ASSESSMENT OF NORMAL TISSUE COMPLICATION PROBABILITY FOR PATIENTS UNDERGOING EXTERNAL BEAM RADIOTHERAPY OF CANCER OF THE CERVIX

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AUGUST, 2014.

DECLARATION

I hereby declare that the work in this thesis titled **"Assessment of Normal Tissue Complication Probability (NTCP) for Patients Undergoing External Beam Radiotherapy (EBRT) of Cancer of the Cervix"** was carried out by me in the Department of Physics, Faculty of Science, Ahmadu Bello University, Zaria, under the supervision of **Dr. Zakari I. Yusuf, Mr. A.S Ajuji and Dr. Adamu Abdullahi**. The work of other researchers have been duly acknowledged and referenced. No part of this thesis has been presented for another degree or diploma at this or any other institution.

_____	_____	_____
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CERTIFICATION

This thesis titled **"ASSESSMENT OF NORMAL TISSUE COMPLICATION PROBABILITY (NTCP) FOR PATIENTS UNDERGOING EXTERNAL BEAM RADIOTHERAPY (EBRT) OF CANCER OF THE CERVIX"** meets the regulations governing the award of the degree of Master of Radiation Biophysics in the Department of Physics, Faculty of Science, Ahmadu Bello University and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

This research work is respectfully dedicated to Mrs. Susan Onuh and to the memory of Chief. John .A. Onuh

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ABSTRACT

The effect of cervical cancer treatment on women was re-examined in the northern Nigeria with a view to observe the resulting effect of the available diagnosis and treatment procedures. Although, modern radiation therapy techniques which includes External Beam Radiotherapy (EBRT), have the ability to conform the dose distribution of ionizing radiation tightly around the volume to be treated, unwanted irradiation to surrounding organs remains a problem. Three basic methods were followed during the radiotherapy planning of these patients which included the pre-planning stage, planning radiotherapy treatment stage and treatment delivery. Various tests were carried out on these patients which helped to confirm the diagnosis after which they were treated using the linear accelerator, computed tomography simulator and the treatment planning system. The probability of a side effect arising in the normal tissue of a patient after radiation therapy was modelled by sigmoid mathematical functions known as normal tissue complication probability (N.T.C.P) models. Hence, to compute N.T.C.P in this research work, the linear equation used in the work developed by Emami et al (1991) was used. This equation has three tissue specific parameters, aG, k & N_0, and three variables (NTCP, dose and volume of the organ). The equation has been applied to compute the above said three parameters of the NTCP model using the doses of normal tissues / organs around the cervix extracted from cervical cancer patients under study at the Usman Danfodio University Teaching Hospital. The graphs obtained from this work show that all the organs (bladder, rectum, gastro-intestine, left femur, right femur and skin) are dose and volume dependent and also exhibit a threshold dose for the whole volume (plotted data) above which a complication arises. The threshold doses for bladder, rectum, gastro-intestine, left femur, right femur and skin are at 5Gy, 6Gy, 21Gy,

5Gy, 2Gy and 7Gy respectively. Fitting equations were also obtained for each curve and a line of best fit was obtained using the method of least square fit. A C++ program code was written to help in the plotting computation and the Gnuplot plotting software was used for both the plots and fitting. This retrospective study was carried out on a total number of 50 non-pregnant cervical cancer patients.

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LIST OF ABBREVIATIONS

CRT	Conformal Radiotherapy
BEV_S	Biological Effective Volumes
CTV	Critical Target Volume
DRR_S	Digitally Reconstructed Radiographs
DVH	Dose Volume Histogram
EBRT	External Beam Radiotherapy
FIGO	International Federation of Gynecologists and Obstetricians
GIT	Gastro-intestine Tract
HPV	Human Papilloma Virus
ICBT	Intracavitary Brachytherapy
ICRU	International Commission on Radiological Units
IMPT	Intensity Modulated Proton Therapy
IMRT	Intensity Modulated Radiation Therapy
IGRT	Image Guided Radiation Therapy
LET	Linear Energy Transfer
LINAC	Linear Accelerator
LQ	Linear Quaadratic
MLC	Multi-Leaf Collimator
MRI	Magnetic Resonance Imaging
NTCP	Normal Tissue Complication Probability
OAR_S	Organ at Risks
OTT	Overall Treatment Time

PET	Positron Emission Tomography
QUANTEC	The Quantitative Analysis of Normal Tissue Effects in the clinic
RBE	Relative Biological Effectiveness
SAD	Source to Axial Distance
SSD	Source to Surface Distance
TPS	Treatment Planning System
WHO	World Health Organization

CHAPTER ONE

1.0 INTRODUCTION

1.1 General Introduction

Cervical cancer is a malignant neoplasm arising from cells originating in the cervix uteri. One of the most common symptoms of cervical cancer is an abnormal vaginal bleeding, but in some cases there may be no obvious abnormal vaginal bleeding until the cancer has progressed to an advanced stage (Kumar *et al*., 2007). Other symptoms of cervical cancer include bleeding after sex (postcoital bleeding), bleeding outside the normal periods, pain and discomfort during sex, an unpleasant smelling vaginal discharge and new bleeding after the menopause. If the cancer spreads out of the cervix and into surrounding tissue and organs, it can trigger a range of other symptoms, including constipation, blood (hematuria), loss of bladder control (urinary incontinence), bone pain ,swelling of one of your legs , hydronephrosis, changes to your bowel and bladder habits amongst others. (Tim *et al.,* 2012). Treatment usually consists of surgery in early stages, and chemotherapy and/or radiotherapy in advanced stages of the disease (Tim *et al*. 2012). Cancer screening using the Pap smear can identify precancerous and potentially cancerous changes in cervical cells and tissue (Canavan *et al*., 2000). In developed countries, the widespread uses of cervical screening programs have dramatically reduced the incidence of invasive cervical cancer.

External beam radiation therapy (EBRT) is a type of radiation therapy that directs a beam of radiation from outside the body at cancerous tissues within the body. EBRT delivers high-energy rays to tumors, using a special X-ray machine called a linear accelerator. This machine allows radiation to be delivered from any angle and shapes radiation beams

to the contour of the tumor. American cancer society (2014).The procedure lasts a few minutes, and is typically repeated several times a week over several months. External beam radiation treatments include the three dimensional conformal radiation therapy (3D-Conformal RT) and the intensity modulated radiation therapy (IMRT). American cancer society (2014).

Normal Tissue Complication Probability is the probability that a given dose of radiation will cause an organ or structure to experience complications considering the specific biological cells of the organ or structure

1.2 Aim of the Study

The aim of this research is to assess the Normal Tissue Complication Probability for the therapy of cervical cancer patients.

1.3 Objectives

The objectives of the study include;

i. **To explore the prospect of estimating the dose given to the cervix and surrounding organs of patients,** the side effects which may result from treatment of the cancer using external beam radiotherapy (E.B.R.T) **and the effect it has to the surrounding organs of the cervix.**
ii. To interpolate clinical data to provide an estimate of Normal Tissue Complication Probability (NTCP) for the organs at risk for any altered fractionated treatment schedule.
iii. To get the best fit of normal tissue tolerance doses to the NTCP model of the linear quadratic model using a method of least square fit.

iv. To estimate the normal tissue tolerance doses for the organs at risk and fit these tolerance doses into the transformed expression of the equation in order to determine the values of the parameters αG and k which determines the steepness of the curve and the volume effect respectively.

1.4 Importance of the Research

External beam radiotherapy (EBRT) has been the traditional method of delivering the radiation. Short pulses of tightly focused beams of X-rays or gamma rays are delivered from outside the body into the cervix for a few minutes each day. Prostate Cancer Foundation (2013). Treatment continues five days a week for about five to six weeks. EBRT allows the X-rays to be directed very accurately to the cervix in three dimensions Prostate Cancer Foundation (2013). EBRT has a track-record of success in "curing" cancers confined to the cervix that is very close to that of surgery or brachytherapy. Prostate Cancer Foundation (2013). The long term overall quality of life after EBRT has also been shown to be the same as for patients undergoing surgery or brachytherapy. From a patient's perspective, the advantages of EBRT are that it is less intrusive and stressful than surgery, with no risk of infection. It is suitable for patients of any age, and is of particular advantage for older women or those with fitness or other health problems that make the risk of surgery greater. Prostate Cancer Foundation (2013).

Findings from this research are expected to be exploited by Physicists and the Oncology Team such as the Medical Doctors, Medical Oncologists, etc. for easier diagnosis and treatment of radiation tissue complications of patients with cancer of the cervix to provide safer treatments of patients who require the use of external beam radiotherapy (EBRT) as part of their treatment.

Therefore, EBRT is very important because it is one of the most important modality of treating cervical cancer. Prostate Cancer Foundation (2013).

1.5 Justification

Worldwide there are more than 273,000 deaths from cervical cancer each year and it accounts for 9% of female cancer deaths. Mortality rates vary seventeen fold between the different regions of the world. (Yang *et al.,* 2004).

Cervical cancer contributes over 2.7 million years of life lost among women between the ages of 25 and 64 worldwide, some 2.4 million of which occur in developing areas and only 0.3 million in developed countries. (Yang *et al;* 2004).

There is a paucity of literature on the evaluation of normal tissue complication probability of cervical cancer treatment using EBRT in northern Nigeria. This is pertinent on the background that globally, N.T.C.P in cervical cancer now constitute a distinct field of study and practice.

The most substantial gains in both clinical exposure and research have taken place in the last decade on the normal tissue complication probability on cervical cancer, tumor control probability and uncomplicated tumor control probability mostly in the United States.

The creation of specific fellowship training opportunities in various aspects of cancer for cancer professionals and also the launching of Journals of Medical Oncology, mostly in the United States of America.

The story in our environment is not quite as rich, therefore necessitating more contributions from clinical experiences and research to the existing body of knowledge in Cancer Oncology. This study will serve as a foundation for multidisciplinary approach to cancer patient care to include Physicist and the entire Oncology Team. The knowledge obtained by participants will serve to decrease neglecting complications in patients with cervical cancer and stigmatization as well as improve screening so as to prevent late presentation and advanced disease.

1.6 Usman Danfodio University Teaching Hospital, Sokoto; The Study Area

1.6.1 Location

Sokoto state was created as a state in 1976. In terms of density, it is ranked 16 out of the 36 states. Sokoto state has been ruled by governors, most are ex-military officers, who succeeded each another at short intervals. It is located in the extreme northwest of Nigeria, near to the confluence of the Sokoto River and the Rima River. As of 2006 census, it had an estimated population of more than 4.2 million. It is the modern day capital of Sokoto State (and its predecessor, the Northwestern State). Over eighty percent (80%) of the inhabitants of Sokoto practice one form of agriculture or the other. They produce such crops as millet, guinea corn, maize, rice, potatoes, cassava, groundnuts and beans for subsistence and produce wheat, cotton and vegetable for cash. Local crafts such as blacksmithing, weaving, dyeing, carving and leather works also play an important role in the economic life of the people. Sokoto is also one of the fish producing areas of the country (www.onlinenigeria.com/map). Thus a large number of people along the river basin engage in fishing. Sokoto is equally endowed with natural and mineral resources.

Agro allied industries using cotton, groundnut, sorghum, gum, maize, rice, wheat, sugar cane, cassava, gum Arabic and tobacco as raw materials can be established in the area (www.onlinenigeria.com/map). Minerals such as Kaolin, gypsum, lime stones, laterite, red mills, phosphate (both yellow and green shade) clay, sand etc., are available in commercial quantities. Mineral based industries using these raw materials could be established in the state. The absence of the Tsetse fly on the open grassland benefits both wild and domestic animals. Sokoto ranks second in livestock production in the country's animal population of well over eight million (www.onlinenigeria.com/map). The availability of these economic potentials provides good investment opportunities, particularly in agro-allied industries such as flour mills, tomatoes processing, sugar refinery, textile, glue, tanning, fish canning, etc. Sokoto is located between the latitudes of 13^{O} 05' N, and longitudes 05^{O}15' E. Sokoto occupies an area space of about 25, 973km^2. It is comprised of 23 local government areas. (www.onlinenigeria.com/map).

1.6.2 Vegetation

Sokoto State is in the dry Sahel, surrounded by sandy savannah and isolated hills. With an annual average temperature of 28.3 °C (82.9 °F), Sokoto is, on the whole, a very hot area. However, maximum daytime temperatures are for most of the year generally under 40 °C (104.0 °F) and the dryness makes the heat bearable (www.onlinenigeria.com/map). The warmest months are February to April when daytime temperatures can exceed 45 °C (113.0 °F). The rainy season is from June to October during which showers are a daily occurrence. The showers rarely last long and are a far cry from the regular torrential rain known in wet tropical regions. From late October to February, during the cold season, the climate is dominated by the harmattan wind blowing Sahara dust over the land. The dust

dims the sunlight thereby lowering temperatures significantly and also leading to the inconvenience of dust everywhere in houses (www.onlinenigeria.com/map). The region's lifeline for growing crops is the floodplains of the Sokoto-Rima river system, which are covered with rich alluvial soil. For the rest, the general dryness of the region allows for few crops, millet perhaps being the most abundant, complemented by rice, corn, other cereals and beans. Apart from tomatoes few vegetables grow in the region. The low variety of foodstuffs available has resulted in the relatively dull local cuisine. (www.onlinenigeria.com/map).

1.7 Area of Concentration

In this research, concentration will be on the assessment of normal tissue complication probability for patients undergoing external beam radiotherapy in the treatment of cervical cancer and estimation of the dose targeted at the cervix and the amount of dose that goes to the organs at risk due to radiation.

1.8 Statement of Research Problem

The E.B.R.T gives doses to the tumor bed compared and also high doses to the head of femur, bladder, rectum, uterus and small intestine which can damage other organs, particularly the bowel, bladder and rectum. Irritation of the bowel is a common side effect that can manifest in patients for six months or longer after treatment. Rates of occurrence of incontinence and impotence are similar to that experienced with surgery, but tend to occur later. With radiotherapy a large percentage of women may develop fertility problems and many develop mild to moderate inflammation of the bowel. It is also important to mention that it is not uncommon after radiotherapy to develop a change

in bowel habit, with looser and more frequent bowel movements, increased flatus and possible bleeding. Once again, the skill, experience and result record of the Radiation Oncologist and standard of the treating equipment are paramount to the outcome. Therefore the research statements are;

i. To determine the dose to be given to patients that will cause damage to the continuous normal tissues and its surrounding organs.
ii. To determine the curative dose given to patients to prevent a recurring cancer.
iii. To find better therapies that will be suitable for patients to minimize the side effects of EBRT.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Review of Previous Work

2.1.1 Cervical cancer

Cervical cancer is the second most common cancer among women in developing countries. Each year there are approximately 493,200 new cases of cervical cancer. Almost 80% of which occur among women living in developing countries and more than 200,000 women die of the disease. (Ferlay *et al.*, 2010). The vast majority of cases are affected with infection of one or more types of Human Papilloma Virus (HPV), which is sexually transmitted. (Walboomers *et al*., 2010). HPV (Human Papilloma Virus) first enters the cells covering the cervix and then slowly causes changes that with timespan result in cancer. Although exposure to oncogenic strains of HPV (Human Papilloma Virus) generally occurs at the time of sexual initiation, invasive cancer may not develop until 10 to 20 years later.

Radiation safety is a measure of establishment of effective features, procedures, rules and system that make nuclear practice safe to people and environment. Radiation therapy is a preferred treatment for cervical cancer patients because it targets cancer cells, with less damage to healthy tissues in the cervix. Radiation safety manual (2012).

External beam radiotherapy therapy (EBRT), also called external radiation therapy, is a method for delivering a beam or several beams of high-energy x-rays or gamma rays to a patient's tumor. Beams are generated outside the patient and are targeted at the tumor site.

These high energy x-rays/gamma rays can deposit their energy to the area of the tumor to destroy the cancer cells and, with careful treatment planning, spare the surrounding normal tissues (www.myradiotherapy.com). This machine allows radiation to be delivered from any angle and shapes radiation beams to conform to the contour of cervical cancer tumors. The sources of beam involve the linear accelerator (LINAC) and Cobalt-60.The linear accelerator, or linac, is capable of producing high-energy X-rays or electrons for the treatment of cervical cancer. Using treatment planning computers and software, the size and shape of the beam is controlled, as well as how it is directed at the body, to effectively treat the tumor while sparing the surrounding normal tissue (www.myradiotherapy.com).

2.2 Previous Works

Radiation therapy is an integral part of the treatment of patients inflicted with cancer. It is estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment (Halperin *et al*., 2008). Radiation therapy affects both tumor cells and uninvolved normal cells; the former to the benefit and the later to the detriment of patients. With the goal of achieving uncomplicated local regional control of cancer, balancing between the two is both an art and a science of radiation oncology. Unfortunately, after over 100 years of practicing radiation oncology and in spite of much recent progress, knowledge on either of the two is far from perfect.

From a historical point of view, the first formal attempt to address at least one of the goals, namely normal tissue tolerance to radiation, was carried out by Rubin and Cassarett (Rubin *et al*., 1972). Even though this publication was a collection of anecdotal

reports, it has served radiation oncologists as a raw reference to build on their own experience.

The decade of the 1980s was a quantum leap of progress in the field of radiation oncology. With the monumental work of researchers on four National Cancer Institute multi-institutional contracts, the science and practice of radiation oncology changed from a two-dimensional (2D) to a three-dimensional (3D) volumetric process (Halperin *et al*., 2008). During the work on these contracts, it became apparent to the clinicians that information on the tumoricidal doses of radiation as well as normal tissue complication doses, especially on partial volumes, is mostly empirical and totally inadequate. A committee was formed to address a part of this dilemma by comprehensively reviewing the available published data. In the process of this review by the committee, it became clear that much of the data is nonexistent and they would have to rely on the collective experience of eight clinicians from major institutions in the United States. (Halperin *et al*., 2008).

Moreover, in order to shed some light on the volumetric aspect of these issues, it was decided that organs be divided into one-third, two-thirds, and whole organ volumes. In spite of the clear indication in the manuscript on the paucity of solid experimental/prospectively driven data, this publication, so-called Emami's paper, has gained much popularity. The main goal of this publication was to address a clinical need based on available information up to that time and points to the fact that there is a need for extensive and comprehensive research in this area. Obvious limitations of the publication were as follows:

i. It was a literature review up to 1991.

ii. It completely pre-dated the 3D-CRT/IMRT- IGRT era.

Even at that time dose-volume histograms were not in routine clinical use (Halperin *et al*., 2008). It was a tabulation of the estimates for three of the aforementioned arbitrary volumes (Marks *et al*., 2010). It was only for external beam radiation with conventional fractionation. (Bentzen *et al.,* 2010).

Over the last two decades, since the publication of "Emami's paper" the practice of radiation oncology has been completely revolutionized:

i. Multidisciplinary management of cancer has become the standard of care.
ii. Choice of an endpoint for complication analysis and modeling has significantly altered.
iii. There has been a major revolutionary change in technology:
iv. CT simulation has become routine along with the fusion of other modalities such as MRI, PET, and 4DCT.
v. 3D-CRT/IMRT/IGRT has become standard with the array of evaluation tools.

As a result, dose distributions have become very complex and as of recent. (Lawrence *et al.,* 2010). Multiplicity and complexities of factors affecting radiation including normal tissue complications have made it impossible to have actual data for every clinical situation facing practicing radiation oncologists. Therefore, there is a need to have reasonable predictive models for plan evaluation, to improve tumor control, and to predict and hopefully prevent normal tissue injury (Mayo *et al* 2010). Optimally, databases on biophysical models should be used in summarizing complicated dose-volume data to help describe clinical outcomes and ultimately aid in the prediction of clinical toxicity (Bhandare *et al*., 2010).

During the last two decades, a vast amount of published information has become available to address the relationship between dosimetric parameters and the clinical outcomes of normal tissues. Because of different analytic methodologies, calculation methods, endpoints, etc., the data is noisy and sifting through these data for practicing radiation oncologists is a nearly impossible task. Realizing this difficulty and the obvious need for a simplistic format, a group of physicians and researchers were formed with the name "The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)." (Deasy *et al*., 2010).

The first goal was to review the available literature of the last 18 years. Volumetric/dosimetric information of normal tissue complication and provide a simple set of data to be used by the busy community practitioners of radiation oncology, physicists, and dosimetrists. (Rancati *et al*., 2010). The second goal of the QUANTEC group was to provide reliable predictive models on relationships between dose-volume parameters and the normal tissue complications to be utilized during the planning of radiation oncology. The result of several years of work by this group has recently been published (Constine *et al*., 2010). Although these publications contain a comprehensive review of published information and can be a guide for future research on this issue, they still have many shortcomings mainly due to the basic complexity of the subject. This shortcoming has been clearly indicated in the QUANTEC publication and the need for much more data in the future has been emphasized. However, the presented data in the publication is still cumbersome and lacks the "user-friendliness," which is required to be used in the day-to-day practice of a busy community clinician (Bhandare *et al*., 2010). There are numerous factors that affect the radiation-induced complications of

normal tissues on any given clinical situation. Thus, the experience and judgment of the clinician still plays the most important role in treating patients. As for predictive models, the problem lies in finding a reasonable model, acquiring sufficient data, and applying the statistical methods properly. (Werner-Wasik *et al*., 2010).

So far, in spite of major efforts, there is no model that has been demonstrated to predict radiation responses with sufficient accuracy for widespread clinical use. Most of the modeling at this point is still phenomenological and "descriptive" rather than predictive. The development of reliable and user-friendly predictive models is quite unlikely in the near future. (Pan *et al*., 2010)

2.3 Background of Study

Today, more than 6 million individuals worldwide receive radiation therapy as part of their cancer treatment each year. Hall and Giacca (2006). The ideal radiation therapy is one where there is a sufficiently high dose to eradicate the tumor and no dose at all elsewhere to avoid unwanted effects in healthy tissue. This is however not a practically achievable dose distribution, and everyday clinical task is to arrive at the best compromise where each patient's treatment plan has a high probability of eliminating the tumor while simultaneously having a low risk of damaging the surrounding non-malignant tissues. The field of radiation therapy has the previous decades undergone considerable technological developments in patient imaging, treatment planning and delivery and we now have better means to create and deliver suitable dose distributions. (Jemal, *et al*., 2008).

The process of treatment planning consists of three major parts. First, the patient is imaged using one or more three-dimensional (3D) imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound imaging. Second, on these images, the volumes suspected to contain microscopic and macroscopic tumor tissues, and the organs that are to be irradiated (organs at risk, OARs) are identified. In the third step, the treatment plan is created by optimizing how the dose will be distributed within the patient, i.e. how much dose that should be received by the tumor and how much the dose to the healthy organs should be restricted. The results of the treatment planning procedure are a 3D dose distribution, the absorbed dose calculated in a large number of volume elements (voxels) inside the patient, and the corresponding treatment machine settings required to deliver this dose distribution in the patient. Absorbed dose is, however, a physical quantity that describes the amount of energy from ionizing radiation absorbed per unit mass and is seldom linearly related to the biological effect in human tissue. Thus, for each treatment regimen we must not only optimize the dose distribution, but also how much dose that should be delivered at each treatment (fraction) to achieve the desired outcome. This optimization is a compromise between our competing objectives of tumor elimination and unwanted effects in normal tissue. To deliver the planned dose to the tumor and surrounding tissue at each fraction, the patient needs to be immobilized in an accurate and reproducible position relative to the treatment machine. Current developments of patient positioning techniques involve X-ray imaging and adjustment immediately prior to treatment; this increases the correspondence between the planned and delivered absorbed dose distributions in both the tumor and surrounding OARs. (Verellen,*et al*., 2008).

2.4 Fractionation

Earlier in the 20th century it was recognized that delivering the same amount of ionizing radiation in a large number of fractions during a longer period of time resulted in reduced normal tissue effects. Thames (1987). However, for many decades there were conflicting interpretations regarding if this was due to a time effect, a dose per fraction effect or a combination of both. Thames (1987). The relationship between overall treatment times (OTT), total dose, and dose per fraction were not understood until the late 1970's and early 1980's. (Barendsen, *et al*., 1982), Douglas and Fowler (1975), (Thames *et al*., 1984)**.** The response to altered fractionation for both normal and tumor tissue was then mathematically described by the linear-quadratic (LQ) model. (Fowler *et al*., 1984). This model was derived from the concept of cell-survival curves: the proportion of cells surviving irradiation is described with two parameters, α and β. The quotient, α/β, is the quantification of the tissue's fractionation sensitivity and if this quotient is known one can calculate the effect of a change in dose per fraction. Delivering the same total dose in a large number of fractions results in reduced normal tissue toxicity. However, the daily fraction dose cannot be arbitrarily small since this will lead to a very long Overall Treatment Time (OTT) which in turn becomes a problem due to accelerated tumor repopulation (Withers *et al*., 1988). The model has also been used to design many clinical studies (Bentzen, 1994).

The LQ model was further developed to recognize other factors such as OTT, dose rate, low-dose hypersensitivity, and incomplete repair between fractions (Pop *et al*., 1996). It is the model most widely utilized in the clinic today and, given knowledge on the relevant parameters, it can be expected to give results in line with observed clinical data when the

dose per fraction is between 1 and 6-8 Gy. Until now, most treatments have been delivered using around 2 Gy per fraction, and the knowledge about how tumor and normal tissues respond to high doses per fraction is limited. There is currently a debate on whether the LQ model accurately describes the fractionation effect at large doses per fraction and several competing models have been suggested (Park *et al*., 2008).

2.5 Complications and Normal Tissue Complication Probability

Unwanted radiation-induced toxicity, side effect, in normal tissue has always been an inherent risk of radiation therapy. As treatment techniques have improved over time with regards to the irradiation of normal tissue, overtime, the most debilitating complications have been avoided. This has given the possibility to identify and deal with toxicity that may be considered 'less severe' but could be detrimental to the patient's quality of life. In this regard, patient-reported outcomes (PROs) are becoming an important supplement to more traditional assessments and scoring of toxicity. (Jackson et *al*., 2010).

In the early 1990's, Emami and co-workers made one of the first efforts to compile available data and present them in a form suitable for implementation in everyday clinical work (Emami *et al*., 1991**)**. They suggested dose levels for 5% and 50% risk of complication for various organs at risks (OARs) and toxicities. Specifically, they used a 'volume parameter' to quantify how sensitive the OAR was to a change in irradiated volume – the volume effect. This meant that they had a normal tissue complication probability (NTCP) model i.e. a link between an inhomogeneously irradiated OAR and the risk of complication. (Kutcher *et al*., 1991). Many such NTCP models have been proposed over the years **(**Kallman *et al*., 1992), (Jackson *et al*., 1993), (Tucker *et al*., 2004), (Bentzen *et al*., 2010). Regardless of their different aspirations on being

biologically founded, they are all similar in that they consider how the total dose, the dose per fraction and the amount of irradiated volume affect the risk of complication.

In this research a cohort of information was collected from patients which include the dose of E.B.R.T, dose absorbed by the organs at risk, patients set up, plan summary, fraction groups, couch positions and the beam set up parameters.

Furthermore, organs can express radiation damage in several different ways and the N.T.C.P for each of those must be separately calculated for each patient. Once the best volume and dose has been determined, it can assist in creating treatment plans with lower risks of complication.

2.6 Physics of Radiation Therapy

2.6.1 Ionizing radiation

Ionizing radiation is energy sufficiently strong to remove an orbital electron from an atom. This Radiation can have an electromagnetic form, such as a high-energy photon, or a particulate form, such as an electron, proton, neutron, or alpha particle (Valentine *et al.*, 2013).

By far, the most common form of radiation used in practice today is the high-energy photon. Photons that are released from the nucleus of a radioactive atom are known as gamma rays. When photons are created electronically such as in a clinical linear accelerator, they are known as x-rays. Thus, the only difference between the two terms is the origin of the Photon (Valentine *et al*, 2013).With the advent of high-energy linear accelerators, electrons have become a viable option in treating superficial tumors up to a depth of about 5 cm.

Electron depth dose characteristics are unique in that they produce a high skin dose but exhibit a fall off after only a few centimeters. Electron absorption in human tissue is greatly influenced by the presence of Air cavities and bone. The dose is increased when the electron beam passes through an air space and is reduced when the beam passes through bone. High-energy radiation is delivered to tumors by means of a linear accelerator. A beam of electrons is generated and accelerated through a waveguide that increases their energy from the KeV to MeV range. These electrons strike a tungsten Target and produce X-rays. X-rays generated in the 10–30-KeV range are known as Grenz rays, whereas the energy range for superficial units is about 30–125 KeV. Orthovoltage units generate X-rays from 125–500 KeV (Valentine et *al.*, 2013).

The intensity of an x-ray beam is governed by the inverse square law. This law states that the radiation intensity from a point source is inversely proportional to the square of the distance away from the radiation source. In other words, the dose at 2 cm will be one fourth of the dose at 1 cm. Photon absorption in human tissue is determined by the energy of the radiation, as well as the atomic structure of the tissue in question. The basic unit of energy used in radiation oncology is the electron volt (eV).

2.7 Dose-Volume Effects

The calculation of NTCP is quite unique. For normal tissues, the volume of the organ irradiated to certain dose levels is used to predict the probability of causing complications. The dose volume relationship will differ for each organ. Either a critical dose must be reached, or a critical volume must receive a certain dose before complications arise.

The normal tissue is constructed of functional sub-units (FSU). Kirkpatrick and Dawson (2010). The irradiation of a Single FSU to a certain dose level might alter the functionality of the organ and cause complications. If so, then this organ will be classified under the critical element model, in an organ that has serial architecture. Dawson and Viswanathan (2010). Serial organs have a minimal dose-volume effect because once any of the critical elements are damaged, the function of the entire organ is impaired (Kirkpatrick *et al*, 2010). Alternatively, irradiating a certain proportion of the total organ volume may be required before the functionality of the organ is impaired and complications arise. This is known as the critical volume model in an organ that has parallel architecture. Kirkpatrick and Viswanathan (2010). In the case of parallel architecture, the FSUs may be more appropriately termed tissue rescue units since the organ possesses a certain functional reserve of tissue rescue units that assist in the repair of the functionality following partial volume irradiation. The critical element and critical volume models are extreme cases and most organs will be a combination of the two. Normal tissues are considered as hierarchically structured renewing systems. In clinical practice any reaction to treatment is generally observable (and sometimes measurable) only in terms of the current functionality of the tissue in question. What is going on at molecular level generally expresses itself only later, and indirectly. Laboratory tests, X-ray films or other examinations usually look precisely at functional expressions of damage, rather than damage itself. Normal tissues are considered to be large three compartment systems, namely;

i. A functioning compartment consisting of fully differentiated cells adjusted to performing specific tasks, these cells have a finite lifetime, after which they are eventually shed.

ii. A pipe-line like compartment for the maturation of partially differentiated cells into fully differentiated replacement cells for the functioning compartment and finally, a production compartment, consisting mainly of transition cells supplying the pipeline with partially differentiated cells for further work-up." Dawson and Pan (2010).

In principle each compartment is subject to lethal and/or sub lethal damage, depending on the kind of assault, and generally with different characteristic sensitivity. In the case of radiation therapy, the production compartment is by far the most susceptible to both types of damage.

2.8 Treatment of Cervical Cancer

According to Ahmed *et al*., (2010), Koh and Rose (2004), the choice of treatment modality is based on the International Federation of Obstetricians and Gynecologists (FIGO) stage, pelvic node status at the time of presentation, performance status and the anticipated side effects resulting from the type of treatment intervention that will be given. The authors note that early cervical cancer FIGO stage 1A is treated with surgery due to its excellent prognosis. While, FIGO stage IB to IIA is treated by either surgery or radiation therapy depending on the most appropriate choice of management based on side effect. They contend that between surgery and radiation therapy for treatment of FIGO stage IB and IIA, there is no difference in survival or recurrence. Makin and Kamanu (2010) confirm the above and pointed out that radical radiotherapy is preferred in centers

where surgical expertise is not available or in women who are medically unfit for surgery. With regard to locally advanced cervical cancer (FIGO stage11B-1VA), Ahmed *et al.,* (2010) stated that this is treated by radical radiotherapy, consisting of a combination of EBRT and ICBT (Intracavitary Brachytherapy). The role played by EBRT before ICBT is emphasized by Eifel (2003) , Limbergen and Haie-Meder (2009) as that of shrinking the volume of central disease such that there is adequate dose distribution coverage of the tumor during treatment, thereby controlling the disease. This is supported by Ahmed *et al* (2010) who noted that considerable tumor shrinkage can be seen during this initial phase of treatment when EBRT is given to the whole pelvis to encompass the cervix, uterus, upper vagina, parametria, and regional lymph nodes. ICBT (Intracavitary Brachytherapy) is then used to boost the dose to primary tumor while limiting the dose to the bladder and rectum.

2.9 Epidemiology and Etiology

Basic and epidemiologic research conducted on cervical cancer during the past 15-20 years have provided overwhelming evidence for an etiologic role for infection with certain types of sexually-transmitted human papillomavirus (HPV) as the primary cause of cervical cancer. The relative risks of cervical cancer following human papillomavirus (HPV) infection as ascertained in case-control and cohort studies are among the highest in cancer epidemiology. Other cervical cancer risk factors, such as smoking, parity, use of oral contraceptives, diet, other infections, and host susceptibility traits must be understood in the context of mediation of acquisition of HPV infection or in influencing events of the natural history of cervical neoplasia that occur following the establishment of a persistent HPV infection. Virtually all cervical carcinoma specimens contain HPV

DNA, which suggests that HPV infection is a necessary cause of cervical neoplasia. (Franco *et al*, 2011).

2.10 Anatomical Relations of the Cervix

The cervix projects into the vaginal vault. Adjacent are the anterior, posterior and lateral vaginal fornixes. Anteriorly the cervix is related to the base of the bladder and posteriorly to the rectum. Laterally related to the ureters.The cervix is a cylinder-shaped neck of tissue that connects the vagina and uterus. The cervix is made of cartilage covered by smooth, moist tissue, and is about 1 inch across. There are two main portions of the cervix. The part of the cervix that can be seen from inside the vagina during a gynecologic examination is known as the ectocervix. An opening in the center of the ectocervix, known as the external os, opens to allow passage between the uterus and vagina. The endocervix, or endocervical canal, is a tunnel through the cervix, from the external os into the uterus. The overlapping border between the endocervix and ectocervix is called the transformation zone. (Ludmir *et al*., 2000).

2.11 Staging of Cervical Cancer

The International Federation of Gynecologists and Obstetricians (FIGO) in 2009 revised the staging of cervical cancer. This was to provide uniform terminology between health professionals in terms of assessing extent of disease. This is important in the management of cervical cancer since staging is the most important prognostic factor, followed by bulk of disease (Ahmed *et al*., 2010). Each stage describes the extent of disease and is used to decide on the appropriate treatment that should be applied, either surgery, radiation therapy, or a combination of both, or use of chemotherapy as neo or an adjuvant

treatment. Most types of cancer have stages from 1-1V. The lower the number, the less the cancer has spread. Some types of cervical cancer have a stage 0. Stage 0 is also known as non-invasive cervical cancer or carcinoma in situ. In stage 0, cancer cells are present on the top layer of the cervix only. They have not gotten into deeper layers of the cervical tissue or other organs. The remaining stages are called invasive cancer. In these stages, the cancer has invaded into deeper layers of the cervix. The new FIGO staging system adapted from Han and Kohn (2010) and (Wijk *et al*., 2009) is described in detail in Table 2.1. The current study includes all the FIGO stages presented at the Sokoto Centre available within the study period.

Table 2.1 FIGO Staging of Carcinoma of the Cervix

Stage	Clinical findings
0	Carcinoma- in situ: also called pre invasive or intra epithelium carcinoma.
1	Growth confined to the cervix. Upward spread to the corpus does not change the classification.
Ia	Spread beyond the cervix to the upper two- thirds of vagina spread to the parametrium but not as far as the lateral pelvic wall.
llb	Spread to the parametrium but not as far as the lateral pelvic wall.
111a	Spread to the lower third of the vagina
111b	Spread to the pelvic side wall and, or hydronephrosis or non-functioning kidney due to ureteric compression by tumor.
lVa	Spread to the bladder or rectum
lVb	Spread to the distance sites outside the true pelvis

Clinical staging is carried out under general anesthesia. Initially a colposcopy and curettage is performed by a gynecologist.

2.12 Histological Classification of Cervical Cancer

The World Health Organization (WHO) recognizes two main histological types of invasive cancer. Squamous carcinoma which constitute about 85% of all cases and Adenocarcinoma which constitute about 10-12% of all cases. Several other types of carcinoma e.g. adenosquamous carcinoma, adenoid cystic carcinoma, small cell carcinoma, undifferentiated and metastatic carcinoma make up the remaining 3-5%of all cases. In this study, it was proposed to include all of the above classifications in the sampled patient cohort that received definitive radiotherapy.

2.13 External Beam Treatment Plan

Treatment planning systems have revolutionized the art of radiotherapy in the past decades. With the use of fast-computerized treatment planning systems at Sokoto Centre, physicians have the ability to conform isodose lines around the desired target volume and spare the normal tissues adjacent to the target. Each patient must be planned with great care to ensure an optimum dose distribution to the tumor while sparing normal tissues. Central tumors are located centrally in the body. In order to spare the normal tissues, beams are created from different angles to aim at the target volume. Each beam is tightly conformed around the Clinical Target Volume (CTV) using Multileaf Collimators (MLCs).

Inverse planning is one of the modern methods used in planning. In this method, goals of planning are given to the planning system and the planning system generates a solution. Objectives are given in the form of dose constraints to a volume. If this volume is the tumor, the goal is to treat the whole volume with the maximum dose prescribed. On the

other hand, if the volume is the rectum or the bladder, the goal is to spare this volume as much as possible.

2.14 External Beam Radiotherapy

External photon beam radiotherapy is usually carried out with more than one radiation beam in order to achieve a uniform dose distribution inside the target volume and as low as possible a dose in healthy tissues surrounding the target. ICRU Report No. 50 recommends target dose uniformity within +7% and –5% of the dose delivered to a well-defined prescription point within the target. Modern photon beam radiotherapy is carried out with a variety of beam energies and field sizes under one of two set-up conventions: a constant source to surface distance (SSD) for all beams or an isocentric set-up with a constant source to axis distance (SAD).

i. In an SSD set-up, the distance from the source to the surface of the Patient is kept constant for all beams, while for an SAD set-up the Centre of the target volume is placed at the machine isocentre;
ii. Clinical photon beam energies range from 2.5MV for ^{60}Co up to 18-25MV for high energy Linacs.
iii. Field sizes range from small circular fields used in radiosurgery, through standard rectangular and irregular fields, to very large fields used for total body irradiation (TBI).

2.15 Volume Definition

Volume definition is a prerequisite for meaningful 3-D treatment planning and for accurate dose reporting. ICRU Reports No. 50 and 62 define and describe several target

and critical structure volumes that aid in the treatment planning process and that provide a basis for comparison of treatment outcomes. The following volumes have been defined as principal volumes related to 3-D treatment planning:

i. Gross tumour volume (GTV),
ii. Clinical target volume (CTV),
iii. Internal target volume (ITV) and
iv. Planning target volume (PTV).

Gross Tumor Volume; "The Gross Tumor Volume (GTV) is the gross palpable or visible/demonstrable extent and location of malignant growth" (ICRU Report No. 50).The GTV is usually based on information obtained from a combination of imaging modalities (computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, etc.), diagnostic modalities (pathology and histological reports, etc.) and clinical examination.

Clinical Target Volume; "The clinical target volume (CTV) is the tissue volume that contains a demonstrable GTV and/or sub-clinical microscopic malignant disease, which has to be eliminated. This volume thus has to be treated adequately in order to achieve the aim of therapy, cure or palliation" (ICRU Report No. 50).The CTV often includes the area directly surrounding the GTV, which may contain microscopic disease and other areas considered to be at risk and requiring treatment (e.g. positive lymph nodes). The CTV is an anatomical–clinical volume and is usually determined by the radiation oncologist, often after other relevant specialists such as pathologists or radiologists have

been consulted. The CTV is usually stated as a fixed or variable margin around the GTV (e.g. CTV = GTV + 1 cm margin), but in some cases it is the same as the GTV (e.g. prostate boost to the gland only).There can be several non-contiguous CTVs, which may require different total doses to achieve treatment goals.

Internal Target Volume; The ITV consists of the CTV plus an internal margin. The internal margin is designed to take into account the variations in the size and position of the CTV relative to the patient's reference frame (usually defined by the bony anatomy); that is, variations due to organ motions such as breathing and bladder or rectal contents (ICRU Report No. 62).

Planning Target Volume; "The planning target volume (PTV) is a geometrical concept, and it is defined to select appropriate beam arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV" (ICRU Report No. 50).The PTV includes the internal target margin (ICRU Report No. 62) and an additional margin for set-up uncertainties, machine tolerances and intra-treatment variations. The PTV is linked to the reference frame of the treatment machine and is often described as the CTV plus a fixed or variable margin (e.g. PTV = CTV + 1 cm).Usually a single PTV is used to encompass one or several CTVs to be targeted by a group of fields. The PTV depends on the precision of such tools as immobilization devices and lasers, but does not include a margin for the dosimetric characteristics of the radiation beam (i.e. penumbral areas and

buildup region), as these will require an additional margin during treatment planning and shielding design.

2.16 Organ at Risk

The organ at risk is an organ whose sensitivity to radiation is such that the dose received from a treatment plan may be significant compared with its tolerance, possibly requiring a change in the beam arrangement or a change in the dose. Specific attention should be paid to organs that, although not immediately adjacent to the volume of interest, have a very low tolerance dose (e.g. the eye lens during nasopharyngeal or brain tumor treatments). Organs with a radiation tolerance that depends on the fractionation scheme should be outlined completely to prevent biasing during treatment plan evaluation.

2.17 Patient Data Acquisition and Simulation

2.17.1 Need for patient data

Patient data acquisition is an important part of the simulation process, since reliable data are required for treatment planning purposes and allow for a treatment plan to be properly carried out. The type of gathered data varies greatly, depending on the type of treatment plan to be generated (e.g. manual calculation of parallel opposed beams versus a complex 3-D treatment plan with image fusion). General considerations include:

i. Patient dimensions are almost always required for treatment time or monitor unit (MU) calculations, whether read with a caliper, from CT slices or by other means;
ii. The type of dose evaluation dictates the amount of patient data required (e.g. DVHs require more patient information than a point dose calculation of organ dose);

iii. Landmarks such as bony or fiducial marks are required to match positions in the treatment plan with positions on the patient (Bentel *et al*., 1996).

2.17.2 Nature of patient data

The patient information required for treatment planning varies from rudimentary to very complex, ranging from distances read on the skin, through manual determination of contours, to acquisition of CT information over a large volume, or even image fusion using various imaging modalities (Bentel *et al*, 1996).

2.17.3 Two dimensional treatment planning

A single patient contour, acquired using lead wire or plaster strips, is transcribed on to a sheet of graph paper, with reference points identified. Simulation radiographs are taken for comparison with port films during treatment.

For irregular field calculations, points of interest can be identified on a simulation radiograph, and SSDs and depths of interest can be determined at simulation. Organs at risk can be identified and their depths determined on simulator radiographs. Wiliams and Wilkins (1998).

2.17.4 Three dimensional treatment planning

A CT data set of the region to be treated, with a suitable slice spacing (typically 0.5–1 cm for the thorax, 0.5 cm for the pelvis and 0.3 cm for the head and neck), is required. An external contour (representative of the skin or immobilization mask) must be drawn on every CT slice used for treatment planning. The tumor and target volumes are usually

drawn on CT slices by the radiation oncologist. Organs at risk and other structures should be drawn in their entirety if DVHs are to be calculated. Williams and Wilkins. (1998).

2.17.5 Treatment simulation

Patient simulation was initially developed to ensure that the beams used for treatment were correctly chosen and properly aimed at the intended target. At present, treatment simulation has a more expanded role in the treatment of patients, consisting of:

i. Determination of the patient treatment position;
ii. Identification of the target volumes and organs at risk;
iii. Determination and verification of the treatment field geometry;
iv. Generation of simulation radiographs for each treatment beam for comparison with treatment port films;
v. Acquisition of patient data for treatment planning Wiliams and Wilkins (1998).

2.17.6 Patient treatment position and immobilization devices

Depending on the patient treatment position or the precision required for beam delivery, patients may or may not require an external immobilization device for their treatment. Immobilization devices have two fundamental roles:

i. To immobilize the patient during treatment;
ii. To provide a reliable means of reproducing the patient's position from simulation to treatment, and from one treatment to another.

The simplest immobilization means include masking tape, Velcro belts or elastic bands. The basic immobilization device used in radiotherapy is the head rest, shaped to fit

snugly under the patient's head and neck area, allowing the patient to lie comfortably on the treatment table. Wiliams and Wilkins (1998).

Figure 1 shows common headrests used for patient comfort and immobilization during treatment.



Fig.2.1. Headrests used for patients positioning and immobilization in external beam radiotherapy at the Usman Danfodio University Teaching Hospital, Sokoto.

Modern radiotherapy generally requires additional immobilization accessories during the treatment of patients.

2.18 Conventional Treatment Simulation

2.18.1 Simulators

Simulators provide the ability to mimic most treatment geometries attainable on megavoltage treatment units and to visualize the resulting treatment fields on radiographs or under

fluoroscopic examination of the patient. They consist of a gantry and table arrangement similar to that found on isocentric megavoltage treatment units, with the exception that the radiation source in a simulator is a diagnostic quality X ray tube rather than a high energy Linac or a cobalt source (Khan *et al*, 1998). Some simulators have a special attachment that allows them to collect patient cross-sectional information similarly to a CT scanner; the combination is referred to as a CT simulator. The photons produced by the X ray tube are in the kilo voltage range and are preferentially attenuated by higher Z materials such as bone through photoelectric interactions. The result is a high quality diagnostic radiograph with limited soft tissue contrast but with excellent visualization of bony landmarks and high Z contrast agents. A fluoroscopic imaging system may also be included and would be used from a remote console to view the patient's anatomy and to modify beam placement in real time. A conventional treatment simulator has the capability to reproduce most treatment geometries available on radiotherapy treatment units. Simulators use a diagnostic x ray tube and fluoroscopic system to image the patient (Khan *et al*, 1998). Figure 2.2. Shows a photograph of a computerized tomography treatment simulator



Fig 2.2. A Computerized Tomography treatment Simulator which is being used at the Usman Danfodio University Teaching Hospital, Sokoto. The machine was manufactured by GE and the model is bright speed. It's a four slice CT.

2.18.2 Localization of the target volume and organs at risk

For the vast majority of sites the disease is not visible on the simulator radiographs, and therefore the block positions can be determined only with respect to anatomical landmarks visible on the radiographs (Khan *et al*, 1998).

2.19 Computed Tomography Based Virtual Simulation

2.19.1 Computed tomography simulator

Dedicated CT scanners for use in radiotherapy treatment simulation and planning are known as CT simulators. The components of a CT simulator include: a large bore CT scanner (with an opening of up to 85 cm to allow for a larger variety of patient positions and the placement of treatment accessories during CT scanning); room lasers, including a movable sagittal laser, allowing for patient positioning and marking; a flat table top to more closely match radiotherapy treatment positions; and a powerful graphics workstation, allowing for image manipulation and formation (Khan et *al*, 1998). An example of a modern CT simulator is shown in Fig. 2.2.

2.19.2 Virtual simulation

Virtual simulation is the treatment simulation of patients based solely on CT information. The premise of virtual simulation is that the CT data can be manipulated to render synthetic radiographs of the patient for arbitrary geometries. These radiographs, Digitally Reconstructed Radiographs (DRRs), can be used in place of simulator radiographs to determine the appropriate beam parameters for treatment. The advantage of virtual simulation is that anatomical information may be used directly in the determination of treatment field parameters (Khan *et al*, 1998).

2.19.3 Virtual simulation procedure

A CT simulation begins by placing the patient on the CT simulator table in the treatment position. The patient position is verified on the CT pilot or scout scans. Prior to being scanned, it is imperative that patients be marked with a reference isocentre. Typically, a

position near the centre of the proposed scan volume is chosen, radio-opaque fiducial markers are placed on the anterior and lateral aspects of the patient (with the help of the room lasers to ensure proper alignment) and the patient is tattooed to record the position of the fiducial markers to help with the subsequent patient set-up on the treatment machine. This reference isocentre position can be used as the origin for a reference coordinate system from which the actual treatment isocentre position can be determined through translational motions of the table. The treatment isocentre can be identified on the patient through table motions and the use of a movable sagittal laser (Khan *et al*, 1998).

Target structures and organs of interest can be outlined directly on the CT images using tools available in the virtual simulation software. DRRs and Biological Effective Volumes (BEVs) created from the CT information and outlined data are used to simulate the treatment.

The determination of the treatment beam geometry and shielding is carried out with respect to the target position and critical organ location. Standard beam geometries (e.g. four field boxes, parallel opposed pair and lateral oblique beams) can be used together with conformal shielding to increase the healthy tissue sparing. Alternatively, more unorthodox beam combinations can be used to maximize healthy tissue sparing in the event that a critical organ or structure is in the path of a beam. It is imperative that when choosing beam geometries consideration be given to the prospective dose distributions. Additionally, the physical limitations of the treatment unit and its accessories with respect to patient position must be considered. For example, care must be taken that the gantry position does not conflict with the patient position. Once a reasonable beam

arrangement has been found, the field limits and shielding design may be obtained. Since the precise target location is known, the determination of the shielding design and treatment field limits becomes a matter of choosing an appropriate margin to account for physical and geometric beam effects such as beam penumbra. Once the relevant treatment parameters have been obtained, the treatment beam geometry, the CT data including contours and the electron density information are transferred to the Treatment Planning System (TPS) for the calculation of the dose distribution (Khan *et al*, 1998).

2.20 Conventional Simulator versus Computed Tomography Simulator

The increased soft tissue contrast in combination with the axial anatomical information available from CT scans provides the ability to localize very precisely the target volumes and critical structures. The CT simulation phase allows for accurate identification and delineation of these structures directly on to the CT data set. This ability, in conjunction with the formation of DRRs and BEVs on which organs and targets are projected on to synthetic representations of simulator radiographs, allows the user to define treatment fields with respect to the target volume and critical structure location. By contrast, conventional simulation requires knowledge of tumor position with respect to the visible landmarks on the diagnostic quality simulator radiographs. Since these radiographs provide limited soft tissue contrast, the user is restricted to setting field limits with respect to either the bony landmarks evident on the radiographs or anatomical structures visible with the aid of contrast agents such as barium. Another important advantage of the CT simulation process over the conventional simulation process is the fact that the patient is not required to stay after the scanning has taken place (Khan *et al*, 1998). The patient

only stays the minimum time necessary to acquire the CT data set, and this provides the obvious advantage that the radiotherapy staff may take their time in planning the treatment as well as trying different beam configurations without the patient having to wait on the simulator table.

2.21 Linear Energy Transfer

Linear energy transfer (LET) is the linear density of energy lost by a charged ionizing particle travelling through matter. Since the energy loss is part of the definition, LET is a positive quantity (ICRU; 2011). LET depends on the nature of the radiation as well as on the material traversed. A high LET will attenuate the beam more quickly, generally making shielding more effective and preventing deep penetration. On the other hand, the higher concentration of deposited energy can cause more severe damage to any microscopic structures near the particle track. If a microscopic defect can cause larger-scale failure, as is the case in biological cells and microelectronics, the LET helps explain why radiation damage is sometimes disproportionate to the absorbed dose (ICRU; 2011). Dosimetry attempts to factor in this effect with radiation weighting factors. Linear energy transfer is closely related to stopping power, since both equal the energy loss per unit distance, dE/dx. The stopping power and LET concepts are different in the respect that total stopping power has the nuclear stopping power component and this component does not cause electronic excitations. Hence nuclear stopping power is not contained in LET. While medical physicists and radiobiologists usually speak of linear energy transfer, most non-medical physicists talk about stopping power (ICRU; 2011).

2.22 The Oxygen Effect in Radiation Therapy

The ability of oxygen to potentiate radiation is called the oxygen effect. If cells are exposed to oxygen the effect is markedly reduced. In other words, oxygen is a radio sensitizer, In fact, the most potent one known. Large cancers have a tendency to outgrow their blood supply with a consequent development of hypoxic but viable tumor cells, such hypoxic foci are less sensitive to radiations than surrounding well oxygenated tissues, and may give rise to local recurrence following radiation therapy (Churchill- Davidson *et al.,* 1954).

Many studies, both in vivo and in vitro confirm the fact that for a given lethality, anoxic cells require two or three times the dose required for well oxygenated cells. The first applications of hyperbaric oxygen were made in 1954 where the preliminary results of high pressure oxygen radiation therapy were reported. Later, considerable work was done utilizing experimental tumor systems, relating the effects of anoxia, normal air breathing, 100 percent atmospheric breathing and hyperbaric oxygen. (Churchill- Davidson *et al*., 1954).

2.23 Relative Biological Effectiveness

The expression "relative biologic effectiveness" RBE is commonly used in radiobiology to compare the effectiveness of two radiations in producing a given change. RBE is an expression based upon the dose of baseline radiation needed to produce a given magnitude of effect in a specific system as related to the dose of another radiation needed to produce exactly the same magnitude of effect in the same system.

To a great extent, the RBE of various radiations depends upon the rate of energy loss (LET) along the paths of the individual ionizing particles or photons. Radiations with low LET values produce diffuse ionization throughout the media. In contrast, the individual tracks of particles with high LET values will be short and dense so that the effects will be much more pronounced over the same given track length and will demonstrate a higher RBE (Sinclair *et al.*, 2003).

2.24 The Use of Radioactive Materials for Radiation Therapy

Medical use of radioactive materials falls broadly into two categories: diagnostic and therapeutic procedures. About one-third of all patients admitted to hospitals are diagnosed or treated using radiation or radioactive materials. This branch of medicine is called nuclear medicine, and the radioactive materials are called radiopharmaceuticals.

For most diagnostic nuclear medicine procedures, a small amount of radioactive material is administered, either by injection, inhalation or oral administration. The radiopharmaceutical collects in the organ or area being evaluated, where it emits photons. These photons can be detected by a device known as a gamma camera. The gamma camera produces images that provide information about the organ function and composition, and help physicians locate and identify tumors, size anomalies, or other physiological or functional organ problems. Two examples of nuclear medicine procedures are the use of technetium-99m in the diagnosis of bone, heart or other organ problems and radioactive iodine in the imaging of the thyroid gland (www.nrc.gov/materials/miau/med.use).

Therapeutic uses of radioactive materials include teletherapy, brachytherapy, and therapeutic nuclear medicine. The purpose of all three is to kill cancerous tissue, reduce the size of a tumor, or reduce pain.

In teletherapy**,** an intense beam of radiation from a powerful source external to the patient is focused on the cancerous tissue. An example of teletherapy is the use of a device called the Gamma Knife, which focuses radiation from numerous cobalt-60 sources to a specific location deep within brain tissue (www.nrc.gov/materials/miau/med.use).

In brachytherapy, one or more lower-activity radioactive sources are placed close to, or within, cancerous tissue, such as in the breast, prostate, or cervix. Brachytherapy sources include sealed "seeds" injected or surgically implanted, then removed after the prescribed dose is received by the patient. Intravascular brachytherapy systems use small sources that are placed into arteries using catheters (www.nrc.gov/materials/miau/med.use).

In therapeutic nuclear medicine, high dosages of radioactive materials are injected into, or ingested by, the patient. One example is the use of radioactive iodine to destroy or shrink a diseased thyroid (www.nrc.gov/materials/miau/med.use).

2.25 Nutritional Dependency of Cancer Response to Irradiation

The patient's general health and nutritional status play an extremely important role in his overall chances for cure. Growing cancer, even a small one requires a tremendous amount of nutritional support. Often in the patient's initial phases of cancer growth he will exhibit a normal or increased appetite but with a progressive weight loss. If this is

allowed to continue unchecked, the patient will become markedly debilitated and exhibit signs of a malnutrition state (Andrews *et al*, 1968).

Such a patient obviously is a much poorer candidate for surviving the radical treatments which will be necessary to eradicate his cancer whether this be radical surgery, radiation therapy, or chemotherapy. A declining nutritional status with anaemia is a very common early finding in cancer patients. Under this circumstances normal tissue tolerance is decreased and wound healing is slow. If anemia and a negative nitrogen balance are allowed to continue, patients will exhibit a marked impairment of healing of radiation-induced injuries. In a patient of good nutritional status, these injuries correct themselves very promptly with the completion of therapy (Andrews *et al*, 1968).

It has been reported that a severe decline in general nutritional status may precipitate late changes within the treatment field even months or years following the completion of a course of radiation therapy. Many of these changes are probably based upon an accentuation of vascular damage which appears to progress at a much faster rate within previously irradiated fields. (Andrews *et al*, 1968).

2.26 Principles of Radiation Therapy

Radiation is energy that is carried by waves or a stream of particles. Radiation works by damaging the genes (DNA) in cells. Genes control how cells grow and divide. When radiation damages the genes of a cancer cell, it can't grow and divide any more. Over Time, the cells die. This means radiation can be used to kill cancer cells and shrink Tumors. To understand how radiation works as a treatment, it helps to know the normal life cycle of a cell. The cell cycle goes through 5 phases, one of which is the actual

splitting of the cell. When a cell splits, or divides, into 2 cells, it's called mitosis (Lawrence *et al*, 2008).

2.27 The Cell Cycle and Radiation

The cell cycle phase is important in cancer treatment because usually radiation first kills the cells that are actively dividing. It doesn't work so fast on cells that are in the resting Stage (G_0) or are dividing less often. The amount and type of radiation that reaches the cell and the speed of cell growth affect whether and how quickly the cell will die or be damaged. The term radio sensitivity describes how likely the cell is to be damaged by Radiation. Cancer cells tend to divide quickly and grow out of control. Radiation therapy kills cancer cells that are dividing, but it also affects dividing cells of normal tissues. The damage to normal cells causes unwanted side effects (Kastan *et al*, 2004). Each time radiation therapy is given there needs to be a balance between destroying the cancer cells and minimizing damage to the normal cells. Radiation does not always kill cancer cells or normal cells right away. It might take days or even weeks of treatment for cells to start dying, and they may keep dying off for months after treatment ends. Tissues that grow quickly, such as skin, bone marrow, and the lining of the intestines are often affected right away. In contrast, nerve, breast, brain and bone tissue show later effects. For this reason, radiation treatment can have long-term side effects that might not be seen until long after treatment is over. (Kastan *et al*, 2004).

In the past, it was thought that once an area was treated with radiation it could not be treated with radiation again because of damage to the normal cells in the treatment area. But research suggests that a second course of radiation therapy can be given to some Patients.

2.28 External Beam Radiation

External beam radiation is the most widely used type of radiation therapy. The radiation comes from a machine outside the body and is focused on the cancer. It's a lot like getting an x-ray, but for longer. This type of radiation is most often given by machines called Linear accelerators (Linacs). The radiation is aimed at the cancer, but it also affects the normal tissue it passes through on its way into and out of the body. External beam radiation can be used to treat large areas of the body. It also can treat more than one area, such as the main tumor and nearby lymph nodes. External radiation is usually given daily over several weeks. American Cancer Society (2014).

2.29 Types of External Beam Radiation

2.29.1 Three-dimensional conformal radiation therapy (3D-CRT)

This uses imaging scan pictures and special computers to very precisely map the location of a tumor in 3 dimensions. The patient is fitted with a plastic mold or cast to keep the body part still during treatment. The radiation beams are matched to the shape of the tumor and delivered to the tumor from several directions. Careful aiming of the radiation beam may help reduce radiation damage to normal tissues and better fight the cancer by increasing the radiation dose to the tumor. Photon beams or particles (like protons) can be used in this way. A drawback of 3D-CRT is that it can be hard to see the full extent of some tumors on imaging tests, and any part not seen will not get treated with this therapy American Cancer Society (2014).

2.29.2 Intensity modulated radiation therapy (IMRT)

This is an advanced form of external radiation therapy. As with 3D-CRT, computer programs are used to precisely map the tumor in 3 dimensions. But along with aiming photon beams from several directions, the intensity (strength) of the beams can be adjusted. This gives even more control over the dose, decreasing the radiation reaching sensitive normal tissues while delivering higher doses to the tumor. Some newer radiation machines have imaging scanners built into them. This advance, known as image guided radiation therapy (IGRT), lets the doctor take pictures of the tumor and make minor adjustments in aiming just before giving the radiation. This may help deliver the radiation even more precisely, which may result in fewer side effects, although more research is needed to prove this. American Cancer Society (2014).

A variation of IMRT is called volumetric modulated arc therapy. It uses a machine (called Rapid Arc®) that delivers the radiation quickly as it rotates once around the body. This allows each treatment to be given over just a few minutes. Although this can be more convenient for the patient, it's not yet clear if it's more effective than regular IMRT. Because of its precision, it's even more important that a person remain in the right place and be perfectly still during treatment. A special cast or mold may be made to keep the body in place during treatment. Again, miscalculations in tumor size and exact location can mean missed areas will not get treated. Because IMRT uses a higher total dose of radiation, it may slightly increase the risk of second cancers later on. This is something researchers are looking into. American Cancer Society (2014).

A related technique, intensity modulated proton therapy (IMPT), uses proton beams instead of photon beams. Protons are parts of atoms that cause little damage to tissues they pass through but are very good at killing cells at the end of their path. Very little of the dose goes beyond the tumor at the end of the beam's path. This means that proton beam radiation may be able to deliver more radiation to the cancer while reducing side effects on nearby normal tissues. Despite this theory, a 2012 study of proton beam therapy on localized prostate cancer did not show fewer side effects compared to the more common photon beam radiation. IMPT is often used for tumors near critical body structures such as the eye, the brain, and the spine. Protons can only be put out by a special machine called a cyclotron or synchrotron. This machine costs millions of dollars and requires expert staff. Because of this, proton beam therapy is expensive, and very few treatment centers in the United States offer it. More studies are needed to compare outcomes between proton and photon treatment so that each is used for the cancer type for which it works best. American Cancer Society (2014).

2.30 Possible Side Effects of Radiation Therapy

Normal body tissues vary in their response to radiation. As with tumors, normal tissues in which cells are quickly dividing may be affected. This causes some of the side effects of radiation treatment. Since radiation is a local treatment, side effects depend on the area of the body being treated. The early effects of radiation may be seen a few days or weeks after treatments have started and may go on for several weeks after treatments have ended. Other effects may not show up until months, or even years, later. The most common side effects include skin changes, infertility, lack of sexual appetite etc. Beaumont Health System (2013).

2.31 Interactions of Radiation with Matter

There are three main interactions of radiation with matter. This includes;

2.31.1 Photoelectric effect

In the photoelectric effect, a photon interacts either with an electron which is bound in an individual atom or with an electron in condensed matter, usually a solid, which is not bound to an individual atom but may be shared among many atoms. The atomic photoelectric effect involves the absorption of a photon by an atomic electron which is then ejected from the atom. This can occur only when the incoming photon has energy greater than the ionization energy (EB) of the electron to be removed. Since an atom is much more massive than an electron the ejected electron takes practically all the energy and momentum of the photon. The kinetic energy (K) of the ejected electron is then

$$K = hf - EB \tag{2.1}$$

The ejected electrons are known as photoelectrons and, since the atom is ionized, the Process is one form of photoionization. A photon loses all its energy to an atomic electron which is raised to a higher energy level. The mass attenuation coefficient for photoelectric absorption decreases with increasing photon energy; i.e. as a general rule high energy photons are more penetrating than low energy radiation. For a fixed value of the energy the attenuation coefficient increases with the atomic number Z of the substance. Archana (2009).

2.31.2 Compton effect

In the Compton Effect, the photon scatters from a free electron or a loosely bound atomic electron. The scattered photon has less energy than the incident photon and the excess

energy is transferred to the electron. Convincing evidence that light is made up of particles (photons), and that photons have momentum, can be seen when a photon with energy hf collides with a stationary electron. Some of the energy and momentum is transferred to the electron (this is known as the Compton Effect), but both energy and momentum are conserved in this elastic collision. After the collision, the photon has energy $hf^{/}$ and the electron has acquired a kinetic energy K.

Conservation of energy: $hf = hf' + K$ (2.2)

Combining this with the momentum conservation equations, it can be shown that the wavelength of the outgoing photon is related to the wavelength of the incident photon by the equation 2.3

$$D1 = 1' - 1 = \left({}^{h}/_{m_e c}\right)(1 - cosq) \quad (2.3)$$

The combination of factors ${}^{h}/_{m_e c} = 2.43 \text{ x } 10 - 12$ m, where m_e is the mass of the electron, is known as the Compton wavelength. The collision causes the photon wavelength to increase by somewhere between 0 (for a scattering angle of 0°) and twice the Compton wavelength (for a scattering angle of 180°). Archana (2009).

2.31.3 Pair production

Pair production refers to the creation of an elementary particle and its antiparticle, usually when a photon (or another neutral boson) interacts with a nucleus. For example an electron and its antiparticle, the positron, may be created. This is allowed, provided

there is enough energy available to create the pair – at least the total rest mass energy of the two particles – and that the situation allows both energy and momentum to be conserved. Other pairs produced could be a muon and anti-muon or a tau and anti-tau. However all other conserved quantum numbers (angular momentum, electric charge, lepton number) of the produced particles must sum to zero – thus the created particles shall have opposite values of each other. Archana (2009).

The biological detriment to an organ depends upon;

i. The physical average dose received by the organ.
ii. The pattern of the dose distribution that results from the radiation type and energy.

For the same dose to the organ, alpha or neutron radiation will cause greater harm compared with gamma rays, x rays, or electrons because the ionization events produced by alpha or neutron radiation will be much more closely spaced.The SI unit of equivalent dose H_T is J/kg and its name is the Sievert (Sv). The old unit of the equivalent dose H_T is the rem. The relationship between the Sievert and the rem is given by Eqn 2.4

$$1\ S_V = 100\ \text{rem} \tag{2.4}$$

The organ dose $D_{T,R}$ is a measure of the energy absorption per unit mass averaged over the organ.The equivalent dose H_T is a measure of the biological harm (detriment) to the organ or tissue T as a result of organ dose $D_{T,R}$. If an organ is irradiated by more than one type of radiation, the equivalent dose H_T is given by Eqn 2.5

$$H_T = \sum W_R\, D_{T,R} \tag{2.5}$$

Effective dose E is defined as the summation of tissue equivalent doses, each multiplied by the appropriate tissue weighting factor W_T, to indicate the combination of different doses to several different tissues in a way that correlates well with all stochastic effects combined.

$$E = \sum W_T \; H_T \tag{2.6}$$

The unit of effective dose E is J/kg and its name is the Sievert(S_V) (Radiation safety manual, 2010).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Measurements and Sampling

3.1.1 Introduction

The measurement and sampling was done at the Usman Danfodio University Teaching hospital, Sokoto. The materials used for this research includes;

i. The Treatment planning system.
ii. Teletherapy machine (linear accelerator).
iii. Immobilization devices.
iv. Records of patients from the hospital.
v. CT-Simulator.
vi. Gnuplot software.
vii. Monitor.
viii. The use of experts in the field were used.

3.2 Patients Group

A random selection of cervical cancer patients, who were treated at the Usman Danfodio University Teaching Hospital, Sokoto in the period between March 2012 and November 2013**,** were included in the study. The population sample size was a total of fifty patients treated in a supine position on one of the linear accelerator (LINACS). The LINAC is a dual modality machine manufactured by Elekta which makes use of both electrons and photons (x-rays). The machine has Multiple energies between the range of 6 and 15MeV for photons and 2 – 18MeV

for electrons. These patients were investigated retrospectively. All the fifty patients were treated with the "kneefix" immobilization device.

3.3 Treatment Technique

All patients were simulated in the supine position on a CT-Simulator. The CT-simulator was manufactured by GE and its model is the bright speed model. It is a four slice CT whose serial no is XN0004B-SK-001-GAN. Five skin marks, one at the center of the anterior field and two anti-rotational tattoos on both the lateral sides of the patient were marked and simulation films were taken. Treatment fields of Anterior-posterior (AP) and Posterior-anterior (PA) fields or a four Field technique (AP, PA, right and left lateral fields) were planned with 2 cm margins defined by the clinician from bony anatomy. All patients' treatment parameters were recorded on the patients file and transferred to the treatment machine using the LANTIS^{TM} (record and verify system). Patients were treated with a 100 cm Source to Axis Distance (SAD) isocentric technique. Each treatment session of a patient was therefore carried out at one couch position.

3.4 Immobilization Device

A new immobilizing device "kneefix" was implemented at UDUTH in October, 2010. A localizer system was developed to locate the device reproducibly on the simulator or treatment couch. The "kneefix" device is made up of light weighted closed cell foam, which is easy to clean. The knee cushions have three possible positions (A, B, and C), which are located in absolute coordinates on the table top. The treatment couch position is currently absorbed into the patient's digital file as a setup parameter, which is then verified. The couch position during treatment is however, captured and recorded on LANTIS^{TM} (record and verify system).

3.5 Treatment Machines

The data from the LINACs, where most of cervical cancer patients were scheduled for treatment in the radiotherapy department at UDUTH, were used for this study. The treatment machines had weekly mechanical quality control in which isocentric couch, collimator and gantry rotations, vertical, lateral and longitudinal couch movements; the accuracy of the Optical Distance Imaging (ODI), lasers, back pointer and treatment field light indicator were checked based on the Task Group 40 protocol published by the American Association of Physicists in Medicine (AAPM).

3.6 Methods

3.6.1 Data collection

All patients had a portal imaging pre-treatment verification film on the treatment machine. This film was compared with the simulator image and approved by the radiation oncologist. The treatment couch digital readout of this verified patient position was taken as the intended or planned setup position in the study. Using LANTIS^{TM}, the digital daily treatment couch absolute positions of each patient in terms of the X, Y, and Z position were recorded. These corresponded to the medio-lateral, supero-inferio and anterior-posterior position of the patient respectively. We generated dose values which were used to treat the cervical tumor from the treatment planning system and the values for the volumes were obtained from the beam set up parameter of the individual patient.

3.6.2 Laboratory Tests.

A total of 50 adult non-pregnant females with cervical cancer between the ages of 23 and 89 years of age were used for this study. They had different stages of cervical cancer ranging from stages 1 to stage IV. Different laboratory test were carried out on these patients in order to

determine the extent to which the cancer has spread. The laboratory tests that were carried out on the patients include;

i. Pelvic examination; In this examination, the doctor felt the patients' uterus, vagina, ovaries, fallopian tubes, cervix, bladder, and rectum to check for any unusual changes. A Pap test was done at the same time.

ii. Pap test; A Pap test is used to find cell changes in the cervix. It can find problems that can be treated before they turn into cervical cancer. A Pap test also can find cancer early. If cervical cancer is found early, it's easier to cure. This test is done during a pelvic exam. The patients lie on an exam table with a sheet over their legs and stomach. After which their feet is then placed on holders called stirrups with their knees allowed to fall to the side. The nurse or doctor uses a plastic or metal instrument called a speculum to look into their vagina. He or she then uses a small, soft brush to take a few cells from the cervix (opening to the womb) of the patients. This test takes only a few seconds.

iii. Human Papilloma Virus test; if the Pap test are unclear, the doctor performs an HPV test. An HPV test is similar to a Pap test, where the test is done on a sample of cells from the patient's cervix. Certain strains of HPV, such as HPV-16 and HPV-18, are seen more often in women with cervical cancer and may help confirm a diagnosis. If the doctor says the HPV test is positive, that means it found the presence of HPV.

If the Pap test showed some abnormal cells, and the HPV test is also positive, the doctor suggests one or more of the following diagnostic tests:

i. A colposcopy and cervical biopsy. This test can find out whether and where cancer cells are on the surface of the cervix.

ii. An endocervical biopsy (or curettage). This test is to find out whether cancer cells are in the cervical canal.

iii. A cone biopsy or loop electrosurgical excision procedure (LEEP). These tests are sometimes recommended to remove cervical tissue for examination under a microscope.

3.7 Experimental Procedures

Three basic procedures were carried out on the cervical cancer patients during the study. These procedures include;

i. Pre-planning stage; This stage involves three basic steps. The steps include:

- Clinical evaluation and staging: This process involves finding out how far the cancer has spread. Information from exams and diagnostic tests were used to determine the size of the tumor, how deeply the tumor has invaded tissues within and around the cervix, and the spread to lymph nodes or distant organs (metastasis). This is an important process because the stage of the cancer is the key factor in selecting the right treatment plan. A staging system is a way for members of the cancer care team to summarize the extent of a cancer's spread. The systems used for staging in this research is the FIGO (International Federation of Gynecology and Obstetrics) system
- Treatment intent: The intention of treatment was decided by the entire medical oncology team. For stage 1 – II cervical cancer patients, the intention of the treatment was curative and for stage III – IV cervical cancer patients the treatment intent was palliative.

- Choice of treatment: The choice of treatment of cervical cancer could either be Radiotherapy, chemotherapy, surgery. In this study, all the patients had definitive radiotherapy.

ii. Planning radiotherapy treatment

- Method of patient immobilization; This could either be pelvic or leg immobilization. The patients considered in this study had pelvic immobilization.
- Image acquisition of tumor and patient data for planning using CT-Simulator and treatment planning systems; The CT-Simulator is an isocentrically mounted diagnostic x-ray machine which can reproduce treatment conditions and has the facility for screening by means of an image intensifier linked to a closed circuit television. It has a couch which is capable of all the movements of a treatment unit, a gantry which can be rotated through 360^{o} , and two pairs of cross wires mounted in the beam which can be set to any field size following the 50% isodose line of the beam.
- Delineation of volumes; We delineated the volume of the irradiated organ using the treatment planning system.
- Computation of dose distribution; We computed the dose that was targeted at the cervix and distributed to the surrounding organs of the cervix i.e. bladder, rectum, gastro-intestine, head of femurs and the skin into the computerized treatment planning system.

iii. Treatment delivery

- Dose prescription
- Implementation of treatment
- Verification
- Monitoring treatment
- Recording and reporting treatment
- Evaluation of outcome

3.8 Statistical Analysis

Data obtained were analyzed using Gnuplot plotting software which is a command line based interactive plotting program. A C++ program code was written to help in the plotting computation. Windows was used for the analysis.

Also, the expression of the equation of the normal tissue complication probability (NTCP) model was used to analyze the data. This equation is given as;

$$NTCP\,(D,v) = \exp[-N_0 V^{-k}\, exp\{-aGD\}] \qquad (3.1)$$

Where;

$NTCP\,(D,v)$ = the normal tissue complication probability with respect to the normal tissue dose delivered per fraction and volume of the normal tissue.

N_0 and k are the tissue / organ specific, non-negative adjustable parameters.

V is the uniformly irradiated partial volume of the tissue / organ (This research work made use of whole volume)

D is the normal tissue dose delivered with d dose per fraction.

The Tables below gives the parameters of aG, k and N_0, for the organs of interest (bladder, rectum, gastro-intestine, head of femurs and skin) for this research work.

Table 3.1: Parameters aG, k and N_0, for the organs of interest. Emami (1991)

Organs	aG	k	N_0	End Point
Bladder	0.1171	2.9239	7007.99	Symptomatic bladder contracture and volume loss
Skin	0.0886	0.5867	351.42	Necrosis / ulceration
	0.0976	0	393.94	Telangiectasia
Small intestine	0.1126	0.7617	302.92	Obstruction / perforation
Femoral head & neck	0.1126	0	1045.23	Necrosis
Rectum	0.0732	0	241.84	Severe proctitis / necrosis / stenosis / fistula
Bladder	0.1171	2.9239	7007.99	Symptomatic bladder contracture and volume loss

Table 3.2: Parameters aG, k and N_0, for the interested organs (Emami *et al,* 1991).

Organ	aG	K	N_0	References
Bladder	0.0476	0.1582	42.61	Emami et al,1991; Rubin et al, 1975; Rubin, 1989; Storey et al, 2000; Marks et al, 1995
Skin	0.0857	0.6015	283.51	Necrosis:- Emami et al,1991; Rubin et al, 1975; Archambeau et al 1995
	0.0885	0	219.39	Telangiectasia:- Emami et al,1991; Archambeau et al 1995
Small intestine	0.1071	0.3737	345.60	Emami et al,1991; Rubin et al, 1975; Rubin, 1989
Femoral head & neck	0.0842	0	280.26	Emami et al,1991; Rubin et al, 1975
Rectum	0.0490	0.2001	42.44	Emami et al,1991; Rubin et al, 1975; Rubin, 1989; Chen et al, 2000; Wachter et al, 2002;Storey et al, 2000; Schultheiss et al, 1997; Boersma et al, 1998; Kutcher et al, 1996

CHAPTER FOUR

4.0 RESULTS AND DISCUSSION

4.1 Volume Calculations for Patients with Three-Dimensional Plans

Using the beam set up parameters for patients given in the appendix 1, the tumor volume for patients with three-dimensional plans was estimated from the dimensions of the set field size used to treat the particular patient. For example, for a patient treated using four isocentric fields namely a 13 cm x 15 cm anterior posterior field and 8.6 cm x 15cm left and right lateral oblique field, the tumor volume was determined from the geometric boundaries of the set treatment fields i.e. 13cm x 15 cm x 8.6cm. This is an overestimation of the "tumor volume" because the treated volume included normal tissue around the tumor. As a result of this method used, the tumor volume of the three-dimensional plans was in most cases very large and in order to solve this problem, the tumor volume was scaled down to a smaller volume and this was done by dividing the tumor volume by a constant reference volume. The reference volume was taken to be 9.9cm^3. This value was gotten by taking 10% of the actual volume (Table 4.3) of the irradiated organ for each patient since the reference volume must always be a constant volume.

4.2 Ntcp Calculations With Respect to the Linear Quadratic Model

All the 50 patients who were eligible for this study had a three dimensional treament plan. The Normal tissue complication probability equation is given as follows;

$$NTCP\ (D, v) = \exp[-N_0 V^{-k}\ exp\{-\alpha T D\}] \qquad (4.1)$$

Where N = tissue/organ, non-negative adjustable parameter.

D = Normal tissue dose.

v = uniformly irradiated partial volume of the organ i.e. $v = V/V_{ref}$

Where V is the uniformly irradiated organ and V_{ref} is the reference volume

k = tissue/organ, non-negative adjustable parameter.

Using equation 4.1, the values of the constants given in Table 4.1, the volume of irradiated organ given in Table 4.3 and the values of the doses given to the organs in Table 4.2, the NTCP values for the different organs (bladder, rectum, gastro-intestine, head of femurs and skin) were calculated and presented in Table 4.3. The values of the Normal Tissue Complication Probability for the various organs were found to be in the range of 0 and 1 except in the case of the Gastro-intestine where extremely small values were found in some patients. This could be as a result of large volume of the area that absorbed doses of radiation.

Table 4.1: Values of the fitted parameters for this work and that of Emami. The symbol E stands for error.

Organ	This Work					Emami's Work(Emami et al, 1991)		
	k	αG	N	$\Delta k(E)$	$\Delta \alpha G(E)$	k	αG	N
Bladder	2.9652	0.1107	7007.99	2.807	0.0631	0.1582	0.0476	7007.99
Rectum	0.8041	0.0502	80.68	0.8041	0.023	0	0.0732	80.68
GIT	0.7348	0.1141	302.92	0.0269	0.0015	0.7617	0.1126	302.92
Right femur	2.3641	0.1037	1045.23	2.3641	0.0089	0	0.1126	1045.23
Left femur	2.2685	0.0735	1045.23	2.2685	0.0391	0	0.1126	1045.23
Skin	1.6420	0.0882	351.42	1.0553	0.0004	0.5867	0.0886	351.42

Table 4.2: Doses (Gy) for the various Organs of interest

Bladder dose(Gy)	Rectal dose(Gy)	Gastro-Intestine(Gy)	Head of Femur dose Left(Gy)	Right(Gy)	Skin dose(Gy)
17	21	2	18	18	16
15	18	3	17	17	15
20	20	1	1	1	14
40	26	31	29	29	17
28	28	28	24	24	16
28	36	28	27	27	16
30	29	28	29	29	19
27	35	28	28	28	17
44	26	44	26	26	17
29	18	6	17	17	13
21	21	20	7	5	12
27	29	25	26	26	15
27	25	29	27	27	17
31	31	12	30	30	16

28	47	28	25	20	18
28	30	28	27	27	19
11	19	0	9	9	8
18	24	18	18	18	12
46	28	31	26	26	16
30	30	31	2	2	22
31	31	31	31	31	22
32	32	7	8	8	5
46	0	0	0	0	0
30	32	21	31	31	21
45	29	28	27	27	16
27	28	27	6	6	17
30	30	26	28	28	19
32	31	33	3	3	25
28	32	27	27	26	15
32	32	31	32	32	22
29	17	0	0	0	12
28	31	0	0	0	19
26	24	0	0	0	12
14	14	0	0	0	12
36	36	0	0	0	15
49	28	0	0	0	15
19	24	0	21	21	12
27	30	31	14	19	20
31	32	0	0	0	22
29	30	0	0	0	18
30	32	20	31	31	22
28	45	28	20	20	18
28	47	27	20	20	18
46	28	31	27	26	16
28	32	27	27	26	15
30	28	28	29	29	19
30	27	29	29	29	19
44	27	44	26	26	18
44	28	44	26	26	17

Table 4.3: Volume (cm^3) of irradiated Organs and values of NTCP for the different Organs

Volume of Irradiated Tissue (cm^3)	NTCP Values for the different Organs					
	Bladder	Rectum	Gastro-Intestine	Head of Femur		Skin
				Left	Right	
1000.00	0.2128	0.0866	2.0741e-20	0.1616	0.4231	0.1084
1320.00	0.1415	0.0588	2.5878e-18	0.1407	0.3819	0.0882
1300.00	0.3366	0.0766	9.3522e-23	0.0017	0.0029	0.0705
0893.04	0.9006	0.1474	0.1772	0.4427	0.7793	0.1309
2116.80	0.6526	0.1762	0.0883	0.3089	0.6455	0.1084
0000.00	0.0000	0.0000	0.0000	0	0.0000	0.0000
1453.20	0.7134	0.1915	0.0883	0.4427	0.7793	0.1821
1664.00	0.6189	0.2917	0.0883	0.4162	0.7565	0.1309
2216.76	0.9365	0.1474	0.6700	0.3625	0.7051	0.1309
1920.00	0.6841	0.0588	2.8476e-13	0.1407	0.3819	0.0551
2520.00	0.3796	0.0866	0.0025	0.0169	0.0242	0.0421
2470.00	0.6189	0.1915	0.0333	0.3625	0.7051	0.0882
2210.00	0.6189	0.1339	0.1144	0.3894	0.7318	0.1309
1855.35	0.7406	0.2234	4.1323e-07	0.4690	0.8003	0.1084
1626.90	0.6526	0.5045	0.0883	0.3356	0.5032	0.1555
1679.60	0.6526	0.2072	0.0883	0.3894	0.7318	0.1821
1731.60	0.0439	0.0673	2.21512e-25	0.0295	0.0935	0.0109
2184.00	0.2525	0.1210	0.0005	0.1616	0.4231	0.0421
2340.00	0.9494	0.1762	0.1772	0.3625	0.7051	0.1084
1911.00	0.7134	0.2072	0.1772	0.0027	0.0054	0.2710
3610.00	0.7406	0.2234	0.1772	0.4947	0.8195	0.2710
2250.36	0.7655	0.2407	6.1727e-12	0.0226	0.0705	0.0027
1320.00	1.20e05	0.0000	2.2151e-25	0.0011	0.0014	0.0001
2754.00	0.7134	0.0010	0.0048	0.4947	0.8195	0.2402
1934.48	0.9433	0.2400	0.0883	0.3894	0.7318	0.1084
2142.00	0.6189	0.1919	0.0662	0.0124	0.0360	0.1309
1677.00	0.7134	0.1765	0.0479	0.4162	0.7565	0.1821
2420.60	0.7655	0.2077	0.2511	0.0042	0.0095	0.3676
1864.05	0.6526	0.2237	0.0662	0.3894	0.7051	0.0882
1768.00	0.7655	0.2407	0.1772	0.5199	0.8371	0.2710
1662.50	0.6841	0.2407	2.21512e-25	0.0011	0.0014	0.0421
2340.00	0.6526	0.0510	2.21512e-25	0.0011	0.0014	0.1821
1440.00	0.5831	0.2235	2.21512e-25	0.0011	0.0014	0.0421
2220.00	0.1109	0.1210	2.21512e-25	0.0011	0.0014	0.0421
3072.00	0.8460	0.0318	2.21512e-25	0.0011	0.0014	0.0882
2028.00	0.9641	0.3094	2.21512e-25	0.0011	0.0014	0.0882
2895.00	0.2940	0.1762	2.21512e-25	0.2315	0.5414	0.0421
2016.00	0.6189	0.1210	0.1772	0.0869	0.4637	0.2104
1758.64	0.7406	0.2073	2.21512e-25	0.0011	0.0014	0.2710
2565.00	0.6841	0.2400	2.21512e-25	0.0011	0.0014	0.1555
0343.00	0.7134	0.4702	0.00255044	0.4947	0.8195	0.2710
2400.00	0.6526	0.5045	0.0883999	0.2071	0.5032	0.1555
2432.00	0.6526	0.1763	0.0662042	0.2071	0.5032	0.1555

2223.00	0.9494	0.2401	0.1772	0.3894	0.7051	0.1084
3078.00	0.6526	0.1763	0.0662042	0.3894	0.7051	0.0882
2565.00	0.7134	0.1616	0.0883999	0.4427	0.7793	0.1821
1892.80	0.7134	0.1616	0.114458	0.4427	0.7793	0.1821
1800.00	0.9365	0.1763	0.670082	0.3625	0.7051	0.1555
1134.60	0.9365	0.0012	0.670082	0.3625	0.7051	0.1309
1008.00	1.2056e05	0.0012	2.21512e-25	0.0011	0.0014	0.0001

4.3 Fitting Parameters

Clinical dose data were used to calculate the NTCP values using equation (4.1) in order to estimate the values of k and αG. The least square fitting was done using the equation given as follows;

$$f(x) = \exp[-a * exp\{-bx\}] \quad (4.2)$$

Where a and b are the fitting parameters. Comparing equation (4.2) with equation (4.1)

k was calculated from the fitting equation as;

$$a = NV^{-K} \quad (4.3)$$

$$k = \frac{(\ln N - Lna)}{\ln V} \quad (4.4)$$

Where a is the fitting parameter.

The calculated values of k and αG are listed in table 4.1 along with those of Emami and coworkers. Due to the unavailability of adequate data, no attempt was made to correlate the NTCP with a reference volume. To solve this problem and to simplify the calculation, the organs were assumed to have the same reference volume. A C++ program code was written to help in

the plotting computation and the Gnuplot plotting software was used for both the plots and fitting.

Values of k for the organs in Table 4.1 indicate that the Organs (bladder, skin, right and left femur) which have higher values of k>1, have high volume dependency than those of GIT and rectum which have lower values of k<1 i.e. the volume is directly proportional to the value of k. None of the organs in this work show lack of dependency on volume.

4.4 Explanation of Demographic Parameters

Table 4.4: Stage of Cervical Cancer at Presentation

Stage of cervical cancer	Frequency
1	2
11	18
111	25
1V	5
Total	50

Table 4.4 shows the frequency of the different stages of cervical cancer that was considered in this work. The higher the number of the stage, the farther the cancer has metastasized. Most patients that were used in this work have stage iii cervical cancer as can be seen in the distribution.

Table 4.5: Dose of radiation (Gy) distribution (EBRT)

Radiation dose	Frequency
20 – 29	3
30 – 39	9
40 – 49	5
50 – 59	32
60 – 69	0
70 – 79	0
80 – 89	1
Total	50

Table 4.5 shows the frequency of the dose of radiation distribution. The dose of radiation is the dose given to the cervix of the cervical cancer patients during treatment. From the distribution, it can be seen that the dose range of 50 – 59 Gy has the highest frequency. This could probably be due to the fact that most patients in this research work are presenting at an advanced stage of cervical cancer.

Table 4.6: Fractionation Schedule of Total Radiation Dose (Gy)

Fractionation Schedule	Frequency
5 – 9	1
10 – 14	5
15 – 19	4
20 – 24	0
25 – 29	39
30 – 34	1
Total	50

Table 4.6 gives a distribution of the fractionation schedule. The fractionation schedule gives the number of Gy per fraction that will be administered to a patient for a period of time until the total radiation dose is given. From the distribution, it is seen that the range between 25 – 29 has the highest distribution.

Table 4.7:Bladder Dose (Gy) Distribution

Distribution	Frequency
11 – 20	7
21 – 30	27
31 – 40	8
41 – 50	8
Total	50

Table 4.7 shows the distribution of the dose that goes to the bladder after the cervix has been exposed to a certain dose of radiation. From the table it can be seen that 27 patients received a

dose ranging from 21 – 30Gy, 8 patients received a dose ranging from 31 – 50Gy and 11 patients had a dose ranging from 11 – 20Gy when the cervix was exposed to a certain amount of radiation. This same explanation goes for tables 4.8 – 4.12 which show the amount of dose that goes to the organs after the cervix have been exposed to a certain dose of radiation.

Table 4.8: Rectal Dose (Gy) Distribution

Distribution	Frequency
11 – 20	5
21 – 30	25
31 – 40	15
41 – 50	5
Total	50

Table 4.9: Gastro Intestinal Dose (Gy) Distribution

Distribution	**Frequency**
0 – 9	12
1 – 10	4
21 – 30	17
31 – 40	17
41 – 50	5
Total	50

Table 4.10: Right Femoral Dose (Gy) distribution

Distribution	Frequency
0 – 9	10
1 – 10	5
11 – 20	7
21 – 30	21
31 – 40	5
41 – 50	2
Total	50

Table 4.11: Left Femoral Dose (Gy) Distribution

Distribution	Frequency
0 – 9	12
1 – 10	7
11 – 20	6
21 – 30	22
31 – 40	3
Total	50

Table 4.12: Skin Dose (Gy) Distribution

Distribution	Frequency
0 – 9	13
1 – 10	2
11 – 20	29
21 – 30	6
Total	50

4.5 Explanation of Graphs

The result of the experimental findings is discussed and analyzed in this chapter. The analyzed relations of the NTCP equations of the various organs (bladder, rectum, head of femurs, gastro-intestine and skin) were then plotted against the various organ doses. Thus, having the objectives of the work in mind. The objectives of this work were obtained. The results will be seen to provide the required results.

Fig 4.1 – 4.6 show graphical representations of the curves of NTCP plotted between the various organ doses (bladder, rectum, gastro-intestine, head of femurs and skin) while keeping the whole volume of the irradiated organ constant. This was done to demonstrate the applicability of the linear quadratic model of the NTCP equation. Each figure has three curves which shows 3/3 partial volume, whole volume and 1/3 partial volume of irradiated organ whose labelling have been properly differentiated with the colored lines. The whole volume curve gives the line for the plotted data obtained from this research. By 1/3 and 3/3 partial volume, we mean that the original volume (whole volume) of the irradiated organ considered in this study was divided and

multiplied by three respectively. This was done in order to see the effect of NTCP on dose and volume.

For each figure, it can be observed that there exists a relationship between the N.T.C.P value and the various organ doses (bladder, rectum, gastro-intestine, head of femurs and skin) given. As the doses for these organs increases, the probability of complication gets larger for these organs. From the plot of the ordinary equation of the linear quadratic model, the expected shape of the curve is supposed to be an S-shape curve or a sigmoid curve. But In this research work, Fig 4.2 – 4.6, do not clearly exhibit the S-curve behavior. This may probably be due to the fact that doses higher than 50Gy were not administered to the organs (rectum, gastro-intestine, head of femurs and skin) shown in these figures. From previous works Rubin and Cassarett (1968), Emami (1991) and Khewar (2005) where patients were given doses as high as 125Gy, the graph clearly exhibits this sigmoid shape and from these works, it is seen that the higher the doses, the more likely that the S-curve shape is obtained. The fitting equations have been incorporated into all the graphs along with the values of the fitting parameters (a and b) as shown in Figures 4.1 – 4.6. It should be noted that the value b is the same as αG (comparing Equation 4.1 with 4.2) and the value a is gotten in order to obtain the value of k which explains the volume effect on the curves.

Fig 4.1 shows a curve of NTCP against bladder dose. In this curve, it is observed that the values of NTCP do not appreciate until a threshold dose is applied. The shape of the curve is sigmoid and it is seen from this graph that the curve for the whole volume and 1/3 partial volume begins to rise when a dose of about 5Gy and 15Gy was administered respectively. For the 3/3 partial volume, the threshold dose is obviously negative. This difference in threshold value simply

means that when we have 1/3 of the whole volume of the organ irradiated at a particular dose say 15Gy, there is no probability of complication (about 0%) as compared to a higher probability of complication (15%) when the whole volume of the organ is irradiated. Tripling the whole volume of the bladder by three is not reasonable as seen in the figure as doses less than zero cannot be administered to the patients. For the bladder to experience no complication, then it should not be exposed to doses greater 5Gy. This study, therefore shows that for bladder cases, the smaller the volume of the irradiated organ, the lesser the complication to the bladder and vice versa. The fitting equation and the value of the fitting parameter have been incorporated into the plot (Fig 4.1). The value of the fitting parameters a and b (aG) have been calculated to be approximately 10.3413 and 0.1101 respectively. Comparing equation 4.2 with 4.1, the value of a, was calculated in order to determine the value of k. From equation 4.1, it is seen that the volume effect is highly dependent on the value of k. Values of k indicate that the organs which have higher values of k have high volume dependency than that of the lower value of k i.e. the volume dependency of the organs is directly proportional to the value of k. Therefore, the higher the value of k, the more probable that more volume of the irradiated organ becomes complicated.

Fig 4.2 shows a curve of NTCP against gastro-intestinal dose (GIT). In this curve, it is observed that as the doses to the GIT increases, the probability of complication also increases. The threshold values for 3/3 partial volume, whole organ volume and 1/3 partial volume of the intestine are at about 12Gy, 21Gy and 32Gy respectively. It is observed that at a certain dose say 20Gy for the whole volume and 1/3 partial volume, no complication occurs but for the 3/3 volume the complication probability rises to 0.1(10%). At 10Gy for 3/3 partial volume, the probability of complication is 0%. This implies that at a dose of 20Gy, no portion of the GIT

becomes complicated or damaged for whole volume and 1/3 partial volume. But for the 3/3 volume, 10% of the GIT becomes damaged at 20Gy with no complication at a dose of 10Gy. This study therefore shows that it is safer to administer doses as high as 20Gy to the GIT for whole volume and 1/3 partial volume but not for 3/3 partial volume. If the volume of the GIT must be tripled during treatment, then a maximum dose of 12Gy should not be administered to the GIT otherwise this will result to complications. Again, the whole volume, 1/3 partial volume and 3/3 partial volume curve does not completely show the sigmoid shape within the range of dose values but simply reduces the exponential shape though if we increase the dose further, the S-curve shape may come out better. Another reason could be as a result of the value of aG (b), which is a slope parameter that affects the steepness of the S-shape curve. From the equation of the linear quadratic model (equation 4.1), it will be observed that the higher the value of aG, the less steep the curve becomes and the lower the value of aG, the steeper the curve. From Table 4.1, it will be observed that the value of aG for the GIT is higher than that of all the other organs except for the bladder and the k value (which explains the volume effect) for the GIT is lower than that of the bladder. This explains why a smaller portion of the curve is damaged when comparing it to the bladder since the lower the value of k, the more probable that less volume of the irradiated organ becomes complicated. The value of the fitting parameters a and b (aG) have been calculated to be approximately 60.3413 and 0.1141 respectively.

Fig 4.3 shows a curve of NTCP against left femoral dose. It is seen from the graph that as the dose to the left femur increases, the probability of complication also increases. The threshold values for whole volume and 1/3 partial volume is given as 5Gy and 18Gy respectively while the threshold value for 3/3 volume falls within the negative portion of the graph. At a certain

dose say about 17.5Gy, it will be observed that no complication arises for 1/3 partial volume but a large portion of the curve gets complicated for the whole volume and 3/3 partial volume. This study therefore, shows that for left femur, it is safer to administer doses at smaller volumes say 1/3 of the whole volume because at smaller volumes, little or no damage is done to the left femur. At whole volume, even though the probability of complication is about 0.1(10%) more portion of the left femur is damaged. For the 3/3 volume it is seen that the damage done to the left femur rises to about 0.5(50%) with a greater portion of the femur being damaged. Just like in Fig 4.2, this curve does not show the sigmoid shape within the range of values and simply reduces the exponential shape and unlike Fig 4.2 and 4.1, the curve is steeper. This may be due to the fact that doses not greater than 35Gy were absorbed by the left femur also, the value of aG (Table 4.1) which is the parameter that determines the steepness of the curve is quite low. The higher the value of k, the greater the volume of the damaged organ (equation 4.1) and from table 4.1, the k value for left femur, bladder and right femur are close which explains why at 17.5Gy about the same whole volume of these organs are damaged. The value of the fitting parameters a and b (aG) have been calculated to be approximately 6.7145 and 0.0174 respectively.

Fig 4.4 is a curve of NTCP against right femoral dose. Also, this curve does not show the sigmoid shape within the range of values and simply reduces the exponential shape as in the case of Fig 4.2 and 4.3 but then it is observed that the curve is less steep when compared to Figures 4.2 and 4.3. This is due to the fact that from Table 4.1, the right femur has a higher value of aG (the higher the value of aG, the less steep the curve from the linear quadratic model) than that of the Gastro-intestine and left femur. The value of the NTCP for the 1/3 volume and whole volume begins to appreciate at a dose of 12Gy and 2Gy respectively. At a dose of 12Gy,

it will be observed that the probability of complication to the whole volume and 3/3 partial volume is 14% and 50% respectively with no complication for 1/3 partial volume. Therefore, this research work brings out the fact that for right femur, it is better to irradiate smaller volumes (1/3) at a given dose of 12Gy as this dose gives no complication. For whole volumes, a dose of about 2Gy gives no complication while for 3/3 volume the threshold dose falls within the negative portion of the curve. Again, it is observed that a fairly large portion of the whole volume becomes damaged. This is due to the large value of k. The higher the value of k, the larger the volume of the organ that becomes damaged. The volume effect is largely dependent on the k-parameter (equation 4.1) .The k value is approximately 2.4 which is quite high when compared to some of the organs (rectum, GIT, left femur and skin). The fitting parameters a and b were calculated to be 5.6019 and 0.1026 respectively.

Fig 4.5 is a curve of NTCP against rectal dose. This curve does not show the sigmoid shape within the range of values and simply reduces the exponential shape as in the case of fig 4.2 - 4.4. It will be observed that Fig 4.5 is the steepest of all the curves and this is due to the fact that the value of aG is lowest for the rectum. This confirms the explanation that the lower the value of aG the steeper the slope. The NTCP value for whole volume and 1/3 partial volume begins to appreciate at a dose of about 6Gy and 27Gy respectively. For 3/3 partial volume, the NTCP appreciates at a region within the negative portion of the curve. At a dose of say 30Gy, it will be observed that the probability of complication for 3/3 partial volume, whole volume and 1/3 partial volumes are 45%, 11% and less than 1% respectively. This study therefore shows that for rectum, it is safer to administer doses not greater than 30 Gy to 1/3 of the whole volume. This is because at 30Gy for 1/3 partial volume, the rectum experiences little or no complication whereas in the case of the whole volume of the irradiated organ, the probability of complication

is at about 0.11. For 3/3 partial volume the probability of complication is at 0.45 which means that tripling the whole volume of the irradiated organ will cause more damage to the rectum and therefore should be avoided. For the rectum to be free of complications at whole volumes, it has to be irradiated at a dose not greater than 6Gy as seen in the graph. It will be observed that at 30Gy, half of the volume of the curve for the plotted value (whole volume) is damaged. This may probably be due to the value of k (Table 4.1) since the volume dependency of the organ is directly proportional to the value of k. If we compare what happens to all the other organs at 30Gy, we will observe that for right femur, a very large portion for both the partial and whole volumes of the organ is damaged. The same observation is found for left femur and bladder due to the fact that they have a high value of k (Table 4.1). For GIT and rectum, a smaller portion of the whole and partial volume is affected because their k values are quite low. Doses beyond 25Gy were not absorbed by the skin but then it can be observed from the graph (Fig 4.6) that if the dose values were to be extended to 30Gy, a large volume of the organ will be affected due to the fairly high value of k (Table 4.1). The fitting parameters a and b (aG) were calculated to be 6.2854 and 0.0453 respectively.

Fig 4.6 is a curve of NTCP against skin dose. In this curve, it is observed that the values of NTCP begins to appreciate at a dose of about 7Gy for whole volume, 18Gy for 1/3 partial volume and below 0 for 3/3 partial volume. These threshold values simply mean that for whole volume, one starts to observe complications when a dose of about 7Gy is administered. While for 1/3 partial volume complication begins at 18Gy. This study therefore shows that irradiation of the whole volume and 1/3 partial volume of the skin at a maximum dose of 7Gy and 20Gy is safer for the patients. If doses greater than these values (7Gy and 20Gy) are administered to the whole and 1/3 partial volumes of the skin, complications will be seen. Irradiation of the skin at

3/3 of the whole volume is quite unreasonable as doses less than zero cannot be administered to the patients therefore, the decision of the clinical oncologist may be required. The whole volume curve would have exhibited the sigmoid shape if the dose values were extended beyond 25Gy. Fig 4.6 is a steep curve this may be due to the fact that the value of aG which is a parameter that determines the steepness of the curve is low when compared to that of the Bladder, Gastro-intestine and Right femur. The value of the fitting parameters a and b have been calculated to be approximately 9.6614 and 0.0909 respectively.

Table 4.1 shows the values of the constants (αG and K) calculated for this research and the values used by Emami et al (1991). It can be seen that the constant values (k) for the Bladder, Rectum, Right femur, Left femur and Skin is high when compared with the values gotten by Emami et al (1991). Only the value for the GIT shows a close range. Also, the value of the constants (αG) for all the organs used in this work shows a close range of value when compared with the work done by Emami et al (1991). These differences in values could be as a result of the fact that this research work made use of whole volume of the organ irradiated when compared with that of Emami et al (1991) who used partial volume. Another reason could be as a result of the fact that the treatment planning system used by Emami et al (1991) was a 2D-treatment planning system whereas this work made use of a 3D-treatment planning system.

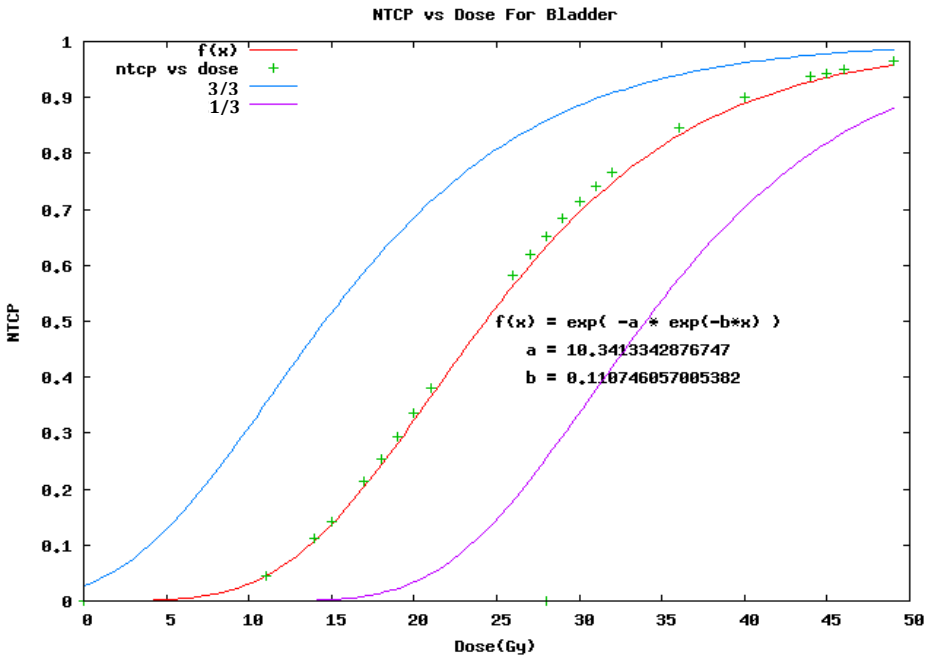


Fig 4.1; Curve of NTCP against Bladder dose.

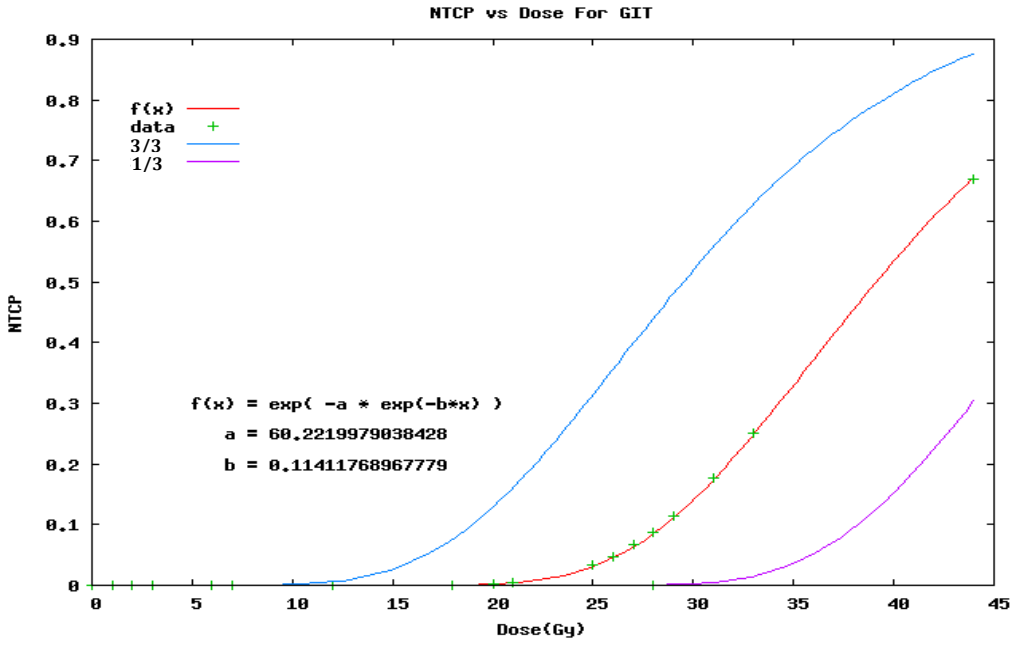


Fig 4.2; Curve of NTCP against GIT dose.

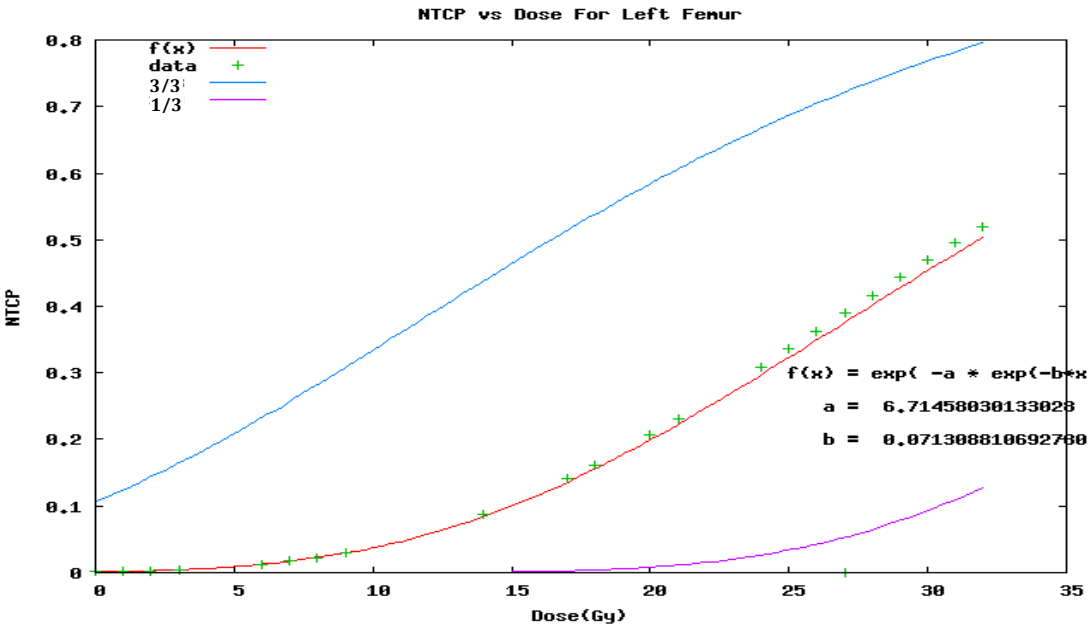


Fig 4.3; Curve of NTCP against left femur dose.

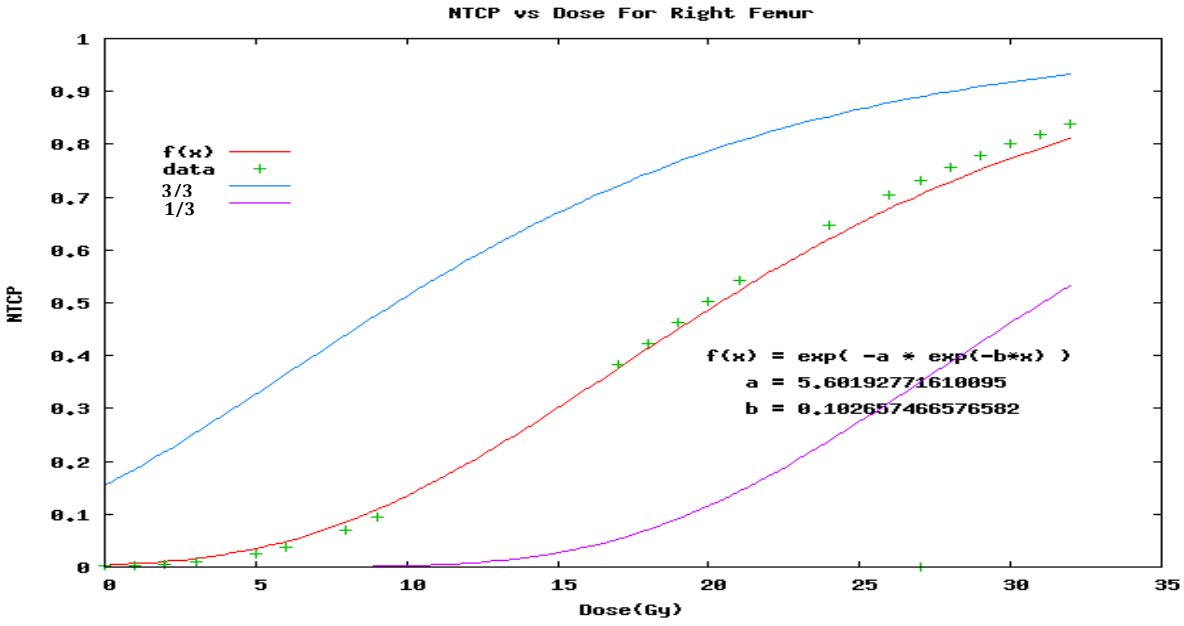


Fig 4.4; Curve of NTCP against right femur dose.

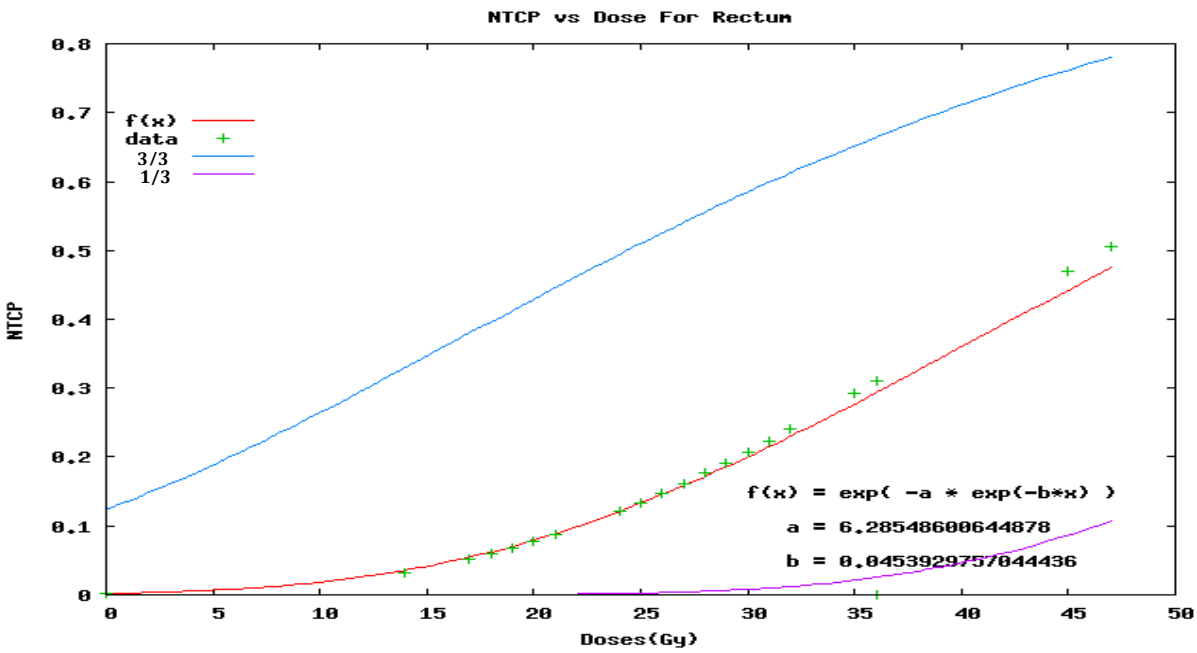


Fig 4.5; Curve of NTCP against rectal dose.

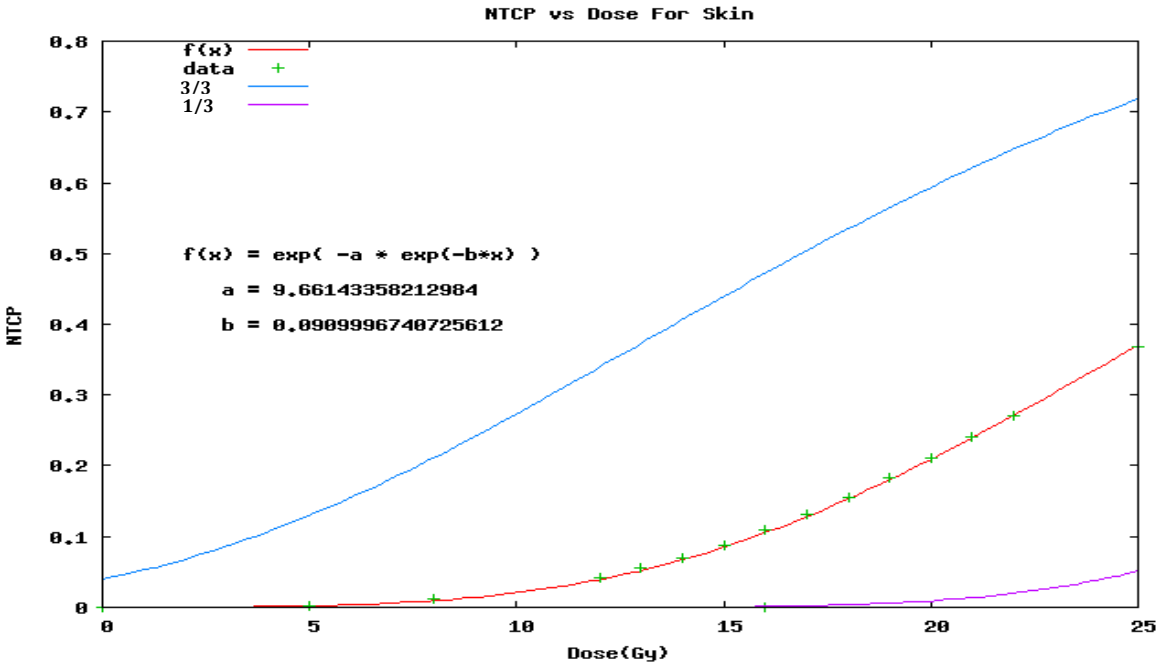


Fig 4.6; Curve of NTCP against skin dose.

CHAPTER FIVE

5.0 CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusion

This study was carried out on patients undergoing cervical cancer treatment at the Usman Danfodio University Teaching Hospital Sokoto where the teletherapy machine (linear accelerator), CT-simulator and the 3D- treatment planning system were used.

The various stages of cervical cancer in the sampled patients were from stages 1 – 1V. Different fractionation schedules were used for different patients and various doses of radiation were also administered to the different patient depending on the stage of cervical cancer.

From the various graphs, it is seen that a fairly good result have been found between the curves. For each figure, it was generally observed that a good relationship exists between the N.T.C.P value and the organ (bladder, rectum, gastro-intestine, head of femurs and skin) doses given. As the doses increases for all the organs, the probability of complication gets larger for these ranges (0%-100%). This observed result is in agreement with what other researchers have done Rubin and Cassarett (1968), (Emami *et al*., 1991) and Khewar (2005). For all the organs, it was observed that the smaller the volume of the organ, the lesser the complication to these organs (bladder, rectum, gastro-intestine, head of femurs and skin). Therefore, hospitals should bear it in mind when administering doses to these organs that it is specifically safer to administer doses to 1/3 partial volumes of the irradiated organs. Also, as the value of αG for all the organs decreases (Table 4.1), the curves becomes steeper. The value of αG determines how sharp the dose increases in these organs.

This study has shown that the bladder at 1/3 and whole volume of the organ should not be exposed to doses greater than 15Gy and 5Gy respectively otherwise complications would be experienced. In this research work, the whole volumes of the sampled patients' bladder were exposed to doses ranging from 11Gy-49Gy with a mean dose of 38Gy. At 38Gy, the probability of complication is about 75% showing that patients are in great danger. For the gastro-intestine, if doses beyond 21Gy, 32Gy and 12Gy for whole volume, 1/3 volume and 3/3 volume respectively are absorbed, complications begins to arise. This study shows that the whole volumes of the gastro-intestine of the sampled patients were exposed to doses ranging from 1Gy – 44Gy with a mean dose of 43Gy. At 43Gy, the probability of complication is about 61% which poses a great danger to the patients. The whole and 1/3 partial volumes for left femur has threshold values of 5Gyand 18Gy respectively and for right femur 1/3 partial volume and whole volume have a threshold value of 12Gy and 2Gy respectively. The whole volumes of the patients' left and right femur used in this research work were exposed to doses which varied from 1Gy to 33Gy with a mean dose of 31Gy. At 31Gy, the probability of complication for left and right femur is about 49% which means less than half of the left and right femur is damaged. The whole and1/3 partial volumes for the rectum have a threshold dose of 6Gy and 27Gy respectively. The dose of the whole volume absorbed by the rectum ranged from 14Gy to 44Gy with a mean dose of 43Gy and at 43Gy, the rectum experiences complication of about 40% which means less than half of the rectum of these patients considered in this research work experienced complication. The whole and1/3 partial volumes for the skin have a threshold dose of 7Gy and 18Gy respectively For skin, the whole volume absorbs a dose within the range of 5Gy and 25Gy with a mean dose of 20Gy. At 20 Gy, the skin experiences complication of about

18%. Thus, showing that the patients experienced very little complication compared to the other organs.

For the bladder, rectum, gastro-intestine, right femur and skin, it was observed that the threshold value for 3/3 partial volumes of these organs are negative and since doses below 0Gy (beyond therapeutic range) cannot be administered to patients, the clinical judgment of the treating physician prevails in the treatment decision.

The fitted values of k and αG obtained in this work shows significant discrepancies when compared with the work done by (Emami *et al.,* 1991). This may be due to the fact that in the work done by Emami *et al*, the conventional 2D-Traetment planning system was used unlike the 3D-treatment planning system which was used for this research work. Secondly, doses exceeding 50Gy were not administered to the patients under this study at UDUTH whereas in the case of Emami *et al* doses as high as 125Gy were administered to the patients.

Values of k for the various organs considered in this work indicate that organs which have high values of $k>1$, have a higher volume dependency than organs which have lower values of $k<1$.

The linear quadratic model was the only model used in this work and could not be compared with other models such as the Probit and Logit model due to insufficient time and lack of available facilities.

5.2 Recommendation

iv. More patients should be sampled in order to obtain a more accurate and precise data.

v. Higher doses than the dose values used in this research work should be considered and used to verify the results.

vi. Other models other than the linear quadratic model should also be considered and used to obtain the results.

vii. Dose volume histograms which give a more accurate value for the reference volume should also be used.

viii. This research work has shown that it is better to irradiate 1/3 volumes of these organs as this reduces complications to the barest minimum. Therefore, it is advisable for hospitals to be conscious of the volumes before irradiating.

REFERENCES

Andrews, J.R., Amer. J. Roentgen., Moody J.M. (1956). The dose-time relationship in radiotherapy. 75:590-596

American Cancer Society, Inc . All rights reserved. The American Cancer Society is a qualified 501(c) (3) tax-exempt organization. Retrieved from www.cancer.org/cancer/cervical cancer/overview guide.

Barendsen, G.W. (1982). Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *International Journal on Radiation Oncology BioPhysics*, **8**(11) : 1981-97.

Barendsen, G.W. (1982). In Time and Dose Relationships in Radiation Biology as applied to radiotherapy.

Bentzen S.M., Constine L.S., Deasy J.O. (2010). Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *International Journal on Radiation Oncology BioPhysic*;**76**(3):S3–S9.

Bentzen, S.M. (1994) Radiobiological considerations in the design of clinical trials. Radiotherapy and Oncology, **32**(1): 1-11.

Bentzen S M., Thames H D., Overgaard M. (1989). Latent time for late cutaneous & subcutaneous radiation reactions in a single follow-up clinical study. Radiotherapy Oncology. 15: 267 –270.

Bhandare N., Jackson A., Eisbruch A., (2010). Radiation therapy and hearing loss. *International Journal on Radiation Oncology BiolPhysic*, **76**(3):S50–S57.

Burman C., Kutcher G. J., Emami B., Goiten M. (1991). Fitting of normal tissue tolerance data to an analytic function. *International Journal on Radiation Oncology BiolPhysic*, 21: 123 –135.

Chen S.W., Liang J.A., Yang S.N., Liu R.T., Lin F.J. (2000). The prediction of late rectal complications following the treatment of uterine cervical cancer by high-dose-rate brachytherapy. *International Journal Radiation on Oncology BiolPhysic*. 47: 955-961.

Constine L.S., Milano M.T., Friedman D. (2010). Late Effects of Cancer treatment on Normal Tissues. In: Halperin EC, Perez CA, Brady LW, (Eds.) Perez and Brady's Principles and Practice of Radiation Oncology, 5th ed. Philadelphia, Pa: Lippincott Williams &Wilkins, 320-355.

Deore S. M., Shrivastava S .K., Supe S. J., Viswanathan P.S., Dinshaw K.A. (1993). Alpha/beta value and importance of dose per fraction for the late rectal and recto-sigmoid complications. Stehlentherapie und Onkologie 169: 521 –526.

Dische S., Martin W.M.C., Anderson P. (1981). Radiation myelopathy in patients treated for carcinoma of bronchus using a six fraction regime of radiotherapy. Br. J. Radiol. 54: 29 –35.

Douglas B.G., Fowler J.F. (1975). Letter: Fractionation schedules and a quadratic dose-effect relationship. Br J Radiol,. **48**(570): p. 502-4.

Douglas J.G., Goodkin R., Laramore G.E. (2008). Gamma knife stereotactic radiosurgery for salivary gland neoplasms with base of skull invasion following neutron radiotherapy. Head Neck., **30**(4):492-496.

Emami B., Graham M.V. (1997). Lung. In : Principles and Practice of Radiation Oncology, Parez CA & Brady LW, eds, 3 edition, Philadelphia, pp. 1181-1220.

Emami B., Lyman J., Brown A., Coia L., Goiten M., Munzenride J. E., Shank B., Solin L. J., Wesson M. (1991). Tolerance of normal tissue to therapeutic radiation. *International Journal on Radiation Oncology BiolPhysic*. 21: 109 –122.

Fowler J.F. (1984). The first James Kirk memorial lecture. What next in fractionated radiotherapy? Br J Cancer Suppl,. 6: 285-300.

Fowler J.F. (1989). The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol, **62**(740): 679-94.

Ferlay .J, Shin H.R., bray. (2010). International journal of cancer journal. International du cancer.

Fowler J.F., Bentzen S.M., Bond S.J., Ang K.K., Van der Kogel A.J., Van den Bogaert W, Van der Schueren E. (2000). Clinical radiation doses for spinal cord: the 1998 international questionnaire. Radiotherapy Oncology. **55**(5):295-300.

Fowler, J.F., (2008). Linear quadratics is alive and well: In regard to Park et al. *International Journal on Radiation Oncology BiolPhysic*, **72**(3): 957.

Park C.L., Papiez., and Timmerman R.D. (2008). In reply to Dr. Fowler and Dr. Kavanagh. *International Journal on Radiation Oncology BiolPhysic*, **72**(3): 958.

Gordan K.B., Char D.H., Sagerman R.H. (1995). Late effects of radiation on the eye and ocular adnexa. *International Journal on Radiation Oncology BiolPhysic*. 31: 1123-1139.

Hall, E.J., Giacca, A.J. (2006). Radiobiology for the Radiologist. 6 ed. Philadelphia: Lippincott Williams & Wilkins.

Halperin E.C., Perez C.A., Brady L.W. (2008). Preface to the first edition. In: Halperin E.C., Perez C.A., Brady L.W., eds. Perez and Brady's principles and practice of radiation oncology, 5th ed. Philadelphia, P.A: Lippincott Williams & Wilkins.

Jemal A.(2011). Global cancer statistics. C.A Cancer J, **61**(2): 69-90.

Kallman P., Agren A., Brahme A. (1992). Tumor and normal tissue responses to fractionated non-uniform dose delivery. *International. Journal on Radiation BiolPhysic*. 62: 249–262.

Kirkpatrick J.P., Van Der Kogel A..J, Schultheiss T.E. (2010). Radiation dose-volume effects in the spinal cord. *International Journal on Radiation Oncology BiolPhysic*, **76**(3):S42–S49.

Kutcher G.J., Leibel S.A., Ling C.C., Zelefsky M., Fuks Z. (1996). Dose escalation under dose volume constraints. A model of conformal therapy of the prostate. *International Journal on Radiation Oncology BiolPhysic*.35: 415 –416.

Lawrence T.S., Ten Haken R.K., Kessler M.L., Robertson J.M., Lyman J.T., Lavigne M.L., Brown M.B., DuRoss D.J., Andrews J.C., Ensminger W.D., (1992). The use of 3-D dose volume analysis to predict radiation hepatitis. *International Journal on Radiation Oncology BiolPhysic*, 23: 781-788.

Lawrence Y.R., Li X.A., el Naqa I (2010). Radiation dose volume effects in the brain. *International Journal on Radiation Oncology BiolPhysic*, **76**(3):S20–S27.

Lyman J .T. (1985). Complication probability as assessed from dose volume histograms. Radiat. Res. 104: 513 –519.

MacFaul, P.A., Bedford M.A. (1970). Ocular complications after therapeutic irradiation. Br J Opt/halmol. 54: 237- 244.

Mayo C., Yorke E., Merchant T.E. (2010). Radiation associated brainstem injury. *International Journal on Radiation Oncology BiolPhysic*, **76** (3 Suppl):S36–S41.

Marks L.B., Yorke E.D., Jackson .A. (2010). Use of normal tissue complication probability models in the clinic. *International Journal on Radiation Oncology BiolPhysic*, **76**(3):S10– S19.

Marks R.D., Agarwal S.K., Constable W.C. (1972). Increased rate of complications as a result of treating only one prescribed field daily. Radiology. 107: 615-619.

Marks, L.B., Carroll, P.R., Dugan, T.L., Anscher, M.S. (1995). The response of the urinary bladder urethra and ureter to radiation and chemotherapy. *International Journal on Radiation on Oncology BiolPhysic*. 31: 1257-1280.

Meeuwis K..A., Van Rossum., M.M., Van De Kirkhof P.C. (2010). Skin cancer and pre-malignancies of the female genital tract in renal transplant recipients. Transplant international: official journal of the European society for organ transplantation, 23: 191-9.

McDonald S., Rubin P., Phillips T.L., Marks L.B. (1995). Injury to the lung from cancer therapy: Clinical syndromes, measurable endpoints, and potential scoring systems. *International Journal on Radiation Oncology BiolPhysic*. 31: 1187-1203.

Meek S.L., Buatti J. M., Foote K..D., Friedman W.A., Bova F. J. (2000). Calculation of cranial nerve complication probability for acoustic neuroma radiosurgery. *International Journal on Radiation Oncology BiolPhysic*. 47: 597 –602.

Morgan M.A., Haken R.K.T., Lawrence T.S. (2011). Radiation Oncology. In: DeVita V.T Jr,

Murry C.G., Herson J., Daly T.E., Zimmerman S. (1980). Radiation necrosis of the mandible: A 10 year study. Part_I. Factors influencing the onset of necrosis. *International Journal on Radiation Oncology BiolPhysic*. 6: 543-548.

Morris R.B., Chan E., Silverman S., Jr Meyer J., Fu K.K., Greenspan D. (1981). Osteonecrosis in patients irradiated for head and neck carcinimas. Cancer 47: 1980- 1988.

National Cancer Institute (2012). Radiation Therapy and You: Support for People with Cancer. Accessed at www.cancer.gov/cancertopics/radiation-therapy-and-you on September 6, National Cancer Institute. Radiation Therapy for Cancer FactSheet. Accessed at www.cancer.gov/cancertopics/factsheet/Therapy/radiation on September 6, 2012.

Paes F.M, Serafini A.N. Systemic Metabolic Radiopharmaceutical Therapy in the Treatment of Metastatic Bone Pain. Semin Nucl Med. 2010;40:89-104.

Pan C.C., Kavanagh B.D., Dawson L.A. (2010). Radiation associated liver injury. *International Journal on Radiation Oncology BiolPhysic*,**76**(3):S94–S100.

Park C., (2008). Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *International Journal on Radiation Oncology BiolPhysic*, **70**(3): 847-52.

Park, C.L. Papiez, and R.D. Timmerman. (2008), In reply to Dr. Fowler and Dr. Kavanagh. *International Journal on Radiation Oncolog BiolPhysic*, **72**(3): p. 958.

Parsons J.T., Bova F.J., Fitzgerald C.R., Mendenhall W.M., Million R.R. (1994a). Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. *International Journal on Radiation Oncology BiolPhysic*, **30**(4): 755-763.

Parsons J.T., Bova F.J., Fitzgerald C.R., Mendenhall W.M., Million R.R. (1994b). Radiation retinopathy after external-beam irradiation: analysis of time-dose factors. *International Journal on Radiation Oncology BiolPhysic*, **30**(4):765-773.

Perez C.A., Brad L.W., Roti J.L.R. (1997a). Overview. In: Principles and practice of radiation oncology, 3 ed. Carlos A. Perez and Luther W. Brady, eds. Lippincott-Raven Publishers, Philadelphia, New York, pp. 1 –78.

Perez CA, (1997b). Uterin cervix. In: Principles and practice of radiation oncology, 3rd edition, Perez CA and Brady LW eds., (Lippincott- Raven, Philadelphia New York) 1143-1202.

Pop L.A. (1996). Constraints in the use of repair half times and mathematical modelling for the clinical application of HDR and PDR treatment schedules as an alternative for LDR brachytherapy. Radiotherapy Oncology, **38**(2):153-62.

Rancati T., Schwarz M., Allen A.M. (2010). Radiation dose volume effects in the larynx and pharynx. *International Journal on Radiation Oncology BiolPhysic*, **76**(3):S64–S69.

Roose, D.E., O'Brien P.C., Smith J.G., Spry N.A., Hoskin P.J., Burmeister B.H., Turner S.L., Bernshaw D.M. (2000). A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (Trans-Tasman Radiation Oncology Group, TROG 96.05). *International Journal on Radiation Oncology BiolPhys*. **46**(4): 975 –981.

Rubin P. (1989). The law and order of radiation sensitivity, absolute vs relative. In: Vaeth J.M, Meyer T.L (eds.): Radiation tolerance of normal tissues. Frot Radiat Ther Oncol. Basel Switzerland Karger, vol. 23: pp- 7-40.

Rubin P., Cassarett G.W. (1968). Urinary tract: The kidney. In: Rubin P, Casserett G.W, eds. Clinical radiation pathology. Vol. I. Philadelphia: W B Saunders; pp. 293-333.

Rubin P., Cassarett G .W. (1968b) Urinary tract: The kidney. In: Rubin P, Casserett G.W, eds. Clinical radiation pathology. Vol. II. Philadelphia: W.B Saunders; pp. 423-470.

Rubin P., Cassarett G .W. (1972). A direction for clinical radiation pathology. In:Vaeth, eds. Frontiers of radiation therapy and oncology VI. Baltimore: University Park Press. pp. 1-16.

Rubin P., Casserett G.W. (1973). Concept of clinical radiation pathology, In: Dalrymple G, Gaulden M., Kallomogen G., Vogel eds. Medical radiation biology, Philadelphia: WB Saunders, 8: 160-189.

Rubin P., Cooper R.A., Phillips T.L. (1975). Radiation biology and radiation pathology syllabus. Set RT1: Radiation Oncology. American College of Radiology, Chicago. pp. 2-7.

Thames H.D.,Jr. (1982). Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. *International Journal on Radiation Oncology BiolPhysics* **8**(2): p. 219-26.

Thames H.D., Hendry J.H., Fractionation in Radiotherapy (1987), Basingstoke, Great Britain: Taylor & Francis.

Werner-Wasik M., Yorke E., Deasy J. (2010). Radiation dose volume effects in the esophagus. *International Journal on Radiation Oncology BiolPhys* ; **76**(3 Suppl):S86–S93.

APPENDIX

APPENDIX 1: Beam set up parameters for patients.

Beam Setup Notes

Patient Notes:	
Patient Setup	Patient Treated Head First
Prescription:	Fraction group 1 [FxGroup#1] Dose Prescribed to a point for each beam.
Plan Summary;	There are 4 Active beams and 4 Segments in this plan
Fraction Groups:	Fraction group 1 [FxGroup#1] is delivered 10 times
Couch Positions:	Looking from the foot of the table towards the gantry, position patient such that lasers line up with patient marks. Lateral Couch Movements (RIGHT or LEFT) are to your RIGHT or LEFT. Longitudinal Couch Movements IN are towards the gantry, OUT are away from gantry.

Beam Setup Parameters

Beam:	Number	1	2	3	4
	Name	ANT. P~VIS	POST. ~VIS	LT. LA~VIS	RT. LA~VIS
	# Segments	1	1	1	1
Fraction:	Group	1	1	1	1
	Fractions	10	10	10	10
Machine:	Name	UDUTH Elekta Precise			
	Code	uduth	uduth	uduth	uduth
Beam:	Type	simple	simple	simple	simple
	Energy	6 MV	6 MV	15 MV	15 MV
	SAD (cm)	100	100	100	100
	SSD (cm)	91.9	90.4	86.2	86.1
Gantry:	Angle (deg)	0.0	180.0	90.0	270.0
Collimator:	Angle (deg)	0.0	0.0	0.0	0.0
Diaphragm Size:		Diaphragm Size			
Diaphragm @ SAD (cm)		UPPER 7.0	UPPER 7.0	UPPER 7.0	UPPER 7.0
	BEV -X (cm)	-3.5 X1	-3.5 X1	-3.5 X1	-3.5 X1
	BEV +X (cm)	+3.5 X2	+3.5 X2	+3.5 X2	+3.5 X2
Diaphragm @ SAD (cm)		LOWER 7.0	LOWER 7.0	LOWER 7.0	LOWER 7.0
	BEV -Y (cm)	-3.5 Y1	-3.5 Y1	-3.5 Y1	-3.5 Y1
	BEV +Y (cm)	+3.5 Y2	+3.5 Y2	+3.5 Y2	+3.5 Y2
Couch: Relative		Couch Offsets			
	Angle (deg)	0.0	0.0	0.0	0.0
	Lateral (cm)	0.0	0.0	0.0	0.0
	Height (cm)	2.6 UP	2.6 UP	2.6 UP	2.6 UP
	Long (cm)	2.2 IN	2.2 IN	2.2 IN	2.2 IN
Modifiers:		Modifiers			
	Tray Factor	1.00000	1.00000	1.00000	1.00000
	MLC Present	No	No	No	No
Wedge:	Name				
	Angle				
	Orientation				
		Beam MU/Fraction			
Wedge In MU		--	--	--	--
Wedge Out MU		61.5	64.5	65.7	65.7

Beam Setup Notes

Patient Notes:	
Patient Setup	Patient Treated Head First
Prescription:	Fraction group 1 [FxGroup#1] Dose Prescribed to a point for each beam.
Plan Summary;	There are 4 Active beams and 4 Segments in this plan
Fraction Groups:	Fraction group 1 [FxGroup#1] is delivered 25 times
Couch Positions:	Looking from the foot of the table towards the gantry, position patient such that lasers line up with patient marks. Lateral Couch Movements (RIGHT or LEFT) are to your RIGHT or LEFT. Longitudinal Couch Movements IN are towards the gantry, OUT are away from gantry.

Beam Setup Parameters

Beam:	Number	1	2	3	4
	Name	ANT PELVIS	POST P~VIS	LT. LA~VIS	RT. LA~VIS
	# Segments	1	1	1	1
Fraction:	Group	1	1	1	1
	Fractions	25	25	25	25
Machine:	Name	UDUTH Elekta Precise			
	Code	uduth	uduth	uduth	uduth
Beam:	Type	simple	simple	simple	simple
	Energy	15 MV	15 MV	15 MV	15 MV
	SAD (cm)	100	100	100	100
	SSD (cm)	85.5	88.2	81.2	81.2
Gantry:	Angle (deg)	0.0	180.0	90.0	270.0
Collimator:	Angle (deg)	0.0	0.0	270.0	90.0
Diaphragm Size:		Diaphragm Size			
Diaphragm @ SAD (cm)		UPPER 12.0	UPPER 12.0	UPPER 21.0	UPPER 21.0
	BEV -X (cm)	-6.0 X1	-6.0 X1	-10.5 X1	-10.5 X1
	BEV +X (cm)	+6.0 X2	+6.0 X2	+10.5 X2	+10.5 X2
Diaphragm @ SAD (cm)		LOWER 21.0	LOWER 21.0	LOWER 8.4	LOWER 8.4
	BEV -Y (cm)	-10.5 Y1	-10.5 Y1	-5.0 Y1	-5.0 Y1
	BEV +Y (cm)	+10.5 Y2	+10.5 Y2	+3.4 Y2	+3.4 Y2
Couch: Relative		Couch Offsets			
	Angle (deg)	0.0	0.0	0.0	0.0
	Lateral (cm)	0.6 LEFT	0.6 LEFT	0.6 LEFT	0.6 LEFT
	Height (cm)	1.7 UP	1.7 UP	1.7 UP	1.7 UP
	Long (cm)	0.4 OUT	0.4 OUT	0.4 OUT	0.4 OUT
Modifiers:		Modifiers			
	Blocks	0	0	1	1
	Tray Factor	1.00000	1.00000	0.93300	0.93300
	MLC Present	No	No	No	No
Wedge:	Name			60 Autowedg	60 Autowedg
	Angle			25	25
	Orientation			3	3
		Beam MU/Fraction			
Wedge In MU		--	--	59.4	60.7
Wedge Out MU		58.6	55.0	54.5	55.7

Beam Setup Notes

Patient Notes:	
Patient Setup	Patient Treated Head First
Prescription:	Fraction group 1 [FxGroup#1] Dose Prescribed to a point for each beam.
Plan Summary;	There are 4 Active beams and 4 Segments in this plan
Fraction Groups:	Fraction group 1 [FxGroup#1] is delivered 25 times
Couch Positions:	Looking from the foot of the table towards the gantry, position patient such that lasers line up with patient marks. Lateral Couch Movements (RIGHT or LEFT) are to your RIGHT or LEFT. Longitudinal Couch Movements IN are towards the gantry, OUT are away from gantry.

Beam Setup Parameters

Beam:	Number	1	2	3	4
	Name	ANT. P~VIS	POST. ~VIS	LT. LA~VIS	RT. LA~VIS
	# Segments	1	1	1	1
Fraction:	Group	1	1	1	1
	Fractions	25	25	25	25
Machine:	Name	UDUTH Elekta Precise			
	Code	uduth	uduth	uduth	uduth
Beam:	Type	simple	simple	simple	simple
	Energy	6 MV	6 MV	6 MV	6 MV
	SAD (cm)	100	100	100	100
	SSD (cm)	90.2	90.6	85.5	86.2
Gantry:	Angle (deg)	0.0	180.0	90.0	270.0
Collimator:	Angle (deg)	0.0	0.0	270.0	90.0
Diaphragm Size:		Diaphragm Size			
Diaphragm @ SAD (cm)		UPPER 13.0	UPPER 13.0	UPPER 17.8	UPPER 17.8
	BEV -X (cm)	-6.5 X1	-6.5 X1	-8.9 X1	-8.9 X1
	BEV +X (cm)	+6.5 X2	+6.5 X2	+8.9 X2	+8.9 X2
Diaphragm @ SAD (cm)		LOWER 17.8	LOWER 17.8	LOWER 7.6	LOWER 7.6
	BEV -Y (cm)	-8.9 Y1	-8.9 Y1	-3.0 Y1	-3.0 Y1
	BEV +Y (cm)	+8.9 Y2	+8.9 Y2	+4.6 Y2	+4.6 Y2
Couch: Relative		Couch Offsets			
	Angle (deg)	0.0	0.0	0.0	0.0
	Lateral (cm)	0.4 LEFT	0.4 LEFT	0.4 LEFT	0.4 LEFT
	Height (cm)	1.9 UP	1.9 UP	1.9 UP	1.9 UP
	Long (cm)	2.7 OUT	2.7 OUT	2.7 OUT	2.7 OUT
Modifiers:		Modifiers			
	Tray Factor	1.00000	1.00000	1.00000	1.00000
	MLC Present	No	No	No	No
Wedge:	Name			60 Autowedg	60 Autowedg
	Angle			10	10
	Orientation			3	3
		Beam MU/Fraction			
Wedge In MU		--	--	24.9	23.3
Wedge Out MU		54.6	50.5	60.8	57.0

Beam Setup Notes

Patient Notes:	
Patient Setup	Patient Treated Head First
Prescription:	Fraction group 1 [FxGroup#1] Dose Prescribed to a point for each beam.
Plan Summary;	There are 4 Active beams and 4 Segments in this plan
Fraction Groups:	Fraction group 1 [FxGroup#1] is delivered 27 times
Couch Positions:	Looking from the foot of the table towards the gantry, position patient such that lasers line up with patient marks. Lateral Couch Movements (RIGHT or LEFT) are to your RIGHT or LEFT. Longitudinal Couch Movements IN are towards the gantry, OUT are away from gantry.

Beam Setup Parameters

Beam:	Number	1	2	3	4
	Name	ANT. P~VIS	POST. ~VIS	LT. LA~VIS	RT. LA~VIS
	# Segments	1	1	1	1
Fraction:	Group	1	1	1	1
	Fractions	27	27	27	27
Machine:	Name	UDUTH Elekta Precise			
	Code	uduth	uduth	uduth	uduth
Beam:	Type	simple	simple	simple	simple
	Energy	15 MV	15 MV	15 MV	15 MV
	SAD (cm)	100	100	100	100
	SSD (cm)	91.6	90.4	83.7	83.7
Gantry:	Angle (deg)	0.0	180.0	90.0	270.0
Collimator:	Angle (deg)	0.0	0.0	270.0	90.0
Diaphragm Size:		Diaphragm Size			
Diaphragm @ SAD (cm)		UPPER 15.0	UPPER 15.0	UPPER 20.4	UPPER 20.4
	BEV -X (cm)	-7.5 X1	-7.5 X1	-10.2 X1	-10.2 X1
	BEV +X (cm)	+7.5 X2	+7.5 X2	+10.2 X2	+10.2 X2
Diaphragm @ SAD (cm)		LOWER 20.4	LOWER 20.4	LOWER 9.0	LOWER 9.0
	BEV -Y (cm)	-10.2 Y1	-10.2 Y1	-4.5 Y1	-4.5 Y1
	BEV +Y (cm)	+10.2 Y2	+10.2 Y2	+4.5 Y2	+4.5 Y2
Couch: Relative		Couch Offsets			
	Angle (deg)	0.0	0.0	0.0	0.0
	Lateral (cm)	0.5 LEFT	0.5 LEFT	0.5 LEFT	0.5 LEFT
	Height (cm)	0.0	0.0	0.0	0.0
	Long (cm)	4.9 IN	4.9 IN	4.9 IN	4.9 IN
Modifiers:		Modifiers			
	Tray Factor	1.00000	1.00000	1.00000	1.00000
	MLC Present	No	No	No	No
Wedge:	Name			60 Autowedg	60 Autowedg
	Angle			20	20
	Orientation			3	3
		Beam MU/Fraction			
Wedge In MU		--	--	40.6	40.4
Wedge Out MU		50.3	52.0	51.6	51.5

Beam Setup Notes

Patient Notes:	
Patient Setup	Patient Treated Head First
Prescription:	Fraction group 1 [FxGroup#1] Dose Prescribed to a point for each beam.
Plan Summary;	There are 4 Active beams and 4 Segments in this plan
Fraction Groups:	Fraction group 1 [FxGroup#1] is delivered 27 times
Couch Positions:	Looking from the foot of the table towards the gantry, position patient such that lasers line up with patient marks. Lateral Couch Movements (RIGHT or LEFT) are to your RIGHT or LEFT. Longitudinal Couch Movements IN are towards the gantry, OUT are away from gantry.

Beam Setup Parameters

Beam:	Number	1	2	3	4
	Name	ANT. P~VIS	POST. ~VIS	LT. LA~VIS	RT. LA~VIS
	# Segments	1	1	1	1
Fraction:	Group	1	1	1	1
	Fractions	27	27	27	27
Machine:	Name	UDUTH Elekta Precise			
	Code	uduth	uduth	uduth	uduth
Beam:	Type	simple	simple	simple	simple
	Energy	15 MV	15 MV	15 MV	15 MV
	SAD (cm)	100	100	100	100
	SSD (cm)	91.1	89.3	84.0	84.1
Gantry:	Angle (deg)	0.0	180.0	90.0	270.0
Collimator:	Angle (deg)	0.0	0.0	270.0	90.0
Diaphragm Size:		Diaphragm Size			
Diaphragm @ SAD (cm)		UPPER 13.3	UPPER 13.3	UPPER 18.0	UPPER 18.0
	BEV -X (cm)	-6.7 X1	-6.7 X1	-9.0 X1	-9.0 X1
	BEV +X (cm)	+6.7 X2	+6.7 X2	+9.0 X2	+9.0 X2
Diaphragm @ SAD (cm)		LOWER 18.0	LOWER 18.0	LOWER 9.4	LOWER 9.5
	BEV -Y (cm)	-9.0 Y1	-9.0 Y1	-4.9 Y1	-4.9 Y1
	BEV +Y (cm)	+9.0 Y2	+9.0 Y2	+4.5 Y2	+4.5 Y2
Couch: Relative		Couch Offsets			
	Angle (deg)	0.0	0.0	0.0	0.0
	Lateral (cm)	0.3 LEFT	0.3 LEFT	0.3 LEFT	0.3 LEFT
	Height (cm)	0.2 DOWN	0.2 DOWN	0.2 DOWN	0.2 DOWN
	Long (cm)	2.0 IN	2.0 IN	2.0 IN	2.0 IN
Modifiers:		Modifiers			
	Tray Factor	1.00000	1.00000	1.00000	1.00000
	MLC Present	No	No	No	No
Wedge:	Name			60 Autowedg	60 Autowedg
	Angle			20	20
	Orientation			3	3
		Beam MU/Fraction			
Wedge In MU		--	--	39.9	39.7
Wedge Out MU		51.4	53.7	50.8	50.6

APPENDIX IIA: Computer Program used for the Result Analysis

```
void f_DOS_RHF(char const* ptrrhf);
void f_DOS_LHF(char const* ptrlhf);
void f_DOS_SKIN(char const* ptrskin);
int iniv();
int main() {
Sint tag = 1;
int choice = 0;
const char* pbldr = "bladerfile.txt";
const char* prec = "rectumfile.txt";
const char* pgit = "gitfile.txt";
const char* prhf = "rfemurfile.txt";
const char* plhf = "lfemurfile.txt";
const char* pskin = "skinfile.txt";
while(1){
choice = iniv();
switch( int(choice) ) {
case(1) : f_DOS_BLAD(pbldr);
        break;
 case(2) : f_DOS_REC(prec);
        break;
 case(3) : f_DOS_GIT(pgit);
        break;
```

```
  case(4) : f_DOS_RHF(prhf);
            break;
  case(5) : f_DOS_LHF(plhf);
            break;
   case(6) : f_DOS_SKIN(pskin);
            break;
   case(7) : //{ cout << "I'm Exiting..."; tag = 0; }
            default : { cout << "Default Exit..."; tag = false; }
            break;}
   if(!tag) break;
  }
   return 0;
   }
  int iniv(){
  int choice;
  cout << "\nEnter choice ";
cout << "\n1. bladder;";
  cout << "\n2. rectum;";
  cout << "\n3. git;   ";
  cout << "\n4. right femur;";
  cout << "\n5. left femur; ";
  cout << "\n6. skin.";
  cout << "\n7. ...exit";
```

```
  cout << endl;
  cout << endl;
  cin >> choice;
  return (choice >= 0 && choice <= 9 ) ?  choice : 0;
  }
  void f_DOS_BLAD(char const * ptrbldr) {
  double  No = 7007.99;
  double k = 2.9239;
  double aG = 0.1171;
  extern double DOS_BLAD[50];
  f(No, k, aG, DOS_BLAD, ptrbldr  );
  }
  void f_DOS_REC(char const* ptrrec) {
  double  No = 42.44;
  double k = 0.83001;
  double aG = 0.0490;
  extern double DOS_REC[50];
  f(No, k, aG, DOS_REC, ptrrec  );
}
  void f_DOS_GIT(char const* ptrgit) {
double  No = 302.92;
  double k = 0.7617;
double aG = 0.1126;
```

```
extern double DOS_GIT[50];
f(No, k, aG, DOS_GIT, ptrgit  );
}
void f_DOS_RHF(char const* ptrrhf) {
double  No = 1045.23;
double k = 2.309;    // 2.2
double aG = 0.1126;
extern double DOS_RHF[50];
f(No, k, aG, DOS_RHF, ptrrhf  );
}
void f_DOS_LHF(char const* ptrlhf) {
double  No = 1045.23;
double k = 2.290;
double aG = 0.0732;
extern double DOS_LHF[50];
f(No, k, aG, DOS_LHF, ptrlhf  );
}
void f_DOS_SKIN(char const* ptrskin) {
double  No = 351.42;
double k = 1.65867;
double aG = 0.0886;
extern double DOS_SKIN[50];
```

```
f(No, k, aG, DOS_SKIN, ptrskin  );
}
void f( double No, double k, double aG,double dos[], char const* p) {
ofstream out(p);
double veff[50];
double parvol[50];
for(int i = 0; i < 50; i++)
cout << (veff[i] = volume[i]*0.0999) << endl;   // 0.05 - 0.09 - 0.1
cout << "\n\n";
for(int i = 0; i < 50; i++){
if ( veff[i] == 0) { cout << i << "\t"<<(parvol[i] = 0) << endl; continue; }
parvol[i] = (volume[i] - veff[i])/veff[i];   // ok
cout << i << "\t" << parvol[i] << endl;
}
cout << endl; cout << endl;
for(int i = 0; i < 50; i++){
cout << dos[i]  <<
 "\t"  << exp( -No*pow( parvol[i], -k) * exp(-aG*dos[i]) ) << endl;
 out << dos[i]  <<
  "\t"  << exp( -No*pow( parvol[i], -k) * exp(-aG*dos[i]) ) << endl;
  }
  cout << endl; cout << endl;
  out <<  endl; out << endl;
```

```
  Sfor(int i = 0; i < 50; i++){
cout << dos[i]  << "\t"  << volume[i] << endl;
  out  << dos[i]  << "\t"  << volume[i] << endl;
  }
  }
```

APPENDIX IIB: Computer Program used for the Result Analysis

```
index 0:0  u 1:2 via a,b

v = 9.01001
k = ( log(N) - log(a) )/ log(v)

set label 2 "   a = 10.3413342876747"  at 25.0, 0.45
set label 3 "   b = 0.110746057005382"  at 25.0, 0.40
print ""

print "v = ", v
print "N = ", N
print "a = ", a
print "b = ", b
print "k = ", k

print ""

#f13(x)= exp( -a/3.0 * exp(-b*x) )
#f33(x)= exp( -a*3.0 * exp(-b*x) )

f13(x)= exp( -N*(v/3.0)**-k * exp(-b*x) )
#f23(x)= exp( -N*(v*2.0/3.0)**-k * exp(-b*x) )
f33(x)= exp( -N*(v*3.0)**-k * exp(-b*x) )

plot f(x) t 'f(x)' w l, 'bladerfile.txt' index 0:0 using 1:2 t "data"
with points \
, f13(x)  t '1/3' w l, f33(x)  t '3/3' w l

set t push
set t gif
set o "bldrgif.gif"
replot
set output
set t pop
#    EOF

#!/bladerfile
#

set terminal windows color enhanced
unset grid

set key at 2,1 left top

set title "NTCP vs Dose For Bladder"

set xlabel "Dose(Gy)"
set ylabel "NTCP"
```

```
set label 1 "f(x) = exp( -a * exp(-b*x) ) " at 25.0, 0.5

GNUTERM = "win"
# good to give an approximate initial values because of side effects
N = 7007.99
a = 10
b = 0.1

f(x)= exp( -a * exp(-b*x) )
fit f(x) 'bladerfile.txt'
```

```
int tag = 1;

int choice = 0;

const char* pbldr = "bladerfile.txt";

const char* prec = "rectumfile.txt";

const char* pgit = "gitfile.txt";

const char* prhf = "rfemurfile.txt";

const char* plhf = "lfemurfile.txt";

const char* pskin = "skinfile.txt";

 while(1){

choice = iniv();

switch( int(choice) ) {

case(1) : f_DOS_BLAD(pbldr);

                break;

case(2) : f_DOS_REC(prec);

                break;

case(3) : f_DOS_GIT(pgit);

                break;
```

```
case(4) : f_DOS_RHF(prhf);
                break;
 case(5) : f_DOS_LHF(plhf);
                break;
 case(6) : f_DOS_SKIN(pskin);
                break;
 case(7) : //{ cout << "I'm Exiting..."; tag = 0; }
                default : { cout << "Default Exit..."; tag = false; }
                break;
               } if(!tag) break;}
                  return 0;
                 }int iniv(){
               int choice;
               cout << "\nEnter choice ";
               cout << "\n1. bladder;";
               cout << "\n2. rectum;";
               cout << "\n3. git;   ";
               cout << "\n4. right femur;";
               cout << "\n5. left femur; ";
               cout << "\n6. skin.";
               cout << "\n7. ...exit";
               cout << endl;
               cout << endl;
```

```
cin >> choice;
return (choice >= 0 && choice <= 9 ) ?  choice : 0;
}void f_DOS_BLAD(char const * ptrbldr) {
 double  No = 7007.99;
 double k = 2.9239;
 double aG = 0.1171;
 extern double DOS_BLAD[50];
 f(No, k, aG, DOS_BLAD, ptrbldr  );
   }
 void f_DOS_REC(char const* ptrrec) {
 double  No = 42.44;
 double k = 0.83001;
 double aG = 0.0490;
 extern double DOS_REC[50];
 f(No, k, aG, DOS_REC, ptrrec  );
 }
 void f_DOS_GIT(char const* ptrgit) {
 double  No = 302.92;
 double k = 0.7617;
 double aG = 0.1126;
 extern double DOS_GIT[50
 f(No, k, aG, DOS_GIT, ptrgit  );}
 void f_DOS_RHF(char const* ptrrhf) {
```

```
  double  No = 1045.23;
  double k = 2.309;    // 2.2
  double aG = 0.1126;
  extern double DOS_RHF[50];
  f(No, k, aG, DOS_RHF, ptrrhf  );
  }
  void f_DOS_LHF(char const* ptrlhf) {
  double  No = 1045.23;
  double k = 2.290;
double aG = 0.0732;
  extern double DOS_LHF[50];
  f(No, k, aG, DOS_LHF, ptrlhf  );
  }
  void f_DOS_SKIN(char const* ptrskin) {
  double  No = 351.42;
  double k = 1.65867;
  double aG = 0.0886;
  extern double DOS_SKIN[50];
  f(No, k, aG, DOS_SKIN, ptrskin  );
  }
  void f( double No, double k, double aG,double dos[], char const* p) {
  ofstream out(p);
  double veff[50];
```

```
double parvol[50];
for(int i = 0; i < 50; i++)
cout << (veff[i] = volume[i]*0.0999) << endl;   // 0.05 - 0.09 - 0.1
cout << "\n\n";
for(int i = 0; i < 50; i++){
if ( veff[i] == 0) { cout << i << "\t"<<(parvol[i] = 0) << endl; continue; }
parvol[i] = (volume[i] - veff[i])/veff[i];   // ok
cout << i << "\t" << parvol[i] << endl;
}
cout << endl; cout << endl;
for(int i = 0; i < 50; i++){
cout << dos[i]  <<
"\t"  << exp( -No*pow( parvol[i], -k) * exp(-aG*dos[i]) ) << endl;
out << dos[i]  <<
 "\t"  << exp( -No*pow( parvol[i], -k) * exp(-aG*dos[i]) ) << endl;
   }
 cout << endl; cout << endl;
 out <<  endl; out << endl;
 for(int i = 0; i < 50; i++){
 cout << dos[i]  << "\t"  << volume[i] << endl;
 out  << dos[i]  << "\t"  << volume[i] << endl;
   }
   }
```