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Overview

Does the Time of Radiotherapy Affect Treatment Outcomes? A Review of the Literature

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Abstract

Circadian rhythm-dependent cell cycle progression produces daily variations in radiosensitivity. This literature review aims to summarise the data on whether radiotherapy outcomes differ depending on administration time. A literature search was conducted on Ovid Medline, Embase, Cochrane Central Register of Controlled Trials and PubMed using key words such as 'radiotherapy', 'circadian rhythm', 'treatment outcome' and 'survival'. Articles evaluating the correlation between radiotherapy time and outcomes in cancer patients were included and relevant information was extracted. Nine studies met the inclusion criteria. Four investigated lung cancer patients undergoing stereotactic radiosurgery for brain metastases, with one study observing improved local control and survival in patients treated in the morning. Another two studies with breast and cervical cancer patients observed that the prevalence of toxicities was higher in afternoon and morning cohorts, respectively. Two studies in head and neck cancer patients found trends indicating morning patients experienced less oral mucositis. Increased toxicities and biochemical failure rates were associated with evening treatment in prostate cancer patients. As inconsistencies in the literature exist regarding the time dependency of radiotherapy outcomes, further investigation is warranted.
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Key words: Circadian rhythm; chronotherapy; radiotherapy; side-effects; survival; treatment outcome

Statement of Search Strategies Used and Sources of Information

A literature search was conducted on Ovid Medline, Embase, the Cochrane Central Register of Controlled Trials and PubMed. The key words and subject headings used in the searches included 'radiotherapy', 'circadian rhythm', 'treatment outcome', 'survival' and 'time of treatment'. The searches were limited to English language only. Of 128 generated articles, nine studies were selected for inclusion after independent screening by two authors.

Introduction

Circadian rhythms are predictable 24 h variations in most physiological, biochemical and behavioural processes in mammals [1–3]. The circadian pacemaker is the suprachiasmatic nuclei, which generates cycles in humoral signals, body temperature, autonomic nervous system activity and cognitive performance in response to changes in external environmental cues, such as light [1–3].

The rhythmic expression of clock genes in the suprachiasmatic nuclei and peripheral tissues generates circadian rhythms [2,4] that, among other things, gate cell cycle progression [5–7]. It is well known that each phase of the cell cycle corresponds to a different degree of radiosensitivity [7–10]. The gap 2 (G2) and mitotic (M) phases are the most radiosensitive phases, whereas cells in the synthesis (S) phase are least sensitive to radiation [7–10]. Cells in the G1 phase are more radiosensitive than cells in the S phase but less than cells in the G2/M phase [7–10].

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Studies in animal models have examined the time dependency of radiosensitivity [9,11,12]. One study examining the intestinal crypts of mice observed that radiation in the late activity phase, corresponding to the G2/M phase, resulted in the most radiation-induced apoptosis. Conversely, radiation in the early activity phase, when target cells were in the G1 phase, corresponded to the least amount of apoptosis [11]. Two other studies corroborated the time dependency of radiosensitivity in hamster cells, and blood and bone marrow cells in mice [9,12].

Circadian rhythm-dependent cell proliferation has also been observed in human oral and rectal epithelium [6,13,14], as well as animal and human malignancies [15–17]. During treatment, radiation may injure normal cells that rapidly proliferate due to their heightened radiosensitivity [18], leading to radiation-induced side-effects, such as oral mucositis [19]. These side-effects may be reduced by treating patients when cells are in the radioresistant S phase. As malignant cells and normal body cells can have different circadian rhythmicity [15,17,20,21], it may be possible to deliver radiation treatment when malignant cells are relatively radiosensitive but normal body cells are relatively radioresistant to improve treatment outcomes.

Chronotherapy attempts to align treatment times for specific therapies with circadian rhythms based on experimental studies [22,23]. Chronotherapy has been studied for several chemotherapy drugs [24–26]. For instance, male colorectal cancer patients experienced reduced toxicity and improved outcomes when given chronomodulated chemotherapy with oxaliplatin, 5-fluorouracil and folinic acid [24,25].

Radiotherapy can result in debilitating side-effects that negatively affect a patient's ability to function and their quality of life, and may even result in treatment interruptions or cessation [27]. Chronotherapy could have the potential to reduce treatment side-effects, thus it is important to ascertain the role of chronotherapy in the radiation setting. We conducted a literature review to examine the correlation between the time of radiotherapy and treatment outcomes, including overall survival, treatment response and treatment-induced toxicities.

Materials and Methods

A literature search was conducted on Ovid Medline, Embase, the Cochrane Central Register of Controlled Trials and PubMed. The keywords and subject headings used included 'radiotherapy', 'circadian rhythm', 'treatment outcome', 'survival' and 'time of treatment'. Searches were limited to English only. Results were screened independently by two authors (SC, LR), first based on the title and abstract and later on the full text. Articles that assessed how the time of radiotherapy affected outcomes inclusive of treatment response, overall survival and side-effects were included. Articles that examined chronotherapy in other treatment settings or involved animal subjects were excluded. Information used by the studies to determine correlations between treatment time and outcomes, such as overall survival, local control, time frames for patient allocation, confounding variables and side-effects was extracted. Statistical information including hazard ratios, *P* values and descriptive statistics was also collected. Random effects meta-analyses were conducted if two studies reported on any one end point.

Results

Of 128 generated articles, nine were selected for inclusion [7,28–35] (Table 1).

Non-small Cell Lung Cancer Patients with Brain Metastases

Four retrospective studies investigated the relationship between the time of radiotherapy and treatment outcomes in patients with non-small cell lung cancer (NSCLC) who received stereotactic radiosurgery (SRS) for brain metastases [28–30,34]. All four studies accounted for basic demographic and treatment characteristics, including prognosis, prior whole brain radiotherapy, tumour volume and total radiotherapy dose, in addition to other factors.

A study by Rahn *et al.* [28] retrospectively examined 97 NSCLC patients who received SRS for brain metastases from 1989 to 2007. The study used a prognostic score index to confirm that there was no significant difference in prognosis. Of the 48 patients assessed for local control, the study found that 3-month local control was achieved in 97% (35/36) of patients treated in the morning compared with 67% (8/12) of patients treated in the afternoon ($P = 0.014$). Statistical analysis showed that patients treated in the morning also had improved overall survival (median survival of 9.5 months and 5 months, $P = 0.025$) and that treatment time before 12:30 contributed to better survival ($P = 0.004$, hazard ratio 2.00). The morning group also suffered less central nervous system (CNS)-related death (6% CNS, 94% systemic; $n = 47$) than the afternoon group (24% CNS, 76% systemic; $n = 34$) ($P = 0.026$) [28].

A similar study conducted by Badiyan *et al.* [29] examined 134 NSCLC patients. The study found that the median and 2-year overall survival were not significantly different between the morning and afternoon groups. However, when a cut-off time of 11:42 (identified by receiver operator characteristic analysis) was used to maximise the difference in overall survival between groups, a trend towards improved median (8.1 months and 7.3 months, $P = 0.09$) and 2-year overall survival (31% and 12%) for the morning group was found. Time of day as a continuous variable was not a significant predictor of overall survival (hazard ratio 1.038) [29].

Another study conducted by Badiyan *et al.* [30] examined NSCLC patients treated with SRS for brain metastases. The study found that 1-year local control ($P = 0.016$) and median overall survival ($P = 0.012$) were significantly higher for morning patients. Matched pair analyses were carried out, accounting for Karnofsky performance status and graded prognostic assessment score for analysis of overall

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