

### Chronobiology in Head and Neck Cancer

*“There is vast potential to explore chronobiology of head and cancer”*



Dr. Akhilanand Chaurasia  
King George's Medical university  
India

#### COLUMN ARTICLE

#### Background

Mammalian circadian rhythms result from a complex organization involving molecular clocks within nearly all “normal” cells and a dedicated neuroanatomical system which coordinates the so-called “peripheral oscillators.” The core of the central clock system is constituted by the suprachiasmatic nuclei that are located on the floor of the hypothalamus. The rest-activity rhythm is a reliable marker of the circadian system function in both rodents and man. This circadian organization is responsible for predictable changes in the tolerability and efficacy of anticancer agents, and possibly also in tumour promotion or growth. Our understanding of the mechanisms of circadian rhythm generation and coordination processes has grown rapidly over the past few years. In parallel, we have learnt how to use the predictable changes in cellular metabolism or proliferation along the 24h time scale in order to improve treatment outcome for a variety of diseases including cancer. The chronotherapeutics of malignant diseases has emerged as a result of a consistent development ranging from experimental, clinical and technological prerequisites to multicenter clinical trials of Chronomodulated delivery schedules. Indeed, large dosing-time dependencies characterize the tolerability of anticancer agents in mice or rats, a better efficacy usually results from treatment administration near the least toxic circadian time in rodent tumour models. Programmable in

time multichannel pumps have allowed to test the chronotherapy concepts in cancer patients and to implement Chronomodulated delivery schedules in current practice. Improved tolerability and/or better antitumor activity have been demonstrated in randomized multicenter studies involving large patient cohorts. The relation between circadian rhythmicity and quality of life and even survival has also been a puzzling finding over the recent years.

#### Healthy tissues

Twenty-four-hour changes in cellular proliferation and metabolism also were investigated in healthy tissues of tumour-bearing animals. All studies suggest that the alterations of circadian rhythms appear progressively and vary as a function of the experimental model however its chronology remains to be defined. For instance, rhythms of DNA synthesis were studied in various organs of mice bearing a transplanted Lewis lung carcinoma. In all organs, the changes observed were more pronounced in mice with 10-day-old and 14-day-old tumours than in mice with 6-day-old tumours. Nevertheless, in bone marrow a second peak of DNA synthesis already appeared for mice with a 6-day-old tumour compared with controls. This peak was found to be sharper and occurred earlier for the animals with a 10-day-old tumour. Finally, ultradian rhythms characterized DNA synthesis of animals bearing 14-day-old tumours. In a diethyl nitrosamine (DEN)-induced rat liver carcinoma model after a two-thirds partial hepatectomy,

the circadian rhythms of both proliferation and cholesterol 7-hydroxylase activity were slightly dampened after a 2-week treatment and were abolished thoroughly after a 6-week exposure to DEN. Nearly normal corticosterone rhythms were observed in Wistar rats 1 week after the cessation of a 6-week oral administration of DEN however mean levels of plasma corticosterone were diminished drastically and circadian variations were found to be lacking 3 months later when neoplastic nodules were growing. Changes in body temperature rhythms also were reported. Both the 24-hour mean and amplitude of the rectal temperature were found to be decreased in Fisher rats transplanted with methylcholantrene-induced sarcomas as well as in Holtzman rats bearing Walker 256 carcinomas compared with controls. Conversely a 24-hour rhythm in intraperitoneal temperature, as assessed by telemetry in immunocytoma bearing rats persisted for 7 weeks, with only a slight advance in phase noted. Circadian rhythmicity was suppressed only during the week preceding death.

### Tumour tissues

As early as 1953, daily variations in the mitotic index of human mammary carcinoma and squamous or basal cell carcinoma were described with inter individual variations reported. Reanalysis of these data validated a circadian rhythm in the group of 6 women with breast carcinoma with a maximum near 3 p.m. Ultradian rhythms were found in the group of 31 patients with squamous or basal cell carcinoma. Progressive dampening of skin mitotic activity also was suggested in patients with actinic keratoses or skin cancer. The cell cycle-related parameters of tumour cells and normal mesothelial cells were studied around the clock within the peritoneal lavage fluid from 30 patients with ovarian carcinoma. A circadian maximum in the DNA synthesis of both diploid and aneuploid tumour cells was found between noon and 4 p.m. This time was nearly 12 hours out of phase with the peak of DNA synthesis in mesothelial cells. Ultradian rhythms with 8-hour and 12-hour periods also were documented in the aneuploid tumour cell population. Twenty-four-hour changes were described for DNA synthesis in malignant lymph nodes from 24 patients with non-Hodgkin lymphoma. The maximum occurred near midnight whereas the peak of the S phase in the bone mar-

row of healthy subjects usually was found between noon and 4 p.m. It is interesting to note that when patients were classified according to tumour stage according to the Ann Arbor Classification System, a circadian rhythm in DNA synthesis was validated in the group of patients with early-stage tumour, but not in the group of patients with Stage IV lymphoma. This observation suggested a link between disease stage and circadian rhythm alteration. Noteworthy observations regarding breast cancer in skin surface temperature indicated that circadian rhythms persisted on the surface of breast tumours that were slow-growing and well differentiated. However, rhythms were dampened with the maximum occurring 6 hours earlier than in the noncancerous breast. Conversely, fast-growing, poorly differentiated tumours displayed a shortening in the period of tumour temperature rhythm. Another study in 14 patients also reported a phase advance of approximately 6 hours in the rhythm of skin temperature of the cancerous breast compared with the contra-lateral one. In view of above studies, there is vast potential to explore chronobiology of head and cancer. A number of studies can be conducted to evaluate the effect of circadian rhythm and its effect on management of Head and Neck Cancer.

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