et al. have developed a simple and highly accurate assay known as BodyTime that only requires a small fraction of blood at any given time (Wittenbrink et al., 2018). The BodyTime assay uses a machine learning approach to transfer internal time biomarkers to a gene expression profiling platform for measurement. The assay has been shown to measure NR1D1, NR1D2, CRY1, PER1, PER2, and other biomarkers to estimate the internal circadian time in humans (Wittenbrink et al., 2018). Also, other approaches such as circadian metabolomics have been investigated in a variety of biological samples from laboratory animals, such as blood, saliva, urine, and exhaled breath, and these processes have strong translational potential (Dallmann et al., 2016). These samples can be collected non-invasively
24/7 in individual patients, making it feasible to predict the optimal timing of personalized treatment. Notably, Positron emission tomography imaging may be useful for the identification of circadian rhythms, which in combination with holography will have a great impact on the implementation of personalized chronotherapy in the clinical setting. Positron emission tomography (PET) is a widely utilized noninvasive imaging technology, and in cancer therapy, the glucose analog 18F-furan deoxyglucose (FDG) has been the most often used PET tracer in clinical practice and preclinical studies (Krueger et al., 2020). Krueger have successfully applied FDG in the distribution of circadian rhythms in mice and humans to trace circadian rhyme (Krueger et al., 2020). These advances in the identification and measurement of biomarkers have great potential to optimize the effective management of chronotherapy in the future, as they allow for more precise and personalized chronotherapy interventions that are tailored to the individual characteristics of each patient.

In summary, personalized circadian-based treatment delivery models for cancer are becoming a central goal of the cancer field. Chronotherapy is a concept that is not just applicable to chemotherapy and radiotherapy; rather, the theoretical foundation of chronotherapy may be used to various types of therapy, for instance targeted therapy and immunological therapy. To fully realize the potential of chronotherapy in cancer treatment, multidisciplinary efforts are required from different organizations, including preclinical and clinical research, pharmaceutical companies, and medical centers. Preclinical studies are needed to investigate the intrinsic circadian rhythmicity of normal tissues and cancer tissues to optimize circadian programs for cancer treatment. Besides, clinical trials are necessary to understand the impact of the biological clock on the action of chemotherapy and radiotherapy
and to explore the factors that influence chronotherapy and the potential for personalized approaches. Pharmaceutical companies could assess the efficacy and adverse events of drugs against the criteria of chronotherapy to maximize the effectiveness of cancer treatment. Medical facilities might also aid in the advancement of chronotherapy by enabling the administration of medication outside of normal business hours. In conclusion, the current random controlled trial and previous animal studies strongly suggest the potential of chronomodulation in cancer chemotherapy and radiotherapy. The systemic approach of chronotherapy represents a significant conceptual and methodological advancement to personalize and maximize the effectiveness of cancer treatment, leading to a combined improvement in tolerability and efficacy. Therefore, the implementation of chronotherapy has big opportunity to have a tremendous impact on the overall health outcomes of cancer patients in the future.
Reference


circadian time of vinorelbine combined with chronomodulated 5-fluorouracil in pretreated metastatic breast cancer patients: EORTC trial 05971. *Chronobiol Int, 25*(5), 680-696. [https://doi.org/10.1080/07420520802384036](https://doi.org/10.1080/07420520802384036)


chronomodulated CPT-11 plus chronomodulated 5-fluorouracil and folinic acid in
https://doi.org/10.1016/j.ejca.2005.03.012

22. Giachetti, S., Bjarnason, G., Garufi, C., Genet, D., Iacobelli, S., Tampellini, M.,
Smaaland, R., Focan, C., Coudert, B., Humblet, Y., Canon, J. L., Adenis, A., Lo Re, G.,
Carvalho, C., Schueller, J., Anciaux, N., Lentz, M. A., Baron, B., Gorlia, T., & Lévi, F.
(2006). Phase III trial comparing 4-day chronomodulated therapy versus 2-day
conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line
chemotherapy of metastatic colorectal cancer: the European Organisation for Research
https://doi.org/10.1200/jco.2006.06.1440

Tumolo, S., Coudert, B., Iacobelli, S., Smaaland, R., Tampellini, M., Adam, R., Moreau,
T., & Lévi, F. (2012). Sex moderates circadian chemotherapy effects on survival of
patients with metastatic colorectal cancer: a meta-analysis. *Ann Oncol, 23*(12), 3110-
3116. https://doi.org/10.1093/annonc/mds148

Verma, N. S. (2009). Oral mucositis in morning vs. evening irradiated patients: A
randomised prospective study. *International Journal of Radiation Biology, 85*(6), 504-
509. https://doi.org/10.1080/09553000902883802

25. Halberg, F., Haus, E., Cardoso, S. S., Scheving, L. E., Kühl, J. F. W., Shiotsuma, R.,
Toward a chronotherapy of neoplasia: Tolerance of treatment depends upon host
rhythms. *Experientia, 29*(8), 909-934. https://doi.org/10.1007/BF01930381

https://doi.org/https://doi.org/10.1016/j.clon.2019.02.010


