CHAPTER ONE
INTRODUCTION

1.0 AN OVERVIEW

Radiotherapy originated from two major scientific findings namely the discovery of X-rays by Roentgen in 1895 and then the discovery of radioactivity by Becquerel in 1896. Within two months of their discovery, X-rays were being used clinically to aid in diagnosis of patients and within a year to treat various skin conditions[1]. However, the first successful treatment of proven carcinoma was not until 1899, for an advanced epithelioma of the cheek[2].

Radiobiology is the study of the sequence of events that follows the absorption of energy from ionizing radiation, the efforts of the organism to compensate for the effects of this energy absorption, and the damage to the organism that may be produced[3]. Modern radiotherapy is based largely on experiences made in the first decades after 1895 when Roentgen reported on the discovery of X-rays[4]. Radiation oncology or radiotherapy is a treatment discipline that uses ionizing radiation to eradicate cancerous cells.

The goal of radiotherapy is to deliver a sufficiently high dose of radiation to sterilize the tumour cells with minimal damage to the surrounding normal tissues. The ultimate aim is complete eradication of the tumour with sufficient normal tissue being spared to ensure viability and function. Although dependent on cellular and tissue response in both the tumour and the normal tissue, this goal is ultimately dependent on normal tissue response if complications are to be avoided[3].

Rhabdomyosarcoma is a highly malignant neoplasm that can arise from embryonal mesenchyme anywhere in the body[5-7]. This highly malignant embryonal tumour of childhood spreads by local extension, lymphatic and hematogeneous dissemination[8]. Parameningeal rhabdomyosarcomas are tumours that arise from sites adjacent to the meninges, including the nasopharynx, nasal cavity, middle ear, mastoid, paranasal sinuses, pterygopalatine and infratemporal fossa[8]. Orbital rhabdomyosarcoma is a tumor that arises from either of the two bony cavities in the skull containing the eye and its external structure. Rhabdomyosarcoma and undifferentiated sarcoma are the most common types of malignant soft-tissue tumours in children. Approximately 35 % of these tumours arise in the head and neck region, defined as the region above the clavicles anteriorly and the C7 vertebral body posteriorly. Tumours in the head and neck are difficult to remove surgically with wide, uninvolved margins and radiation therapy is therefore usually needed to secure local control.

Measurement of doses in phantoms, verification and calculation of dose distributions in patients produced by particular beam arrangements are among the principal duties of a physicist in a radiotherapy centre[9]. The radiation oncologist traditionally prescribes the treatment in terms of a uniform dose to the target volume accompanied by constraints on the dose to surrounding organ(s) at risk. However, the endpoints in radiotherapy that are truly of relevance are not only physical dose distributions but the probability of local control, alternatively called the Tumor Control Probability (TCP) and the Probability of Normal Tissue Complications (NTCP)[9-10]. The aim of radiotherapy is to maximize the TCP while the NTCP remains below some "acceptable" level.

In curative radiotherapy the tolerance of normal tissues is in general the limiting factor for the dose that can be given to the tumor. Research and development in radiotherapy is therefore aimed at increasing the tumor effect, relative to the risk of (late) damage in normal tissues. This is in view of the potential late effects, which may affect the mental development, and somatic growth of children irradiated. Thus it is imperative that every aspect of this problem (late effects) be thoroughly scrutinized. Any radiation oncologist who prescribes or delivers radiation therapy to patients has the clinical responsibility to ensure that the patients are followed up for the rest of their lives (i.e. during the time when risk of development of morbidity exists) and to carefully document the morbidity in order to alleviate symptoms and to perform appropriate quality control and feed-back[11].

The primary goal of radiation oncology, as for all medical care, is to achieve the highest possible quality of life for the patient, from the time of his or her first contact with the medical system[12]. Obviously the quality of life of a person is subjective, but from a medical point of view it also has a more strict and objective side such as a general health index[12]. In practice, two main groups of objective functions have been used, namely physical and biological. Biologic objective functions aim at quantifying precisely the treatment outcome upfront i.e. the probability that the patient will have a desirable treatment outcome. From this point of view the radiobiological objective functions seek to prospectively quantify the quality of life of the patient after therapy[12].

1.1 OBJECTIVES

The principal purpose of this work was to calculate radiobiological treatment outcome in rhabdomyosarcoma using a computer software package called BIOPLAN developed by B. Sanchez-Nieto and A.E. Nahum[13]. NTCP and TCP calculated using the BIOPLAN software were compared to observed clinical treatment outcome as documented from clinical follow-up visits. BIOPLAN (BIOlogical evaluation of PLANs) was conceived as a PC-based user-friendly software for the biological evaluation of treatment plans and provides flexibility in the use of models and parameters. This method was applied retrospectively to 39 patients who received radiation treatment for rhabdomyosarcoma during the period from January 1990 to January 2000.

The objective of this study was also to then evaluate the impact of the following:

a) Age of the patient
b) Histology
c) Tumor volume
d) The effect of the primary site of the tumor
e) The effect of the timing of initiation of radiotherapy treatment
f) The effect of the total delivered dose.
g) Sex of the patient

on the overall survival for children with parameningeal and orbital rhabdomyosarcoma who were treated with radiation in order to recommend how treatment delivery and treatment outcome can be improved.

1.2 TREATMENT

Treatment of rhabdomyosarcoma requires interdisciplinary co-operation through a combined oncology clinic. The modalities to be considered in each case are surgery, chemotherapy and radiotherapy, in combinations used for the best management of the individual patient. Rhabdomyosarcoma treatment is planned with two goals in mind:

1. to cure the cancer
2. to save as much function of the affected area as possible.

Only the radiation treatment modality will be evaluated in this work.

1.2.1 RADIATION

Normally a dose of 45 – 50 Gy in 25 – 28 fractions at 1.8 Gy per fraction is prescribed over 5 – 6 weeks[14]. The cure rate for rhabdomyosarcoma depends on many factors, including[6]

- Age of patient
- Exact type of tumor
- Tumour's location in the body
- The size of the tumor at diagnosis
- Whether the cancer has spread (metastasized)

In order to take this information into account in the planning of the treatment one needs to use radiobiological models, which describe the response of the tumors and normal tissues to radiation according to their radiobiological characteristics.

1.3 JUSTIFICATION

Health systems use valuable resources and personnel, thus if such a system is to be used to its greatest effect, the system must undergo regular evaluation and critique such that strategies are devised to optimize the service to the greater community.

Presently, the evaluation of treatment plans is based on the volumetric distribution of the absorbed dose within the patient. Data on dose distributions are almost entirely derived from measurements in water phantoms (which are tissue equivalent) usually large enough in volume to provide full scatter conditions for a given beam. This basic data is used in a dose calculation system devised to predict the dose distribution in an actual patient. During the treatment planning process the patient is simulated by a 3-dimensional representation using computer tomography (CT). The dose distribution within the patient is calculated using the electron density distribution provided by the computer tomography slices which represent the tissue inhomogeneities in the patient. However, this tissue equivalent representation of the patient is not completely accurate since the response of the various organs to radiation depends on many factors that are currently not taken into account during the treatment planning process[10]. Such factors are the volume dependence of the organs to radiation, the internal structural organization of the functional sub units of the normal tissue, the density of clonogenic cells in the targets, the hypoxic cell fraction within the tumor and the fractionation regimen. In order to take this information into account in the planning of the treatment, one needs to use radiobiological models, which describe the response of the tumors and normal tissues to radiation according to their radiobiological characteristics.

Patients who suffer from rhabdomyosarcoma are a very heterogeneous group. The prognosis of such patients is dependent on a number of factors. It is important to define an individual patient’s prognosis for a number of reasons, for example,

1. if complications are anticipated the patient could be more carefully monitored and the complication prevented or treated earlier.
2. it is necessary to define those patients who are most likely to benefit from early radiation treatment.
3. it serves to give a better understanding of determinants of a disease and thus stimulates future research.
4. it may support the planning of future clinical trials, for example, selection of patients, stratification, etc.
5. it is a decision aid to the radiation oncologist.