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Original Article

Radiotherapy scheduling using prime numbers

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Abstract

Background: The optimal delivery of radiation therapy to achieve maximum tumour cell kill while limiting damage to normal tissues underlies any radiation therapy treatment protocol. The biological effectiveness of radiation therapy is closely related to cellular reproductive activity. The scheduling of dose fraction to a time where actively dividing cells are at their most radiosensitive stage (RS) has potential to enhance therapeutic efficacy.

Materials and methods: A prime number is a natural number >1 whose only divisors are 1 and the number itself.

Purpose: We propose that the use of prime numbers in the scheduling of radiotherapy treatments could maximise biological effectiveness by facilitating the irradiation of the greatest number of cells at their most RS stage, and ultimately improve the therapeutic ratio of radiation therapy.

Conclusions: The theoretical clinical implementation of this concept into the scheduling of radiation therapy is discussed.

Keywords: prime numbers; radiation; scheduling

INTRODUCTION

The optimal delivery of radiation therapy to achieve maximal tumour cell kill while minimising normal cell damage to avoid treatment-related acute side effects and late morbidity remains the holy grail of modern radiation therapy. The radiation doses prescribed in current practice are based on the clinically determined radiation tolerance of the surrounding normal tissues, and a balance between normal tissue toxicity and tumour control is often required. A number of factors can influence cellular responses including dose, fractionation, the volume irradiated and individual variation in radiation sensitivity.[1] These factors are continuously challenged as means to improve treatment outcomes. In recent years, technological advances such as 3D conformal radiation therapy, intensity-modulated radiation therapy and, more recently, volumetric-modulated arc therapy have helped reduce the volume of normal tissues irradiated, allowing for the total dose to be increased and for radiation therapy to be delivered in higher than conventional

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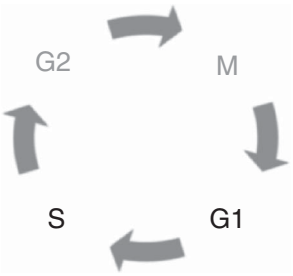


Figure 1. Schematic representation of the cell cycle.
Note: The cell cycle has four phases: G1, S, G2 and M. Cells are most radiation sensitive during the G2 and M phases.

fractionated doses.[2] This has led to improved tumour control probability in a number of cancer types such as head & neck and prostate cancer.[3,4]

Waiting time is a major problem in radiation therapy and may have an impact on tumour control.[5,6] Algorithms facilitating the prioritisation of patients[7,8] and out-of-hours appointments[9,10] were reported to minimise delays. The introduction of short-course radiation therapy regimen or hypofractionated radiation therapy regimen was proposed as an alternative to conventional treatments, to spare resources and improve compliance in certain categories of patients such as those with poor prognosis.[11,12] Short-course regimens have the potential to increase patient throughput and reduce costs.[13]

Over a century ago, Bergonié and Tribondeau observed in epithelial tumours that the radiosensitivity of a cell is directly proportional to its reproductive activity[14] and proposed that radiation therapy should ideally be administered to a cell whenever it is at the peak of its reproductive activity. It is now well established that actively dividing cells are the main target for radiation-induced cell kill, with the survival of cancer stem cells identified as a key factor in radiation therapy treatment failure.[15] The reproductive activity of a cell is represented by the cell cycle. The cell cycle is an ordered set of events culminating in the production of two identical daughter cells and is composed of four phases: G1, S, G2 and M (Figure 1). Failure of irradiated cells to arrest their cell cycle and repair radiation-induced damage is associated with increased radiosensitivity.[16] In addition, the survival of irradiated cells is cell cycle phase dependent: cells are most radiosensitive (RS) during the M phase (in particular metaphase) and the G2 phase of the cell cycle.[17–19] Irradiating cancerous cells during an RS phase of their cell cycle would thus produce the best possible results in terms of cell kill.

It is, however, not possible in practice to identify what could be termed a 'best time to treat': first, it cannot be assumed that all cancerous cells are at the same stage of their cell cycle at a particular moment in time. Second, it also cannot be assumed that all cancerous cells have the same cell cycle duration, and finally it is not currently possible to determine which phase of the cell cycle a cell is in at a particular moment in time. Novel molecular imaging techniques may assist in the future; however, whereas manganese-enhanced magnetic resonance imaging facilitated the detection of cell cycle arrest following irradiation,[20] to date novel positron emission tomography tracers such as 3'-deoxy-3'[(18)F]-fluorothymidine, [(18)F]-FLT are showing debatable benefit in the monitoring of cell proliferation in malignant tumours.[21] Nonetheless, chronomodulated administration of chemotherapy showed significant increase in overall survival in patients with advanced colorectal cancer[22–24] and this strategy should be explored in radiation therapy.

An *optimal outcome* to a course of radiation therapy treatment can be defined as an instance where the total number of cancerous cells, which are killed over the duration of the treatment, is maximised. The effectiveness of radiotherapy is thus optimal when every cancerous cell is irradiated (at least) once during an RS phase of its cell cycle. This follows from the observation that the first time a *set* of cancerous cells with the same cell cycle are irradiated during an RS phase, the highest possible instance of cell death is produced (it is not assumed that all cells die when irradiated at their most RS state, just the most possible). It is therefore desirable to irradiate as many *sets* as possible of cancerous cells, which are at the same stage of their cell cycle, during an RS phase of their cycle. As the overall desired outcome is to maximise the total number of cancerous cells that are killed, then each *set* of cells that are at the same

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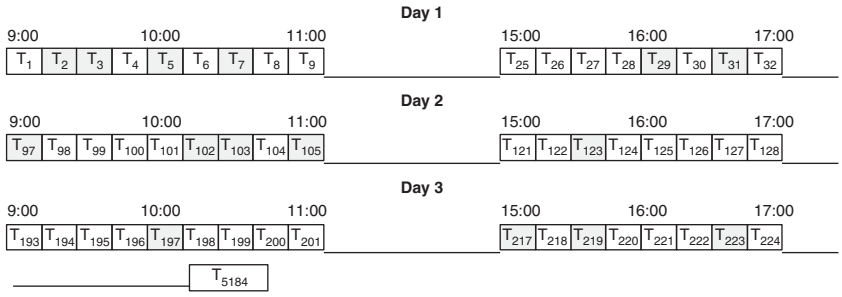


Figure 2. The approach to prime number-driven scheduling of radiation therapy treatment.
Notes: The initial time $\boldsymbol{T_1}$ *is chosen on Day 1 of treatment, the final time unit is defined as the last time unit in the last day of treatment. The total time can be divided into equal time units of 15 minutes in duration each. Each time unit is labelled with a number. Treatment should be delivered in prime numbered units only (grey boxes). Several suitable time units are available each day.*

stage of their cell cycle and at their most RS stage should be irradiated. By irradiating at one *set* of cells' most RS stage, only once, then the number of these cells, which are killed, is maximised. As a result, the probability of cell kill and hence the outcome of any given radiotherapy treatment could be enhanced.

A prime number is a natural number >1 whose only divisors are 1 and the number itself. Equivalently, a natural number is prime when it cannot be expressed as a multiple of any smaller natural number except the number one. We propose that a prime number-based probabilistic approach may facilitate the optimised delivery of radiation therapy to a time where cancerous cells are at their most vulnerable.

THE APPROACH

The overall duration of a fractionated radiation therapy treatment can be defined as a continuous series of equal time intervals, denoted T_i, where each interval is equal to the duration of a single treatment session. Using this structure, each time unit T_i can be numbered sequentially: T_1, T_2, …, T_n where $n =$ (number of time units per day) × (duration of full course of treatment in days).

For instance, for a treatment schedule of 40 sessions of 15 minutes each, prescribed over the course of 8 weeks (overall treatment time: 54 days), each day can be divided into 24 hours × 4 sessions/hour = 96 time units. The treatment starts on a Monday, there are no treatments on Saturdays and Sundays and there are no other days in which treatment sessions are not scheduled (should public holidays, etc. fall in this 8-week period they are treated as weekend days). The time units are labelled T_1, …, T_{5184} where the final treatment takes place in or before the time unit T_{5184} where $5184 = 96 \times 54$ (Figure 2).

The initial time unit T_1 is chosen and *may* be fixed as the first appointment given to the patient. Assuming that the number of (cancerous) cells in each phase of the cell cycle is constant over time, and that every cell has a cell cycle length of at least twice the duration of a treatment session, then the individual treatment session which is to take place each day of the treatment is scheduled to take place in a time unit T_i (contained in the range of time units for each respective day) where the label is a prime number. Prime numbers are not that rare, and therefore there may be many times in the 1 day that are prime number labelled time units but only one is chosen (or two, in the case of hyperfractionation), or none if that day is Saturday, Sunday or public holiday. By scheduling each treatment at a prime number labelled appointment time, no cell will be irradiated at the same point in its cell cycle, which it has been irradiated at before, and the overall biological efficacy of the treatment is likely to be optimum.

In our example, assuming that T_1 is 09·00–09·15 on Day 1, then the first five treatments could take place at the following prime-numbered time points: T_1 i.e. 09·00–09·15 on Day 1; T_{97} i.e. 09·15–09·30 on Day 2; T_{193} i.e. 09·15–09·30 on Day 3; T_{293} i.e. 10·15–10·30

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on Day 4; T_{389} i.e. 10·15–10·30 on Day 5 (1, 97, 193, 293 and 389 are all prime numbers).

DISCUSSION

The therapeutic window of any radiation therapy treatment is dependent on the response of tumour and normal tissue.[25] To improve it, novel approaches have been designed to either enhance tumour cell kill without unacceptable normal tissue toxicity or facilitate resistance of normal tissue to radiation exposure.[26] This approach is unlikely to affect normal tissue toxicities. As normal tissue will generally have longer cell cycles than tumour tissues,[27,28] there should be less chance of irradiating a healthy cell during an RS phase of their cycle. Furthermore, this method ensures that radiation is never administered (in practice) at the same point in a cell's cycle and, as a result, the radiation dose received throughout the cell cycle phases in the surrounding healthy tissue should be equally distributed, ultimately limiting damage to healthy normal cells.

It is envisaged that a simple computer program would be used to implement the prime number radiation therapy scheduling approach. This would require input of treatment session duration, overall treatment duration, preferred start date (or range of preferred start date) and a band of preferred daily treatment times (earliest to latest preferred treatment time). The program would then, taking into account availability on the treatment unit, schedule daily treatments in available prime number-labelled time units within the preferred band of daily treatment times and provide the user with a treatment session schedule and an optimal start date.

A rudimentary randomised clinical trial, associated with limited ethical issues, could easily be carried out in any radiation therapy department with more than one treatment unit. Patients receiving the same type of treatment, matched for age, gender, histology and any other clinical parameters that may bias treatment outcome should then be assigned alternatively (chronologically) to Treatment Room A and Treatment Room B. The scheduling of treatment on Machine A would be conducted using the aforementioned prime number-based scheduling method, using custom-designed scheduling software. The scheduling on Machine B would be conducted using the method currently used by the department. Relevant treatment outcome data collected on follow-up on both patient cohorts would be analysed using standard statistical methods. Patient compliance would need to be monitored.

CONCLUSION

Radiotherapy treatment scheduling using prime numbers may represent a simple approach to exploit the cell-cycle dependence of radiosensitivity and assist novel treatment approaches aiming to improve current treatment outcomes. Prime numbers not being that rare means that several time units will be available each day, every day. It is therefore unlikely that this approach will change the daily throughput of treatment units or be affected by treatment interruptions. Potential limitations to this approach, however, include patient compliance to slight variations in daily appointment times. This approach should be explored in the clinical setting.

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Conflicts of Interest

The authors declare no conflicts of interest.

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