OPTIMIZATION OF RADIOTHERAPY SCHEDULES IN HEAD AND NECK CANCER

THESIS
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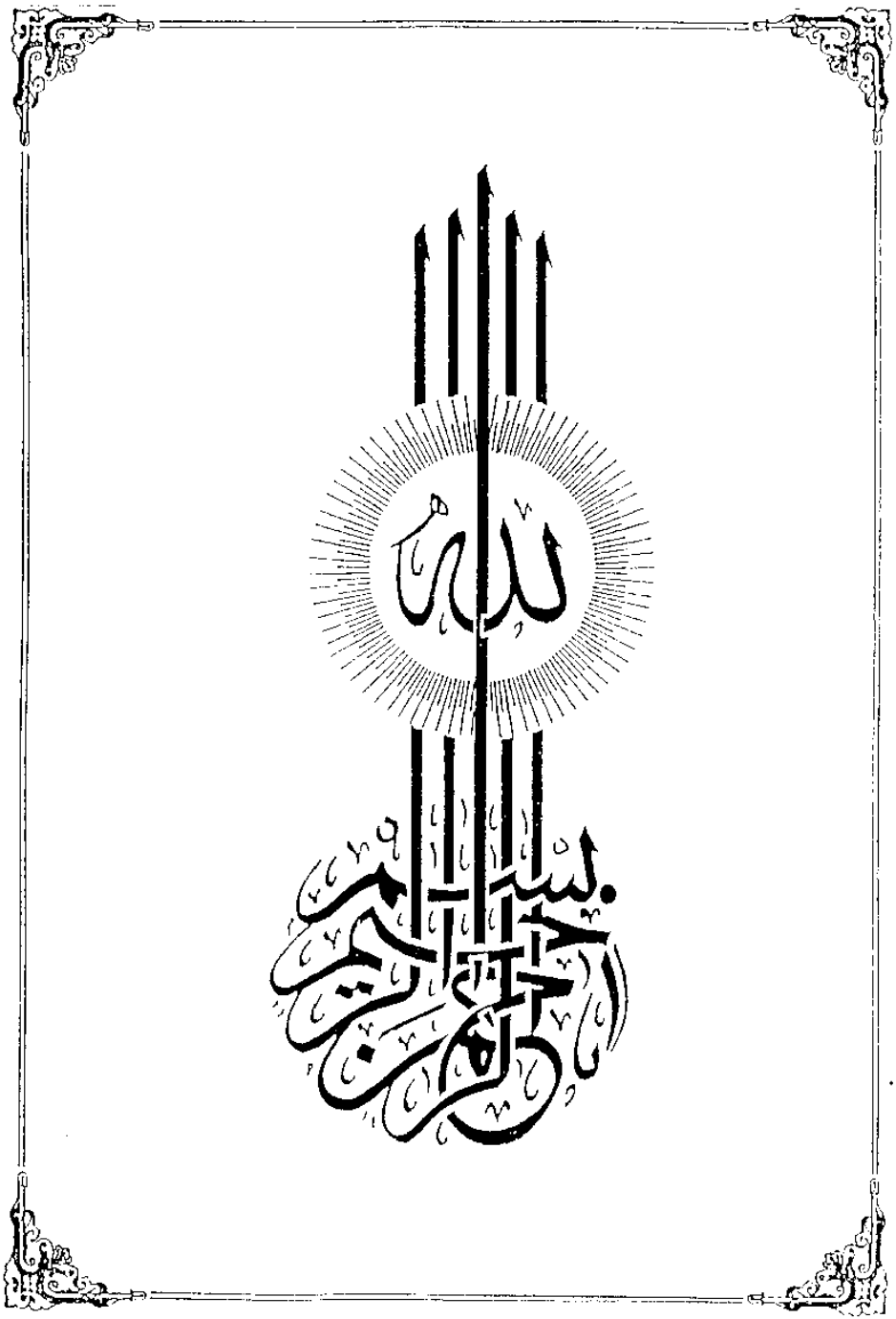

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TO MY HUSBAND AND MY FAMILLY

CONTENTS

LIST OF ABBREVIATIONS

- PLD : Potentially lethal damage.
- TCD_{50}: Total dose required to control 50% of tumours
- L-Q : Linear quadratic model.
- α : Initial slope of cell survival curve. unit is Gy^{-1}
- β : Probability of effect being produced by two tracts. unit is Gy^{-2}.
- α/β : Dose at which the linear and quadratic terms contribute equally to the effect.
- $S_R(t)$: Represent gain of cells due to repopulation of surviving cells.
- $S_K(t)$: Loss of cells due to radiation cell killing.
- B.E.D: Biologically Equivalent Dose.
- T_{pot} : Potential doubling time.
- AJCC : American Joint committe on cancer.
- A.H.F: Accelerated hyperfractionation.
- C.F : Conventional fractionation.
- S.S.D: Source to skin distance.
- C.R : Complete response.
- P.R : Partial response.
- N.R : No Response.
- Gy : Gray.
- cGy : Centigray.
- T.R : Therapeutic ratio.
- LET : Linear energy transfer.

INTRODUCTION

INTRODUCTION AND AIM OF WORK

The local control rates achieved with conventionally. Fractionated external beam radiation therapy in treatment of advanced cancer of head and neck regions are quite low and Justify investigations of alternative approaches. Different investigators have attempted to optimize the radiation therapy schedules through variations in fraction size, number of fractions. Overall treatment time and total dose, by use of unconventional fractionation.

The aim of our work is to select an optimum schedule from the published schedules which gives the highest Therapeutic ratio using L-Q model with time factor for treating locally advanced and recurrent head and neck cancer, and to apply this schedule clinically to assess for its efficiency, as regards the local control rate and normal tissue complications and to compare the results with those obtained by using conventional fractionation. This will be achieved by treating 2 groups of patients. One group treated with the selected schedule and other group with the conventional schedule.

REVIEW

REVIEW OF LITERATURE

BIOLOGICAL CONSIDERATION IN DOSE FRACTIONATION :

There is a great increase of the knowledge of biology of dose fractionation during the past twinty five years.The 4 Rs of radiobiology are:-Repair of sublethal damage,repopulation, redistribution and reoxygenation are all factors contributing to differentiate in fractionated dose response between various normal tissues and tumours.

In clinical radiobiology, there are three general types of tissues to be considered :

1 - Early Responding Tissues :

Such as epithelial surfaces, mucous membranes and haemopoetic system. These tissues are rapidly turning over and the functional cell compartments manifest radiation damage soon after exposure.

2- Slowly Responding Tissues :-

Such as spinal cord, kidney, dermis which have low cell turn over rate and a functional parenchymal cells that retain the ability to revert to a reproductive function in the event of tissue loss, these tissues manifest more delayed radiation injuries which are considered as late effects, having their onset months or years after therapy has been completed.

3- Tumours :- with a spectrum of response rates, most show early response.

I - Repair :-

Kellerer and Rossi in 1972 assumed that lesions responsible for the biological effect of radiation were produced as a result of interaction between sublesions. They assumed that at least two sublesions were required and that these could be produced as a result of the passage of one or two radiation tracts through the target. If the two critical sites within the cell are simultaneously damaged this lead to death of the cell, if only one target doublet is damaged, the cell may be considered as sublethaly damaged. There is abundant radiobiological evidence that such sublethal damage is capable of being repaired by the cell.

Although the cells of the three types of tissues repair radiation inJury, clinical and laboratory studies suggest that they vary in their capacities for such repair. The slowly responding tissues show larger capacity to recover sublethal damage while the acutely responding tissues have a faster repair kinetics. (Ang et al.,1985).

A factor of great importance is the repair time, i.e. the repair completion time. Ang et al., in 1987 and Stewart et al., in 1987 pointed out that the repair of sublethal damage is essentially complete in at least 6 hours, so that for fractionation schedules using two or more daily fractions, the interfraction time must be at least 6 hours to allow for complete repair to occur and to prevent

cumulative injury to result from incomplete repair if the doses are too closely spaced.

A second type of repair mechanism is the repair of potentially lethal damage (PLD) demonstrated by the increased survival of cells allowed to rest in a non proliferative state several hours after irradiation, before being assayed for clonoginic survival. Differences in the capacity to repair potential lethal damage between different tumour cell lines has been suggested by Weichselbaum and his colleagues in 1982 as an explanation for the observed differences in radiocurability of different tumour cell types. Repair of PLD may also be an important factor in determining the tolerance of slowly responding tissues to radiotherapy, since the major determinant of whether an irradiated cell can repair PLD is its proliferative status, then slowly responding normal tissues may be spared some radiation injury through this mechanism. (peters and Ang 1986).

A slow repair process has been demonstrated in mouse lung and in mouse capillaries, the time scale for this repair is about one week which is much longer than that of repair of sublethal damage (Field et al., 1976).

II- Repopulation :

The repopulation of cells after radiation may occur as a result of migration of cells from outside the treatment field

as well as reproduction by surviving cells within the treatment field. Repopulation may occur in three ways, firstly by shortening of cell cycle time, secondly recruitement of resting stem cells into the division cycle, thirdly repopulation may occur by lowering the rate of cell loss during differentiation pathways. (Belli 1972).

When radiotherapy extends over several weeks, repopulation of surviving stem cells during treatment is one phenomenon that distinguishes early from late responding tissues. It relates directly to overall treatment time rather than to fraction number, and the onset of repopulation depends on the tissue kinetics. For example, skin is probably actively regenerating by the third week of a five days/week treatment regimen. On the other hand mucosa of the head and neck begins the regenerative response probably within about 2 weeks from start of treatment (Withers et al., 1988).

In an experiment carried out by Denekamp in 1973 on mouse skin, she plotted the extra_dose required to counteract proliferation in skin as a function of time after first irradiation, she found that; as a fixed number of fractions were spread over a longer time, there was at the first two weeks no increase in the dose required to produce the iso-effect. After that the doomed cells of the basal layer try to divide , but die instead. The resulting depletion of cell