Prognostic factors for radiation responses in patients with cervical cancer: A nested case-control study

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Abstract

Background: The radiation response of cervical cancer is believed to be enhanced by the levels of melatonin because of its roles in the circadian cycle and cancer growth. However, several other factors can affect the radiation response, such as haemoglobin (Hb) levels and tumour size. This study examined the role of circadian rhythms and melatonin levels as prognostic factors for predicting the radiation response in patients with cervical cancer.

Methods: In this nested case-control study, good and poor radiation responses were assessed in patients treated with radiotherapy. Data on tumour size and other biological parameters were collected and analysed with the binary logistic regression using SPSS for Windows version 20.

Results: Among the 56 examined patients, most subjects had good radiation responses. Other common features of the patients were as follows: <50 years old, initial weight >50 kg, no pain before radiation, low erythrocyte sedimentation rates, normal IVP, moderate or well differentiation on pathology and non-keratinised histopathology. The combination of the time of day of radiation as a surrogate of the circadian cycle (morning vs afternoon), the initial Hb level and the clinical tumour size significantly predicted the radiation response in multivariate analysis.

Conclusion: The circadian cycle, tumour size and Hb levels may affect the radiation response in patients with cervical cancer. Further research is needed to identify more suitable prognostic factors using different radiotherapy techniques.

Background

Nature affects life through many systems, including the life cycle or biorhythms.[1–3] The circadian cycle is a biorhythmic daily period that exists in various body systems typified by a specific, intricate and harmonious pattern. The circadian cycle and cell cycle are two critical systems that were initially considered separate, but several studies have proven a close relationship between them.[4–10] This circadian pattern is evident in the concentration of the hormone melatonin.[11–13]

The levels of melatonin, which is produced by the pineal gland, are characteristic of circadian patterns, being low in the afternoon, rising gradually at night and peaking at dawn before declining in the afternoon and late afternoon.[11,12,14,15] Many studies revealed the different roles, functions and potential activities of melatonin, including a circadian biomarker, functions in the development of cancer in association with circadian disruption,[16,17] anti-oxidant activity and inhibition of cancer growth.[18–20] Regarding radiotherapy, melatonin protects cells against the side effects of radiation because it is a scavenger of OH-containing molecules.[18,22] However, it is unclear whether high melatonin levels in the blood are beneficial or harmful.

Cervical cancer originates from the cervical canal, specifically in the region of the endocervical and ectocervical squamous-epithelial junction. This area is susceptible to the transformation of neoplasia

because metaplasia physiologically occurs following the menstrual cycle. Cervical cancer remains a severe malignancy among women of reproductive age globally, being the third most common cancer in women. In developing countries, cervical cancer is the leading cause of cancer death. In the period of 2000–2010, the prevalence of cervical cancer has tended to decline. Specifically, cervical cancer fell from the most common to the second most common cancer in Indonesia, whereas its rank in the US changed from sixth to third.[21,22,23–25]

Although radiotherapy plays a vital role in the treatment of cervical cancer, the standard treatment for locally advanced cervical cancer (radiotherapy vs chemoradiotherapy) has not been established. The survival and locoregional response rates for these treatments have remained relatively low at 25–65 and 50–80%, respectively.[21,22] It is critical to remember that cancer cells are most sensitive to radiation during the G2/M phase of the cell cycle. One reason for the failure of radiotherapy is that treatment is administered when cells are in a radioresistant phase, which permits proliferation to continue. The conventional fractionation treatment method does not specify the timing of radiation exposure (morning, afternoon or evening), and there is generally no adjustment for the timing of radiation among individual patients. At present, the assessment of cell kinetics and identification of cells in the G2/M phase in patients is difficult and impractical.

It is expected that the difference in response to radiation in patients with cervical cancer differs between the morning and afternoon. From various reports, a connection among the circadian cycle, melatonin levels, the cell cycle and malignancy is suspected. It has been proven that cell growth is regulated in a circadian pattern, and melatonin levels similarly reflect circadian patterns. Melatonin has several functions in preventing cancer, and exogenous melatonin is believed to have curative effects against malignancy.[13,26–28]

To our knowledge, no study has examined the effects of melatonin levels and the timing of radiotherapy (morning vs afternoon) on the radiation response. This study aimed to identify the prognostic factors, including the circadian cycle and melatonin levels, which may affect the response to radiation in patients with cervical cancer.

Methods

This study used a nested case-control design as part of a prospective study titled, *Influence of Radiation Patterns Following Circadian Rhythm Upon Response of Radiotherapy of Uterine Cervical Cancer: Melatonin as a Radiosensitivity and Biological Marker* (unpublished data), which examined the existence of circadian effects on the radiation response and side effects in patients with cervical cancer. Melatonin levels were also measured in that study. The target population was patients with stage IIB-IIIB (FIGO) cervical cancer who received no previous treatment and who had histopathological confirmation of squamous cell carcinoma. In addition, the included patients were aged 25–70 years old with a Karnofsky Performance Status $\geq$70 and haemoglobin (Hb) levels >10 g/dL. The standard treatment in this study was radiation alone or radiation combined with chemotherapy.

We modified the WHO response criteria and identified good responses as complete or near-complete responses, whereas poor responses were defined as partial responses, progressive disease or stable disease. This study categorised the subjects according to the time of day of radiotherapy and melatonin levels to clarify the role of melatonin. The study identified potential subjects based on the completeness of medical records of patients with cervical cancer between 2012 and 2014. Poor responses cases was classified as the case group. The control group was randomised the remaining patients with complete melatonin data. To ensure good statistical power in the study we used a ratio of 1:3 between the case and control groups.

The inclusion criteria were the receipt of radiotherapy in the morning (6–8 am) or afternoon (4–6 pm) and consent to participate in the study. The exclusion criterion was the receipt of fewer than 25 fractions of a radiotherapy regimen. Melatonin was measured by ELISA using a melatonin kit (IBL-RE54021, IBL International GMBH, Hamburg, Germany) and peripheral blood sample before the start of the first session radiotherapy. All other possible confounding variables were noted and included in the analysis.

Radiotherapy was administered using the departmental protocol, which was five times a week followed by brachytherapy once a week for three weeks. The response to radiation was assessed on the last day of external radiation, every week during brachytherapy and four weeks after the completion of brachytherapy.

The research was conducted at the Radiotherapy Department Cipto Mangunkusumo Hospital in cooperation with the Department of Obstetrics and Gynecology of FMUI-Cipto Mangunkusumo Hospital, Integrated Laboratory of Medical Faculty FMUI-Cipto Mangunkusumo Hospital and Clinical Pathology Installation of Dharmais Cancer Hospital. The study was conducted between March 2012 and August 2014.

Other investigated variables that might contribute to response included age, time of radiotherapy (measured at 6–8 am for morning and 4–6 pm for the afternoon), overall treatment time, Hb level and the pathological findings. The potential bias of this study was the time of the radiotherapy. This potential bias was minimised with the radiation time alignment by defining the receipt of radiation during or up to 2 h after the allocated time. The instruments used to note the possible confounding variables were based on the patients' medical records. Then, bivariate analysis was performed, and variables significant at $p < 0.25$ were included in multivariate analysis. The statistical analysis used binary logistic regression using SPSS 20.0. to find the model of prognostic factors for radiation responses in patients with cervical cancer.

Results

Subject characteristics of the two groups

Based on the study objectives, the complete medical records of 71 patients with cervical cancer were collected between 2012 and 2014. Among these 71 patients, 14 with poor responses comprised the case

group. The control group consisted of 42 patients who had good responses and were identified from the randomised remaining patients with complete melatonin data.

The clinical and laboratory data of the patients, including age, initial weight and the presence of pain are presented in Table 1. Excluding tumour size (p = 0.002), no significant differences were observed between patients with poor radiation responses and those with good responses.

Potential factors affecting the radiation response

Bivariate analysis was conducted to identify variables significantly predictive of the response to radiation. As shown in Table 2, tumour size (p = 0.002) and transfusion during chemotherapy (p = 0.004) were most significantly associated with the response to radiation. Other variables that were predictive of response included the time of radiation (p = 0.045), pre-radiation melatonin level (p = 0.122), differentiation status (p = 0.119), post-treatment body weight (p = 0.027), initial Hb level (0.058), erythrocyte sedimentation rate (p = 0.097), IVR (p = 0.070) and the receipt of transfusions before radiation (p = 0.080).

Time of radiation affects the radiation response

In this model, decreased Hb levels (adjusted odds ratio [OR] = 8.70, 95% confidence interval [CI] = 1.45–164.65, p = 0.023), the initial Hb level (OR = 13.53, 95% CI = 2.22–3212.46, p = 0.017) and clinical tumour size (OR = 8.85, 95% CI = 1.11–52.19, p = 0.039) were associated with the response to radiotherapy (Table 3). The pre-radiation melatonin level and changes of Hb levels did not predict response.

The results of the multivariate analysis were based on this model, and Nagelkerke's R^2 value for the model was 0.441. There were no multicollinearity assumptions among the independent variables based on the correlation matrix.

Discussion

The demographic characteristics of patients included in this study accorded with those published previously. Specifically, most women were less than 50 years old.

It has been proven that the differential expression of genes between morning and night is regulated by several CLOCK genes that work in accordance with circadian rhythms. The concept of circadian-related radiotherapy aims to deliver radiation with maximum synergy with the radiosensitive atmosphere provided by the time system inside and outside the body. In research using zebrafish, Peyric[31] demonstrated the regulation of the cell cycle by the circadian clock. The M phase of the cell cycle occurs rhythmically and under circadian control.[31] This could explain the better radiation response in the morning because the probability of cancer cell death is higher when cells are in the G2M phase.

Bjarnason[5] reported that mucous cells and human skin cells mainly divide in the evening between 6:00 pm to 12:00 am. Klevec,[32] Lakatua[33] and dan Smaaland[34] found that tumour cell division occurs at an opposite time as healthy cell division. Based on these results, it can be concluded that cancer cells are more likely to be in the G2/M phase in the between 6:00 pm and 12:00 am, whereas normal cell proliferation occurs in the afternoon.

Prior studies reported the role and function of melatonin in cancer in the absence of radiation. Quoting Vijayalaxmi,[20] Georgiou suspected a role of pineal gland products in the development of cancer, especially melatonin, which inhibited carcinogenesis in an *in vitro* study using MCF-7 breast cancer cells. This hormone was specifically demonstrated to increase the number of apoptotic cells and inhibit metastasis.[35] The cancer-inhibiting effects of melatonin are apparently influenced by various factors, including the melatonin concentration in culture media, the pattern of melatonin administration, the oestrogen receptor status,[36,37] growth hormone levels in culture media[36] and the rate of cell proliferation. Melatonin inhibits tumour transduction signals and the metabolic activity of cancer cells through MT1 receptor activity.

The results of this study illustrated that Hb levels affect the radiation response, in line with prior findings that anaemia and decreased Hb levels are prognostic indicators. Decreased Hb levels result in hypoxia, which makes cancer cells resistant to radiation. Oxygen increases radiosensitivity through direct and indirect effects.

The tumour volume is an important factor for the success of cervical cancer treatment. Lee et al.[38] assessed the outcomes of 75 patients with stage IIB cervical cancer treated with chemoradiotherapy using MRI, and overall survival was strongly related to the tumour volume. Specifically, the 5-year overall survival was 75% for patients with tumour volumes of 2.5–10 mL, 70% for patients with tumour volumes of 10–50 mL and 48% for patients with tumour volumes exceeding 50 mL. This is consistent with the results of the present study that a smaller tumour size increases the success of therapy.

The tumour response was measured after 20–25 fractions of radiation, immediately after radiation and 2–4 weeks after radiation. This is in accordance with Mayr et al.,[40] who performed MRI in 68 patients with advanced-stage IB2–IVB cervical cancer before radiation, after 10–12 fractions of radiation, after 20–25 fractions of radiation and 1–2 months after the completion of radiation. From their research, the best time to perform MRI in the context of outcomes, namely the tumour regression rate, was after 25 fractions of radiation. The research team found that this measurement most accurately predicted local control (84% vs. 22%, $p < 0.0001$) and disease-free survival (63% vs. 20%, $p = 0.0005$).

In this study, the examination was performed at a time close to that of radiation. In patients irradiated in the morning, blood collection occurred at 6:00–08:00 am, compared with 4:00–6:00 pm in patients irradiated in the afternoon. For patients irradiated in the morning, based on the literature and preliminary research, it can be predicted that the melatonin concentration 2 h prior to radiation is high even though its levels were already sharply declining. This phenomenon does not apply to patients irradiated in the

afternoon. Although the multivariate analysis did not reveal that melatonin levels affected clinical responses, because the hormone influences variables that meaningfully predicted response, it is possible that melatonin indirectly contributes to good responses. It is also possible that the combination of radiation in the morning and melatonin levels jointly influence the response to radiation.

The bias of the study might become from the Haemoglobin level measurement, which was not featured the patient clinical status since its concentration did not consider the provided blood transfusion.

The application of the study results might be generalised to the cervical cancer patients of stage IIB-IIIB (FIGO) who are indicated to have the radiotherapy as one of the inclusion criteria of the study .

Conclusion

The circadian cycle, large tumour size and Hb levels may affect the response of cervical cancer to radiation. Large tumour size and decreased Hb levels are considered to increase resistance to radiotherapy. Further research is needed to identify the optimal treatment for patients with these radioresistant features. To achieve a better result, more sophisticated radiotherapy techniques such as IMRT, the use of hyperfractionation, the use of radiotherapy combination with chemosensitisers and other methods should be applied. Practical methods for examining melatonin levels in urine are needed for further research. More accurate evaluations of the initial Hb level and tumour volume will be beneficial for designing treatment strategies and determining prognosis.

Declarations

Ethics approval and consent to participate

This research was a part of previous prospective study that was approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia (27/PT02.FK/ETIK/2010). The study subjects completed and signed the informed consent after they have informed and understood about the study.

Consent for publication

All authors were involved in the manuscript writing and approved to publish this study

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

There are no conflicts of interest to declare.

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This study was conducted using private funding from the authors.

Authors' contributions

1. I R; Conceptualizing, Design arrangement, Data collecting, Data analysis, Drafted the manuscript, Finalised the manuscript
2. S S; Conceptualizing, Design arrangement, Supervision, Finalised the manuscript
3. L N; Conceptualizing, Design arrangement, Supervision, Finalised the manuscript
4. M M; Conceptualizing, Design arrangement, Data analysis, Drafted the manuscript, Finalised the manuscript
5. A R H: Conceptualizing, Design arrangement, Supervision, Finalised the manuscript
6. S So; Conceptualizing, Finalised the manuscript
7. N C S; Conceptualizing, Finalised the manuscript
8. S I W; Conceptualizing, Design arrangement, Supervision, Finalised the manuscript

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Abbreviations

CI, Confidence Interval; ELISA, The Enzyme-linked Immunosorbent Assay; ESR, Erythrocyte Sedimentation Rate; FIGO, The International Federation of Gynecology and Obstetrics; FMUI, Faculty of Medicine Universitas Indonesia; Hb, Haemoglobin; IMRT, Intensity Modulated Radiation Therapy; IVP, Intravenous Pyelogram; MCF-7, Michigan Cancer Foundation-7; MRI, Magnetic Resonance Imaging; OH, Hydroxide; OR, Odds Ratio; OTT, Overall Treatment Time; SPSS, Statistical Package for the Social Sciences; US, United States; WHO, World Health Organization

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Tables

Table 1. Subject characteristics

Variable		Radiation response n (%)		p
		Poor (n = 14)	Good (n = 42)	
Age	≤50 years	8 (22.9)	27 (77.1)	0.633[a]
	>50 years	6 (28.6)	15 (71.4)	
Initial weight	≤50 kg	2 (10.5)	17 (89.5)	0.106[b]
	>50 kg	12 (32.4)	25 (67.6)	
Pain before radiation	No	8 (21.6)	29 (78.4)	0.518[b]
	Yes	6 (31.6)	13 (68.4)	
Clinical tumour size	Small (≤40 cm^3)	2 (7.1)	26 (92.9)	0.002[a]
	Large (>40 cm^3)	12 (42.9)	16 (57.1)	
Initial Hb level	High	10 (20.4)	39 (79.6)	0.058[b]
	Low	4 (57.1)	3 (42.9)	
ESR	Low	10 (20.8)	38 (79.2)	0.097[b]
	High	4 (50)	4 (50)	
IVP	Normal	11 (24.4)	34 (75.6)	1.000[b]
	Abnormal	3 (27.3)	8 (72.7)	
Pathological differentiation	Moderate/well	9 (20)	36 (80)	0.119[b]
	Poor/moderate	5 (45.5)	6 (54.5)	
Pathological keratinisation	No	13 (25)	39 (75)	1.000[b]
	Yes	1 (25)	3 (75)	

[a] = chi-squared test; [b] = Fisher's exact test. Hb, haemoglobin; ESR, erythrocyte sedimentation rate.

Table 2. Prognostic factors affecting the radiation response after brachytherapy

Variables		Clinical response (N = 56)		p
		Good (%) (n = 42)	Poor (%) (n = 14)	
Time of radiation	Morning	25 (59.6)	4 (28.6)	**0.045[a]**
	Afternoon	17 (40.5)	10 (71.4)	
Chemotherapy	Yes	23 (54.8)	11 (78.6)	0.356[b]
	No	19 (45.2)	3 (21.4)	
Pre-radiation melatonin level	High	25 (59.5)	5 (35.7)	**0.122[a]**
	Low	17 (40.5)	9 (64.3)	
Pathological keratinisation	Yes	3 (7.1)	1 (7.1)	1.000[b]
	No	39 (92.9)	13 (92.9)	
Differentiation status	Moderate/well	36 (85.7)	9 (64.3)	**0.119[b]**
	Poor/moderate	6 (14.3)	5 (35.7)	
Initial body weight	>50 kg	25 (59.5)	12 (85.7)	0.106[b]
	≤50 kg	17 (40.5)	2 (14.3)	
Body weight after treatment	>50 kg	22 (52.4)	12 (85.7)	**0.027[a]**
	≤50 kg	20 (47.6)	2 (14.3)	
Reduction of body weight ≥5 kg	No	23 (54.8)	4 (28.6)	0.089[a]
	Yes	19 (45.2)	10 (71.4)	
Initial Hb level	High (>10 g/dL)	39 (92.9)	10 (71.4)	**0.058[b]**
	Low (≤10 g/dL)	3 (7.1)	4 (28.6)	
ESR	≤40 mm/jam	38 (90.5)	10 (71.4)	**0.097[b]**
	>40 mm/jam	4 (9.5)	4 (28.6)	
IVP	Normal	26 (89.7)	19 (70.4)	**0.070[a]**
	Abnormal	3 (10.3)	8 (29.6)	
Tumour size (clinically)	Small (≤40 cm^3)	26 (61.9)	2 (14.3)	**0.002[a]**
	Large (>40 cm^3)	16 (38.1)	12 (85.7)	
Reduction of Hb	No	10 (34.5)	6 (22.2)	0.310[a]
	Yes	19 (65.5)	21 (77.8)	

Pre-radiation transfusion	No	29 (69.0)	6 (42.9)	**0.080[a]**
	Yes	13 (31.0)	8 (57.1)	
Transfusion during radiation	No	30 (71.4)	4 (28.6)	**0.004[a]**
	Yes	12 (28.6)	10 (71.4)	
Alignment with radiation time	Yes	36 (85.7)	12 (85.7)	1.000[b]
	No	6 (14.3)	2 (14.3)	
OTT	On-time	29 (69.0)	9 (64.3)	1.751[b]
	Not on time	13 (31)	5 (35.7)	

[a] = chi-squared test; [b] = Fisher's exact test. Hb, haemoglobin; ESR, erythrocyte sedimentation rate

Table 3. Factors affecting the response to radiation

Variable		**Clinical response (N = 56)**		**Adj. OR**	**95% CI**
		Good (%) (n = 42)	**Poor (%) (n = 14)**		
Radiation Time	Morning	25 (59.6)	4 (28.6)	8.70	(1.25–60.73)
	Afternoon	17 (40.5)	10 (71.4)		
Pre-radiation melatonin level	High (³13pg/ml)	25 (59.5)	5 (35.7)	4.78	(0.92–24.67)
	Low (<13 pg/ml)	17 (40.5)	9 (64.3)		
Initial clinical tumour size	Small (≤40 cm^3)	16 (55.2)	12 (44.4)	8.85	(1.45–54.16)
	Large (>40 cm^3)	13 (44.8)	15 (55.6)		
Initial Hb level	No	10 (34.5)	6 (22.2)	13.52	(1.38–132.25)
	Yes	19 (65.5)	21 (77.8)		
Constant				0.037	

Nagelkerke 5)R^2 = 0.441, *Hosmer Lemeshow test* p = 0.803. Adj. OR, adjusted odds ratio; CI, confidence interval; Hb, haemoglobin.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 1PrognosticCaCervicRadioOncologystrobechecklist.docx