Sudan University for Science and Technology
College of Graduate Studies

Evaluation of target Volume localization and Dose Estimation for Pituitary Adenomas 2D and 3D Radiation Dose Distribution

«تقويم موضع حجم ورم الغدة النخامية وتقدير جرعته عندما نستخدم أسلوب ثنائئ البعد (D 2) و ثلاث الأبعاد (D3) في توزيع جراعات الأشعاعية فيها في العلاج»

A Thesis Submitted in Fulfillment of the Requirements for PhD Degree in Radiation Therapy Technology

By:

Diabate Adama

Supervisor by

Associate Prof, Dr. Mohammad Elfadil

Feb, 2014

ملخص البحث

ان الغرض من هذه الدراسة هو تقويم ورم الغدة النخامية عند إستخدم العلاج بالأشعة من الخارج وهذا يؤدي إلى تصعيد الأشعة إلى الأنسجة الطبيعية المجاورة للورم مما قد يتسبب في بعض مضاعفات فيها. و تحتوي عينة البحث على 300 مريض ، من الفئة العمرية التي تتراوح من 17 الى 57 سنة. تم استخدام جهاز محاكاة CT لجمع البيانات من أجل ترسيم الغدة النخامية بما في ذلك حجم الورم الفعلي (GTV) وتخطيط حجم الهدف بنسبة 95% (PTV95%) مع توزيع الجرعة العلاجية بالتساوي في الغدة النخامية من أجل الحصول على تغطية الورم بثلاث ابعاد (3D) مع التجنب بقدر الإمكان من تعرض الأعضاء الحرجة للأشعة. و كان علاج الورم في الغدة النخامية موضوع الأبحاث المرجح للعديد من العلماء حيث يشير نتائج بحثهم الى حدوث بعض مضاعفات أثناء العلاج استخداما العلاج بالأشعة دون الإشارة إلى تقنية مناسبة للحد من إشعاع الأنسجة المحيطة بها ، هذا يدل على توزيع جرعة متماثلة ذات أبعاد الثلاثة (3D) في الغدة النخامية ، وكذلك تقليل الجرعة في الأنسجة المحيطة بها مثل (الفص الصدغي، رباط البصري، والعين)، لأن توزيع جرعة على مستوى ثلاث ابعاد (3D) آمنة لحجم الورم ، ويمنع وصول الجرعة الإشعاعية إلى أعضاء الحرجة المحيطة بها على النحو التالي: الفص الصدغي 1.14 غراي، العين 0.86غراي، ورباط البصري 0.95 غراي أكثر من توزيع جرعة متماثلة ذات ثنائي أبعاد (2D) أثناء فترة العلاج حيث نجد أن ثنائي ابعاد يعرض الاعضاء المجاورة للأشعة الزائدة .

Abstract

The general objective of this study was to evaluate pituitary adenoma treatment with radiotherapy modalities that will lead to escalate radiation to the surrounding normal tissues causing complications. The sample of the study consists of 300 patients; with age ranging from 17 to 57 years old. The CT simulator was used to collect data in order to delineate pituitary adenoma including growth target volume (GTV) and planning target volume (PTV 95%) as an isodose surface for treatment in order to obtain dose distribution in 3D dose coverage to the target while sparing organs at risks. The result of this study showed that, the pituitary adenoma treatment was a subject of researches likely many scholars findings show the complications occurred during the treatment with radiotherapy without mentioning the suitable technique to reduce radiation the surrounding tissues in accordance to this study findings shows the 3D dose distribution technique reduces the unnecessary dose to the surrounding tissues (temporal lobe, optic chiasm, eye) ; 3D dose distribution is safe to the target volume, while the average dose reaching the organs at risks were as follow: temporal lobe 1.14 Gy, eye 0.86 Gy, and optic chiasm 0.95 Gy more than a 2D dose distribution during the treatment.

Table of Contents

List of Tables

List of Figures

List of Abbreviations & Acronyms

ACTH:	Adrenocorticotropic Hormone
C1 /C2Level:	Cervical Spine Level 1 or 2
CT:	Computed Tomography
CTV:	Clinical Target Volume
CRT:	Conformal Radiotherapy
DNA	Deoxyribonucleic Acid
EBRT:	External Beam Radiotherapy
FSH:	Follicle Stimulating Hormone
GTV:	Gross Tumor Volume
Gy :	Gray
ICRU:	International Commission On Radiation Units And Measurements
ITV:	Internal Target Volume
LH:	Luteinizing Hormone
MRI:	Magnetic Resonance Imaging
NTCP:	Normal Tissue Complication Probability
NPC:	Nasopharyngeal Cancer
OARs:	Organs At Risk
PTV:	Planning Target Volume

PTV95%:	95% Isodose Surface Covers the PTV
PTV107%:	107% Isodose Surface Covers the PTV
PRL	Prolactin
RON:	Radiation Optic Neuropathy
3DCRT:	Three Dimensional Conformal Radiotherapy
3D :	Three Dimensions
2D:	Two Dimensions
$TD_{5/5}$:	Tolerance Dose That Within 5 Years Will Cause A Maximal 50% Complication Rate
TLN:	Temporal Lobe Necrosis

Dedication

I dedicate my thesis work to my family. A special feeling of gratitude to my loving parents, mother and father whose words of encouragement and push for tenacity ring in my ears. My wife has never left my side and she is very special indeed. I also dedicate this thesis to my spiritual father, **Dr. Ibrahim Mohammad Al-ameen Ashankyty**, who gave me a special sympathy, care, and protections in terms of giving me opportunities not only to fulfill my PhD program by giving me a registration fees, and convince his colleague **Prof. Mahmoud Shaheen dean of faculty of medicine at University of King Abdel Aziz** to be my first supervisor for PhD who was later changed to **Associate Dr. Mohamed Elfadil,** but Dr**. Ibrahim M.A. Ashankyty** formulated me with any aspect of good deeds and things , he really supported me throughout the professional career . I will also thank **Dr. Edem Nuglozeh** for helping me to develop my research methodological skills. I also dedicate this work and give a special thanks to my best friend Dr. Badrudeen AbdoulRahim Abu Naib who supported me emotionally. And my sincere thanks and acknowledgement to **Dr. Safi Ahmed Abdulla the dean of Medical radiologic Sciences** who was my internal supervisor, and my special thanks to **Dr. Mahadi Ahmed Haroun**, who was an external examiner they gave both of them really gave me hard time during a thesis defending but this is natural, and **Dr. Mahadi Ahmed Haroun** as an examinators committee spokesman he was the first who announced me the approval of my thesis .

Finally, this thesis of PhD is particularly dedicated to **Dr. Ibrahim Mohammad Al-ameen Ashankyty the dean of applied medical sciences at the University of Hail in Kingdom of Saudi Arabia**.

Acknowledgements

I am indebted to my supervisor **Associate Prof. Dr. Mohammad Elfadil the head of Radiotherapy Department** for his endless devotion toward helping me as a student under his supervision. He has not only helped me achieving my academic goals, but has also given me confidence to set my goals high. His wealth of knowledge and scientific expertise is astounding to say the least. I have a special thanks and respects to **Associate Prof. Dr. Mohammed Ahmed Ali** the co-supervisor who guided and encourage me to tackle the problems at hand, whether in his residence or on phone call I have learned a lot from Dr. Mohammad Ahmed Ali; it is truly an honor to be his student under his supervision. I hope one day I can mentor students in the way he has mentored me. I am really indebted to him for his role and support throughout my time at the College of Medical Radiologic Sciences; his leadership inspires all who have the privilege to work with him. The sign of a great leader is someone who is never demanding anything of others yet inspires others to demand greatness from them. He is always looking out for the best interests of others and has always encouraged me to pursue my research interests. His depth of experience, logic and professionalism in helping others is astonishing.

Chapter One
Introduction

1.1 Anatomy of Pituitary

The pituitary gland is the maestro gland of the body system and it controls the activities of other glands in the body. Furthermore, is situated anatomically in the center of the brain over a sella turcica of the sphenoid bone at the base of the skull. It is related to the critical structures of the brain such as optic chiasm, cavernous sinus, carotid artery, and cranial nerves. The pituitary gland as a maestro gland it has three anatomical sections, the anterior lobe, the posterior and intermediate lobe (Amar et al., 2003).

Pituitary adenomas in childhood and adolescence constitute 2-6% of all operated pituitary adenomas. All patients were older than 10 years of age; 60% were males. In 50% the initial complaints, according to hormone measurements and immunostaining 50% were prolactinomas, 20% were pure GH-secreting and 30% were non-functioning adenomas. In conclusion, pediatric adenomas occur mostly in pubertal age, are prevalently macroadenomas and clinically functioning (De Menis et al., 2001).

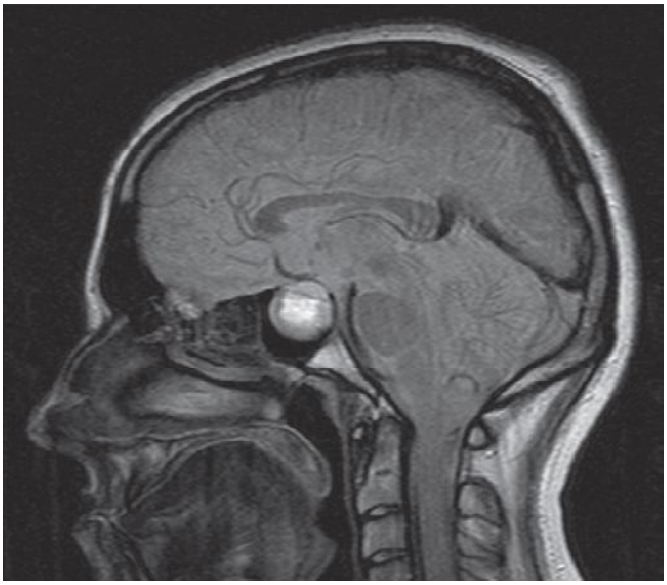


Figure 1.1 Sagittal T1-weighted MRI with high signal in the pituitary adenoma mass, suggesting pituitary[1]

The anterior lobe originated from the roof of the mouth; the posterior lobe originated from the diencephalon to the brain by an infundibular stalk. The stalk contains a fiber tract of axons from neurons in the paraventricular and supraoptic nuclei. Moreover these neurons produce oxytocin and vasopressin and transport them to the posterior lobe, where they are released into the capillary bed (Childs, 2009). The blood supply to the anterior lobe is from superior hypophyseal arteries, and the one to the posterior lobe is from the inferior hypophyseal arteries (Tammy et al., 2004a). In addition (Yeung et al.,2006) claimed that the lobes of pituitary gland have their hormones.

[1](Elsevier, *1st ed, 2012*, Molecular Pathology of Pituitary Adenomas, pp.12).

Therefore, the anterior lobe is responsible for growth, development, homeostasis, metabolism and reproduction.

1.2 Physiology

The pituitary gland is divided into three sections; the anterior lobe which constitute the majority of the pituitary mass and is composed primarily of five hormone-producing cell types (thyrotropes, lactotropes, corticotropes, somatotropes and gonadotropes) each secreting thyrotropin, prolactin, ACTH, growth hormone and gonadotropins (FSH and LH) respectively. There is also a sixth cell type in the anterior lobe-the non-endocrine, a granular, and folliculostellate cells. The intermediate lobe produces melanocyte-stimulating hormone and endorphins, whereas the posterior lobe secretes anti-diuretic hormone (vasopressin) and oxytocin (Ooi et al, 2004). Meanwhile, disorders of the pituitary are predominately those of insufficient hormone release and may have profound effects on the neonate. The potential causes of and clinical symptomatology that may accompany pituitary hormone insufficiency in the neonatal period are explored (Dorton et al, 2000).

1.3 Etiology of Pituitary Tumors

The sellar region is the site of frequent pathology. The pituitary is affected by a large number of pathologic entities arising from the gland itself and from adjacent anatomical structures including brain, blood vessels, nerves, and meninges. The surgical pathology of this area requires the accurate characterization of primary adenohypophysial tumors, craniopharyngiomas, neurologic neoplasms, germ cell tumors, hematologic malignancies, and metastases as well as nonneoplastic lesions such as cysts, hyperplasias, and inflammatory disorders (Sylvia and Asa, 2008a**)**.

Pituitary tumors, often called *adenomas*, are among the most frequent intracranial tumors (10–15%) after meningiomas and gliomas (Saeger et al., 2007). However, the true incidence of pituitary adenoma is difficult to establish with certainty. (McNicol et al, 2007) confirmed that, the cause of pituitary adenoma is unknown; some tumors are part of other endocrine disorders and are associated with genetic changes these can be inherited. Tumors can also be as a result of exposure to radiation. In some cases the DNA changes may occur for no known reason. However, clinically some are associated with familial-isolated tumoral syndromes; familial pituitary adenomas are now thought to account for 5% to 8% of all pituitary tumors. Otherwise, (Tammy et al, 2004b) points out , the neoplasms cases represent about 10% of all intracranial tumors although small, asymptomatic adenomas appear in approximately

25% of all pituitary glands. With the increasing quality of diagnostic studies, these pituitary neoplasms are now estimated to account for 30% of all intracranial tumors. Pituitary adenomas can be classified as functioning or nonfunctioning, as related to the hormones they produce.

In other perspective (Appelman et al, 2011) had highlighted that, the prevalence of hypopituitarism normally occurs in patients after cranial radiotherapy for nonpituitary tumors. Therefore, all patients treated by cranial radiotherapy should have structured periodical assessment of pituitary functions. Furthermore, (McDowell el al, 2011) reported that , the pituitary adenomas incidence vary widely, suggesting that incidence rates generally increased with age and were higher in females in early life and higher in males in later life. In the same reason, (Rostad et al., 2012) emphasized that; pituitary adenomas are relatively common neoplasms, whose pathogenesis is still poorly understood.

The frequency of pituitary adenomas varies greatly according to age and sex. The various adenoma types have their peak occurrence in different age groups and in their female-to-male ratios. (Mindermann,1994).

The prevalence of pituitary adenomas is about16.5% and the majority of them are "incidentalomas", the hormonal evaluation of pituitary adenomas is different from the

type of peripheral endocrine organs. (Mezosi, 2009).In addition, (Caloo et al., 2010), declared that, some specific genes haves been identified that are rarely predisposed to pituitary adenoma. Prolactinomas are adenomas associated with increased PRL levels usually above 100 ng/ml; the serum PRL levels usually correlate with the tumor size (Colao et al., 2004). PRL-producing tumors show the highest incidence among pituitary adenomas in childhood and adolescence (Colao et al., 1998). On the other hand, (Ostrom et al., 2012) justified that; benign brain tumor may have an association with family history of cancer.

1.4 Diagnosis of Pituitary Tumors

Pituitary adenomas are benign neoplasms that can be effectively managed by a variety of therapeutic options. Standard diagnostic interventions include MRI, hormonal assessment, and tissue diagnosis (Buatti, 1997). MRI of the pituitary gland must be technically optimal; analysis of the images has to be directed by clinical and biological data (Bonneville et al., 2005)

The diagnosis of pituitary adenomas (Munir, 2011) highlighted that, CT typically shows an enlarged sella turcica containing a cystic mass, which can be either hypodense or isodense with brain. MRI is better than CT in determining the extent of the cyst and its

exact relationships to the optic nerves, optic chiasm, and hypothalamus. MRI shows a round or ovoid mass lesion in the sella, sometimes extending to the suprasellar cistern.

In addition, (Jacques et al., 2003) confirmed that, the evidence of bony metastasis may be found on skull x-ray; and Magnetic Resonance Imaging cannot be relied on to differentiate between pituitary adenoma and metastases with any certainty. The commonest disorder is the pituitary adenoma, a lesion that is increasingly recognized as a highly prevalent finding. A recent meta-analysis has shown that the postmortem prevalence of pituitary adenoma is 14.4% and that radiologic studies identify a lesion consistent with pituitary adenoma in 22.2% of the population, providing an overall estimated prevalence of 16.9%. Although many of these lesions are considered to be incidental findings, many have unrecognized impact on fertility, longevity, and quality of life, and their clinical significance is increasingly gaining attention (Sylvia, 2008b)

(Mayr et al., 1993) suggested that, the definitive diagnosis depends on the histological identification of the tumor found at surgery. Pituitary metastasis is an uncommon diagnosis. It occurs most frequently in the older patient in whom metastatic disease is most common. Furthermore, half of all pituitary MRI scans performed in a large patient population yielded no visible lesion. Nonadenomatous pituitary lesions should be

considered in the diagnosis of sellar masses observed on MRI, and a high clinical suspicion is required to exclude the presence of a nonfunctioning pituitary adenoma.

For this reasons (John et al., 2009) declared that a three dimension model of the patient's external contour was obtained from planning Computed Tomography data. The computed tomography (CT) and magnetic resonance imaging (MRI) data of 40 consecutive patients with pituitary adenoma were used to construct 3D models to be used in (Prabhakar et al., 2009). Males are diagnosed with larger tumors on average than females. Diagnosis may be delayed for males, giving tumors a chance to grow larger before clinical detection.

1.5 Prognosis of Pituitary Tumors

The prognosis of pituitary tumor depends on the type of adenoma and combination of other factors, indicating the extent of abnormalities , the success of the treatment in normalizing endocrine activity , the morbidity caused by the treatment , and the effectiveness of the treatment in preventing a recurrence (Tammy et al, 2004c). Prognosis is very poor with approximately 66% mortality in the first year of diagnosis (Oh et al, 2012).

The pituitary adenomas present with a variety of clinical endocrine manifestations and arise rarely as part of hereditary genetic syndromes. Molecular analysis of pituitary

adenomas has provided significant insight into pituitary tumorigenesis. Some specific genes have been identified that are rarely predisposed to pituitary neoplasia. The possible activities involve abnormalities in signal transduction pathways, cell cycle regulators, growth factors, chromosome stability and can be evaluated in the clinical significance of genetic alterations and their implications for patient prognosis (Colao et al, 2010). The significant prognostic factors are related to recurrence of brain tumors are tumor diameter and radiation dose (Kobayashi et al, 2012).

1.6 Tools of Treatment

The radiation therapy (treatment with ionizing radiation) has been improved rapidly in the last decade due to new technologies (imaging, computer technology, software, organization) and the radiotherapy process regarding the external radiation is considered as one of the most important tools of cancer treatment (Seegenschmiedt et al., 2012). The further development of radiotherapy is therefore concerned with improving conformation of high dose regions to the tumor regions with the highest possible precision and at the same time reducing the dose of radiation to the surrounding normal tissue. Meanwhile radiotherapy is the use of high energy x-rays to destroy tumor cells whilst doing as little harm as possible to surrounding normal cells (Thwaites et al., 1995). Advances in computer software technology have led to enormous progress that has enabled increasing

levels of complexity to be incorporated into radiotherapy treatment planning systems (Noda et al., 2009a).

The successful radiation treatment of cancer depends vitally on knowledge of the precise amount and location of radiation given to a patient and the opportunity for therapists to exchange this information and the results achieved. As far as radiation measurement is concerned, the ICRU (Reports, 50 (1993), 62 (2001, 2012)) published several early reports recommending dosimetry protocols for photon and electron-beam therapy. However progress in radiation therapy requires the ability to compare clinical results achieved in different centers using different radiation modalities and protocols. Thus a common language for reporting fractionation schedules, doses, and techniques is required for optimum treatment. The ICRU has devoted considerable effort in that direction. Report 50 (1993) on Prescribing, Recording, and Reporting Photon-Beam Therapy provides appropriate guidance for defining tumor, target and planning volumes and gives recommendations for complete reporting of photon treatments. In addition to that (William, 2005) confirmed that, the external photon beam radiotherapy is usually carried out with more than one radiation fields 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. The ICRU report 50 recommends target dose uniformity within +7% and –5% of the dose delivered to a well-defined prescription point within the target.

1.7 Method of Localization for Target Volume

In radiation therapy, the accuracy of dose absorbed to a patient plays an important role for treatment outcome (Mika, 2011). Treatment with 3-dimensional conformal radiotherapy is a suitable non-surgical option for patients with pituitary metastases (Turaka et al., 2012). Based on the practical experience reported here, 3-D conformal radiotherapy allowed dose escalation without excessive toxicity (Hidetsugu et al., 2010). In another perspective advances in computer software technology have led to enormous progress that has enabled increasing levels of complexity to be incorporated into radiotherapy treatment planning systems. Because of these changes, the delivery of radiotherapy evolved from therapy designed primarily on plain 2-dimensional X-ray images and hand calculations to therapy based on 3-dimensional images incorporating increasingly complex computer algorithms in the planning process (Noda et al., 2009b). Furthermore, developments in radiation therapy over the past decade have resulted from increased accuracy of imaging and highly conformal 3- dimensional treatment planning and delivery of radiation therapy. 3-dimensional conformal radiation therapy (3D CRT) with higher doses than previously considered tolerable is now standard for many types of cancer (Cox, 2003).

The 3D technique concentrates the radiation in the treatment area and spares the normal surrounding tissues. Cure rates are increased due to the fact that higher doses can be

applied to the tumor area without a corresponding increase in side effect. However; 3-dimension conformal radiotherapy (3DCRT) is safe and effective for pituitary adenomas. The application of two dimension (2D) and three dimension (3D) target volume localization for pituitary gland and the differences between them and their modes of dose distribution, can be measured with the accuracy of the conformal radiotherapy of dose distribution inside the tumor volume and critical organs in controlling of head and neck tumor ; in order to assess the loco-control tumor region and compare both two and three dimensions target localization, to the planning treatment volume definition in the treatment planning for conformal radiotherapy of pituitary tumors. Meanwhile, in radiotherapy treatment planning the term of two dimensions and three dimensions give the method of treatment dose distribution in the bed of tumor (Purdy,1998;2008). In addition, 3D technique for conformal therapy improves the locoregional control rates of patients compared with the 2D technique (Laurence, 2011).

The conventional radiotherapy improves loco-regional control in head and neck squamous cell carcinomas (Anderson et al., 1999). A less toxic scheme should, however, be investigated and documented before using accelerated radiotherapy as a standard regimen of curative radiotherapy for head and neck cancers. The conventional radiotherapy of head and neck estimates to extent that the total radiation treatment time influences early and late complications (Feuvret et al., 2004; 2006). Recent advances in

software and radiological imaging have opened the way to the development of a new treatment modality called conformal radiotherapy. This relies upon three dimension (3D) planning capabilities that offer advantages over conventional methods two dimension (2D) planning (Prabhakar, 2009). As it is now possible to visualize the part of the body to be treated in three dimensions (3D), tumors can now be identified with greater precision, and the technical aspects of treatment planning have been improved (Michalski, 1998).

1.8 Definition of Terms

The evaluation of target volume localization and dose estimation for pituitary gland two dimensions and three dimensions is the best tools technique for head and neck tumor treatment; because brain tumor is more complicated due to the nature of its cells sensitivity. Moreover, especially if the treatment dose is not perfectly directed to the bed of tumor; as far we are concern with the accuracy in treatment of pituitary tumor in order to shrink the tumor without reaching the radiation toxicity to the surrounding critical organs at risk. Nevertheless, that will require the evaluation of target volume as defined in the ICRU-50 (1993) report “the volume enclosed by an isodose surface, selected and specified by the radiation oncologist as being appropriate to achieve the purpose of treatment”. In addition, for these both treatment techniques of two dimensions and three dimensions there are differences between them; you can notice that in the 2D technique the

distribution of dose inside the tumor it has a certain criteria which may lead treatment policy to not spare normal tissues.

In contrary the 3D technique, the treatment dose is focussed on the tumor bed and the surrounding normal tissues are spared. In these method of treatment techniques, this research will try to estimate the dose distribution between 2D technique and 3D technique inside the tumor bed of pituitary adenomas by using head and neck radiographs whether from CT scanner or MRI scanner, and analyse the results of estimations for both techniques 2D and 3D in order to figure out the characteristics of each for the best use of pituitary tumor treatment achievement in all radiotherapy centres.

1.9 Statement of the Problem

The problem of this study is to determine the control of a significant problem in management of pituitary tumor treatment, in dose distribution of 2D and 3D conformal radiotherapy (CRT) in pituitary tumor, which, will eventually provide an answer to the problem in management of pituitary tumor with the ability to deliver optimized radiation conformation to the target volume. Moreover ,the CRT is important to define clinical needs for geometrical tumor control and it may offer an advantages at tumor sites where an existing local control of tumor is poor , or the dose –response curve is steep for specific tumors, and the dose is compromised by proximity of organs at risk such as optic chiasm , temporal lobe , and eye dose in conformity with treatment line point doses

and given dose by using 2D and 3D techniques to estimate the dose distribution inside the bed of pituitary tumor. In the retrospective study (Lucie et al., 2012) confirms that radiotherapy is efficient in treating optic nerve sheath meningioma. Long-term visual outcome may be compromised by radiation-induced side effects. Mean eye dose has to be considered as a limiting constraint in treatment planning.

1.10 Research Questions or (Null) Hypotheses

This research will formulate questions or (Null) hypotheses which will be the core of the study in order to find the answer for them:-

1.11 General Objectives

The general objective of this study was to evaluate the localization of target and dose estimation for Pituitary adenoma using 2D and 3D in order to study the impact of these techniques on the surrounding critical organs.

1.11.1 Specific Objective

1. To estimate the dose in the eyes, optic chiasm, and temporal lobe
2. To evaluate the treatment lines in given dose of each of 2D and 3D
3. To estimate the dose distribution in 2D and 3D
4. To evaluate the tumor bed coverage of the 2D and 3D target localization to the Planning Target Volume definition in the treatment planning

1.11.2 Significant of the Study

This study is going to add a new innovation for the implementation of conformal radiotherapy perfectly and in a scientifically way within the different radiotherapy centers in Africa and particularly at Radio-Isotopes Centers (RICK) in Khartoum , Sudan ; and it will provide further insights and reveal the potential of this approach for establishing conformal radiotherapy outcomes in the future. As far as this research is concern ,it will open a door and provides so many channels for the application of this new technique in the continent , which will be considered to be a core for future scientific researches in both theoretical and practical in the continent , in addition to that, this study will be considered to be the first specialized topic conducted in order to evaluate between two treatment techniques 2D and 3D treatment line basing on their dose distribution in the pituitary tumor bed region with conformal radiotherapy technique. In addition, (Mellstadt, 2006), confirmed that the coming decades will bring dramatic increases in morbidity and mortality from cancer in the developing world. The burden of cancer is increasing globally, with an expected 20 million new cases per year in 2020, half of which will be in low- and middle-income countries. Despite an already overwhelming burden of health problems, developing countries must somehow address this cancer pandemic and their alarming share of cancer illness.

1.12 Organization of the Study

This study falls into five chapters, with chapter one is an introduction, which included a brief introduction to radiation therapy, problem and objective of the study as well as the importance of the study in term of output. While chapter two it is a literature review and related articles, which includes a comprehensive coverage of the previous study dealing with problem under the study. Chapter three is a methodological chapter which includes the material used to collect the data and method (technique) applied in data collection, where chapter four includes a presentation of the collected data in tables and figures; finally chapter five includes discussion, conclusion, limitation and recommendation of the study.

Chapter Two

Literature Review and Related Articles

2.1 Clinical Significance

The therapeutic dose levels for tumors in the central nervous system and head-and-neck area are often limited by the radiation tolerance of the optic apparatus. Visual impairment from radiation-induced optic neuropathy is uncommon. It usually presents with painless rapid visual loss, vasculature injury is a significant contributor to radiation-induced optic neuropathy (Charles et al., 2010). Therefore, visual loss is associated with a mass lesion; the cause may result from either mass effect or interference with the function of the optic apparatus. Such interference may be the result of abnormalities in the vasculature to the apparatus as a result of the tumor, or chemical factors secreted by the tumor (Jonathan, 2013).

On the other hand , the risk of late normal central nervous system toxicity of external beam Radiotherapy (RT) to doses less than 50 Gy at 2 Gy per fraction is low, with a reported incidence of optic neuropathy resulting in visual deficits of 1-5%, and a risk of necrosis of normal brain structures of 0-2%. Hypopituitarism represents the most commonly reported late complication of RT, and its frequency increases with longer follow-up, occurring in up to 60%of irradiated patients 10 years after treatment (Minniti et al,2011).

2.2 Organs at Risk

In the external beam radiotherapy (EBRT), normal tissues / critical organs within the radiation beam and at the inside of the tumor receive a higher amount of radiation dose, and sometimes may be equal to the tumor dose, which causes normal tissue injury (Rubin , 1968).

The median volumes of gross target volume (GTV), clinical tumor volume (CTV) and planning target volume (PTV) covered by the 95% isodose in higher-order statistics treatment were around 60%. In treatment, the median volume of gross target tumor (GTV), clinical tumor volume (CTV) and planning target volume (PTV) covered by the 95% isodose were 99, 96 and 72%, respectively. Even though the dose coverage of the (PTV) in both phases of treatment were unsatisfactory, radiotherapy with the original higher-order technique had produced good local control; the median volume of the target covered by the 95% isodose (Hitchen et al, 2112).

2.3 Normal Tissue Tolerance Doses

Emami et al (1991) have reviewed available clinical data and presented normal tissue tolerance doses, in terms of $TD_{5/5}$ (the normal tissue tolerance dose at 5% within 5 years after radiotherapy) and $TD_{50/5}$ (the normal tissue tolerance dose at 50% within 5 years after radiotherapy), for 1/3, 2/3 and 3/3 partial volumes of the normal tissue / organ or a reference volume (length or area) of the normal tissue/organ. The partial volume of a tissue or/and organ is presented in terms of fraction with reference to the reference volume. In some cases the reference volume of the organ is considered to be the whole volume of the organ to be a part of the tissue / organ, the tolerance doses are compiled for 5, 10 and 20 cm lengths instead of the volume and 20 cm length of the cord is taken to be the reference length, where volume represents the length.

In some cases the data are limited to only whole volume due to small size of the organs, such as optic nerve, chiasm, eye lens and retina (Pehlivan, 2012). In the same reason, the radiation toxicity of the optic nerves and chiasm to dose and dose–volume measures were reviewed and the risk of toxicity increased markedly at doses less than 60 Gy at 1.8 Gy/fraction and at less than 12 Gy for single-fraction. The evidence is strong that radiation tolerance is increased with a reduction in the dose per fraction (Charles et al., 2010).

2.3.1Temporal Lobes

Small volume of the temporal lobes received a maximum dose of 62.8 Gy. Most of the brainstem was shielded from the lateral portals but 5% of its volume received a dose ranging from 25.4 to 50.4Gy. The spinal cord (at C1/C2 level) received a maximum dose of 40.8 Gy. After modifying higher-order technique by three dimension (3D) customization of the treatment portals, the maximum dose to the brainstem, the optic chiasm and the temporal lobes could be reduced by 8%, 12% and 5%, respectively (Chau et al.,2001).

In the same way, the tumors of the sellar and parasellar region; Previous radiation therapy was performed in 156 (66%) and 24 (11%) patients, respectively. Then median maximum radiation dose to the optic nerve was 10 Gy (range 0.4-16.0). Four patients (1.9%) developed radiation optic neuropathy (RON). The risk of developing a clinically significant RON was 1.1% for patients receiving 12 Gy or less. Patients receiving EBRT had a greater risk of developing RON (Stafford et al., 2003). Furthermore, the location of the gross tumor volume (GTV) and dose distribution in the sagittal plane were superimposed on each other and GTV is coverage by the 50, 90 and 95% isodose lines determined for each phase of treatment (Waldron et al., 2003).

Temporal lobe necrosis (TLN) is the most late-stage complication after radiation therapy. The bilateral temporal lobes are inevitably encompassed in the radiation field and are thus prone to radiation induced necrosis. The wide use of 3D conformal radiotherapy in the treatment of NPC has led to incidence of temporal lobe necrosis (TLN) (Chen et al., 2011).

Pituitary adenomas represent 10 to 20% of all primary brain tumors. The main classifications consider their size, micro- and macroadenomas, and their properties, secreting or non-functioning. Conventional radiotherapy is applied in the post-operative for lesions at high risk of recurrences. Optimal target volume delineation is critical, to the proximity of organs at risk and a risk of late toxicity for patients who have normal life expectancy (Chand et al., 2012).

2.3.2 Temporal bone

The hearing loss and facial weakness is a function of cranial nerve damage. Although this may be true in some cases, the middle and inner ear contain rich networks of other sensitive structures that are at risk after radiotherapy and that may contribute to toxicity afterward (Linskey, 2003). The acceptable level of recurrence when the temporal bone is used as the anterior border of the clinical target volume; achieves tumor control and respects optic tolerance (Bokstein et al., 2008).

The exposure of critical organs to doses of radiation that may exceed organ tolerance; the temporal bone serves as a barrier to tumor spread when regarded as the anterior margin for temporal lobe lesions. The toxicity could be reduced without compromising tumor control. The Clinical Target Volume included the primary lesion, the edema when present and a 2 cm margin except in the direction of the temporal bone. An acceptable level of recurrence (e.g. <5% beyond the temporal bone) is seen when the temporal bone, rather than a 2 cm margin is employed as the anterior border of the CTV. The treatment planning provides tumor control while respecting optic tolerance (Bokstein et al., 2007**)**.

2.3.3 Optic Chiasm

The tumor-controlling doses of up to 40 Gy appears to be a relatively safe technique in treating lesions within or near the sensory and motor nerves (III-VI) of the cavernous sinus. The dose to the optic apparatus should be limited to less than 8 Gy (Tishler et al., 1993). In addition, three dimension (3D) treatment planning techniques were used successfully to provide bilateral sparing of the globe for most patients. It was more difficult to spare the optic nerves, especially on the ipsilateral side, when prescription dose exceeded the normal tissue tolerance doses. Normal tissue complication probability (NTCP) calculations may be useful in assessing complication risk better than point dose tolerance criteria for the chiasm, optic nerve, and retina. It is

important to assess the overall risk of blindness for the patient in addition to the risk for individual visual pathway structures (Martel et al., 1997).

Radiation optic neuropathy (RON) of the dose tolerance permits physicians to be more aggressive in treating patients with sellar or parasellar tumors, especially those with hormone-producing pituitary adenomas that appear to require higher doses to achieve biochemical remission (Stafford et al., 2003). Radiation toxicity of the optic nerves and chiasm to dose and dose-volume measures were increased markedly at doses higher than 60 Gy. The evidence is strong that radiation tolerance is increased with a reduction in the dose per fraction (Mayo et al., 2009). The optic apparatus seems to be more tolerant of irradiation. Careful dose planning is essential, particularly in patients who underwent prior external beam radiation therapy (Hasegawa et al., 2010).

2.4 Target Volume Definition

The target 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: gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV) and planning target

volume (PTV) (Parker, 2005a). The goal of radiotherapy is to achieve uniform target coverage while sparing normal tissue (McGowan et al., 2013)

2.4.1 Gross Tumor Volume

The gross tumor volume (GTV) can be defined by the area of contrast enhancement observed on the CT scan or MRI; the classical concept of GTV plus a safety margin of 2 cm around containing at least all the oedematous area and eventually adjacent brain structures (Kantor et al., 2001). The Gross Tumor Volume (GTV) is defined as “the gross palpable or visible/demonstrable extent and location of malignant growth, and the Gross Tumor Volume may consist of primary tumor, metastatic lymphadenopathy. This volume is then incorporated into the volume which can be considered at risk (ICRU Report No.50). The GTV is usually based on information obtained from a combination of imaging modalities and clinical examination (Parker, 2005b).

2.4.2 Clinical Target Volume

The Clinical Target Volume (CTV) is defined as “a tissue volume that contains a demonstrable gross tumor volume 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. The Gross Tumor Volume and Clinical Target Volume are anatomical and biological concepts (ICRU Report No.50). The Clinical Target Volumes

can be subdivided into Clinical Target 1 (CTV1) and Clinical Target Volume 2 (CTV2). Thus CTV1 is the potential sub-clinical disease extensions derived from the known history of site-specific neoplasms. A second clinical target volume (CTV2) is the microscopic extension of disease adjacent to Gross Target Volume (GTV). However, current imaging modalities do not visualise microscopic disease and currently, arbitrary margins around Gross Tumor Volume (GTV) are used to define CTV2 (Srinivasan et al., 1995). The determination of optimal clinical target volume (CTV) margins around Gross Tumor Volume (GTV) for modern radiotherapy techniques, requiring more precise target definitions, is controversial and complex (Moghaddasi et al., 2012).

2.4.3 Internal Target Volume

The internal target volume (ITV) consists of the clinical target volume (CTV) plus an internal margin. The internal margin is designed to take into account the variations in the size and position of the clinical target volume (CTV) relative to the patient's reference frame (usually defined by the bony anatomy); that is, variations due to organ motions (ICRU Report No. 62).

2.4.4 Planning Target Volume

The Planning Target Volume (PTV) is defined as a "geometrical concept, and it is defined to select appropriate beam sizes and 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 Clinical Target Volume " (ICRU Report No.50). The Planning Target Volume includes the Clinical Target Volume plus margins for patient motion, organ motion, organ shape and variation, and uncertainties in beam placement. It does not include any margin for any beam characteristics such as penumbra, which must consequently be accommodated with adequate margins at the time of beam placement (ICRU Report No.62).

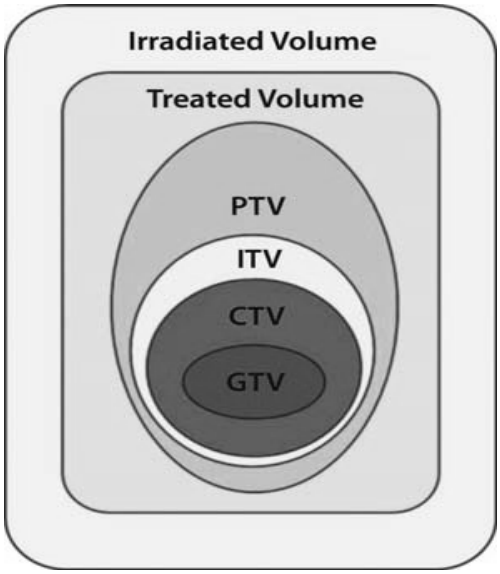


Figure 2.1International Commission on Radiation Units and Measurements[2]

[2]ICRU reports 50 and 62 volumes used in 3D treatment planning. Gross tumor volume (*GTV*) is the volume(s) of known tumor. Clinical target volume (*CTV*) is the volume(s) of suspected microscopic tumor infiltration. Planning target volume (*PTV*) is the volume containing the CTV/GTV with enough margins necessary to account for setup variations and organ and patient motion. Internal target volume (*ITV*) represents the movements of the CTV referenced to the patient coordinate system by internal and external reference points.

2.4.5 ICRU Reference Point

The concept of dose specification has been changed to the "ICRU reference point" instead of to form the isodose encompassing the target volume. Treatment plans have been analyzed to assess the consequences of this change on dose prescription, treatment technique, and the size of the irradiated volume. ICRU recommendations on dose homogeneity may significantly affect treatment technique and field sizes. Small deviations in dose prescription may be of particular influence on late responding normal tissues. Detailed comparisons of individual treatment plans with respect to physical, biological, and clinical data are obviously necessary in order to make sure that the outcome of a radiation treatment is not deviating too much from the clinical experience (Hess et al., 1993). The Planning Target Volume (PTV) is defined by ICRU report 50 as a geometrical concept, used to select appropriate beam sizes and beam arrangements. Clinically, a plan is normally acceptable if the 95% isodose surface covers the PTV. The mean dose to the PTV is well estimated by either the ICRU reference dose or the mean central dose for a variety of treatment techniques for common types of cancer (Kukołowicz, 1997).

The PTV coverage showed no statistical difference between 2D and 3D radiotherapy in terms of V95% or V107%. However, there was more conformity in 3D planning rather than 2D planning. In regarding OARs, 3D planning shows large gain in healthy tissue

sparing; then there was no statistical difference in mean dose received by each OAR. Furthermore, for pituitary adenoma, brain-stem mean dose and brain V90% showed better sparing in 3D planning, brain stem mean dose was 61% in 2D and 51% in 3D and brain V90% was 17.6 in 2D and 8.6 in 3D. Similarly, there was overall significant decrease in doses receive by healthy tissues in term of OARs score which was 0.24 in 3D and 0.40 in 2D planning (Ahmed et al , 2009). However, Bauduceau et al, (2008), found that, the ICRU 50 quality criterion that at least 95% of the PTV (PTV (95%)) should receive at least 95% of the prescribed dose.

2.4.6 Treatment Dose

Treating a patient with radiotherapy, the radiation oncologist normally prescribes doses to both the malignant disease and to relevant normal tissues. The therapist also records doses delivered during treatment session within various volumes or at various points in tissues for the purpose of documentation. Doses will also have to be specified for the purpose of reporting. So, when delivering radiotherapy treatment, parameters such as the volume and dose have to be specified for different purposes: prescription, recording and reporting; according to the ICRU-50 recommendation heterogeneity of dose distribution should be kept within +7% and -5% of the prescribed dose (ICRU Report No .50).The dose-evaluation techniques, including isodose line comparisons, displays of the dose difference

between calculated and measured distributions, and distance-to-agreement comparisons, are useful for display of differences between two different dose distributions, but are often of limited value for the assessment of the discrepancies in terms of significance and/ or cause (Jean et al., 2004). However, the radiotherapy of pituitary adenomas, using modern treatment planning techniques, is effective and safe. To achieve optimal tumor control, doses of 45–48 Gy should be applied (Dietmar et al., 1995).

2.5 Treatment Techniques

The aim of pituitary tumor treatment technique (Tammy et al , 2004) declared that is to normalize pituitary hormonal function or relieve local compressive and/or destructive effects of the tumor, in the same way (John et al, 2009) reported that, the treatment of pituitary tumor with radiation depends on different factors such as; size and location of the tumor. Furthermore, the radiation therapy should be considered in the management of patients with pituitary adenomas, particularly when medical and surgical options have been exhausted (Loeffler et al, 2011). Meanwhile, (Hasegawa et al, 2011b) has highlighted that dose escalation to the target while sparing the organs at risk near the lesion has been difficult over the last decade. However, recent radiotherapy techniques can deliver more sophisticated doses to the target.

2.5.1 Two Dimensional Techniques (2D)

The dose distribution was calculated in a single plane through the patient using two-dimensional treatment planning. In this two dimension planning technique, the anatomical part is defined in a single axial slice and only coplanar beams are used for planning, the inhomogeneity inside the body is not taken into account for dose calculation. This planning method has its own limitations, as variations in the shape and density of the anatomical structures throughout the patient are not fully accounted for. Furthermore; two-dimensional radiotherapy has long been used to control growth in pituitary tumors. Nevertheless, there is still a controversy, because several potentially significant side effects including Hypopituitarism may develop (Purdy, 1997). In the same way , (Anderson et al,1999b) studied that traditional isodose curve in two dimension representation of how dose varies with point dose ,and within a beam along direction, because the treatment planning attempts dose distribution optimization for a given clinical goal in a given clinical situation.

The aspect of conventional two dimension margin methods is still widely used; therefore, it is important to be aware of the possible deficiencies described. In like manner, beam apertures for radiotherapy treatment should be designed by adding a two dimension margin to the gross tumor volume outline in the beam eye view rather than by growing a two dimension margin in the transaxial plane only, then creating the beam profiles are

correct; it does not ultimately provide an accurate planning treatment volume against which the calculated dose distribution can be assessed. Simultaneously, the two dimension technique was associated with an increased risk of locoregional recurrence (Zhang, 2000).

Because the two dimension dose distribution in the target volume is represented as a function of two coordinates of the target depth (axis X) and the target width along scan direction (axis Y) for each product to be treated in the irradiation facility, there will usually be a minimum dose limit to obtain the desired effect and a maximum dose limit that the product can tolerate without degradation in quality (Kaluska et al., 2004b). On the other hand, (Feuvret et al., 2004b) studied that the objective of radiotherapy is to treat patient with the best therapeutic ratio, i.e. the highest local control and the lowest toxicity to normal tissues. The traditional isodose curve is two dimension representation of how dose varies with position within a beam along direction, because the treatment planning attempts dose distribution optimization for a given clinical goal in a given clinical situation (Kara et al., 2005).

In other words (Joshi et al., 2007) pointed out that quality of two dimension image sets and accurate for target volume delineation are necessary to minimize dosimetric uncertainties that may affect the treatment . in the same way (Jason, 2008) showed that production of a two-dimensional treatment plan is assisted by projecting outlines of the

gross tumor onto a single transverse plane, so that the total extent of the tumor can be easily visualized. Therefore, a two dimension margin can then be added to the resulting outline, so as to account for microscopic tumor spread, organ motion, and setup uncertainty. The margin may be differing according to orientation in setup accuracy in the anterior, posterior, left and right directions. Therefore, (ICRU report No 62) recommended that, the two dimensional (2D) planning dose distribution calculation is faster and easier and can be performed by hand moreover is much less accurate. The requirement of dose prescription (Purdy, 2008) reported that the dose supposed to conform as closely as possible to the target volume that will determine the level of the precision and accuracy generally found in two dimension radiation therapy.

2.5.2 Three Dimensional Techniques (3D)

In Purdy (1997a) summary study the radiation therapy treatment plans and delivery capabilities have changed dramatically since the introduction of three-dimensional treatment planning and are continuing to change relatively rapidly in response to the implementation of new advanced technologies. Three-dimensional conformal radiation therapy is the standard of practice in clinics around the world. Three-dimensional conformal radiotherapy provides improved target coverage and lower doses to surrounding normal tissues. Therefore (Boyer et al, 1997) suggested that the three-

dimensional radiation exploits the use of fields in which the beam intensity is varied optimally within the portal boundary, and this approach is capable of generating extremely conformal dose distributions including concave isodose volumes that provide specific avoidance of sensitive normal structures within complex treatment geometries.

A margin of 3-10 mm beyond the visible extent of tumor is included in the treatment planning to allow for patient movement and set-up variation during the treatment. Three-dimensional (3D) treatment planning provides more accurate visualization of dose distribution as compared with 2D planning, with the option of giving a more homogeneous dose within the target and lower dose to the organs at risk of radiation toxicity. More precise delivery is achieved conforming the radiation beams to the shape of tumor (conformal radiotherapy) and increasing the number of beams. This results either in reduction of volume of normal rain receiving high dose of radiation or in a greater dose differential between the target and normal brain tissue. The total dose of 45-55 Gy is achieved by daily doses of 1.8-2.0 Gy, with treatment lasting for 5-6 weeks (Minniti et al., 2011b).

In three dimensional technique Purdy et al (1988b) claimed that three-dimensional radiation treatment planning systems are rapidly being implemented in clinics around the world so that to produce a precise shaping of dose distributions , improving the quality of

radiotherapy, and the efficiency with which radiation therapy can be planned and delivered. Furthermore, three-dimensional conformal radiation therapy conform the prescription dose close to the target volume while limiting dose to organ-at-risk. However, (Gambacorta et al., 2013) highlighted that, the 3D treatment planning was superior to 2D treatment planning in covering areas at risk the areas with suboptimal coverage may lead to an increased risk of recurrence and should be correlated with the patterns of recurrence.

The planned dose distributions exhibit significant potential for sparing closely spaced normal tissue structures in the treatment regions. Therefore , the three-dimensional uses beam's eye viewing for volumes delineation , beam directions and beam shapes to conform to the shape of the projected target and minimize dose to critical normal structures (Verhey, 1999). Three dimension images is based on treatment planning, and the isocenter is usually placed inside the tumor and dose is prescribed at the isodose surface covering the entire three dimension target volume (Uy et al., 2002). Thus, the three dimensional technique is normally used to reduce dose to the critical organs by arranging the primary beam in nonaxial plans (Wu et al., 2004).

On the other hand, (Purdy, 2008c) declared that, three dimension treatments planning more provide details the procedures of a patient's treatment. However, three dimension

conformal radiotherapy capabilities change the techniques of radiation therapy treatments that are possible and that changes the process with which treatment planning and treatment delivery are performed. A 68 year old male patient presented for radiation therapy for treatment of a benign tumor, a glioma of his left optic nerve. The radiation oncologist intended to prescribe 52.2 Gy to the planning target volume, while maintaining a maximum of 54 Gy to the optic nerves and the optic chiasm and a maximum of 40-45 Gy to the globes in order to minimize the possibility of damaging the optic system, which is especially important as this is a benign tumor. The dosimetrist devised a conformal non-coplanar three-dimensional plan with a slightly weighted forward planning component. This plan was created in approximately 15 minutes after the critical organs and the targets were delineated and resulted in an extremely conformal and homogenous plan, treating the target while sparing the nearby critical structures. This approach can also be extended to other tumors in the brain - benign or malignant (Millunchick, 2013).

2.5.3 Conformal Radiotherapy

In addition, (Das et al. 1997) suggested that Three-dimensional conformal radiotherapy conform the volumetric distribution of the desired dose to the shape of the target. The basic rationale for using conformal delivery is to spare adjacent normal tissue from receiving unnecessary radiation. Conformal radiotherapy uses advanced radiotherapy treatment planning in three dimensions to achieve better conformation of treatment volume to target volume. This allows reduction in the volume of normal tissue irradiated around the target. It is possible that the technique might lower doses to the hypothalamus; tumors (Michalski et al., 1998).

In the same way Becker et al., (2002) claimed that the dose homogeneity was reached in the conformal plans with high planning target volume priority in the optimization process. This consequently led to a better probability of tumor control. Better protection of organs at risk and thereby lower normal tissue, complication probabilities were achieved with increased weighting of the organs at risk. The main benefit with conformal radiotherapy is that it is more precise, as it allows doctors to plan in 3D. Conformal radiotherapy can give a better chance of killing the cancer by delivering a higher dose of radiation straight to it. Thus, the conformal therapy is a safe and effective treatment to organ-at-risk and gives a satisfactory long-term tumor control, good functional outcome, and low treatment morbidity (Metellus et al., 2010). Consequently, conformal therapy

delivers a tumoricidal dose to target volume without causing a local recurrence within 5 years (Shah et al, 2012).

Based on these previously discussed researches, most of those studies agreed with the hypothesis of my study, the pituitary gland is maestro gland , it controls the activities of all endocrine system , and it consists of three parts , the first is anterior lobe ; the second is posterior lobe ; and the third is intermediate lobe each one of lobes secret their hormones directly to the system . For the same reason, (Oh et al., 2012b) reported that pituitary tumor has a very poor. On the other hand, (McDowell et al., 2011) hypothesized that the incidence of pituitary tumor is generally increased with age and higher in females in early age and higher in males in later age, and pituitary tumors are benign as declared by (Buatti et al, 1997).

In the detection, (Munir, 2011) showed that MRI is better than CT in determining the extent of the cyst and its exact relationships to the organs at risk. MRI shows a round mass lesion in the sella turcica; sometimes it shows the tumor extending to the suprasellar cistern. The most researchers (Purdy, (1997) ; Anderson et al, (1999)) agreed with my research hypothesis mentioning that ; the two-dimensional (2D) was used to control tumor growth in pituitary, but is still an ineffective , because several potentially significant side effects may develop sometimes . Therefore, two dimension techniques (2D) are associated with an increased risk of locoregional recurrence. On the other hand,

there is a conflict between my study hypotheses with (Purdy et al., 1988, Metellus et al.,2010) study who said that, three-dimension technique (3D) conform the prescribed dose to the target volume while limiting dose to organ-at-risk. Therefore, the conformal therapy is a safe and effective treatment to an organ-at-risk and gives a satisfactory long-term tumor control, good functional outcome. Conformal planning reduced the doses to the optic nerves and chiasm as well (Brizel et al., 1999). The average dose to critical organs is diminished whenever the conformal radiotherapy is used (Ulrike et al 2004).

Chapter Three

Materials and Methods

3.1 Introduction

The irradiation of treatment area control remains a significant problem in management of pituitary tumor, but the dose distribution of 2D and 3D conformal radiotherapy (CRT) in pituitary tumor will eventually provide an answer to the problem in management of pituitary tumor with the ability to deliver a conformed radiation to the target volume. Moreover ,the CRT is important to define clinical needs for geometrical tumor control and it may offer an advantages to the tumor sites where an existing local control of tumor is poor , or the dose –response curve is steep for specific tumors, and the dose is compromised by proximity of organs at risk such as: optic chiasm , temporal lobe , and eye dose in conformity with the treatment line as a reference point doses and given dose by using 2D and 3D techniques to estimate the dose distribution inside the bed of pituitary adenoma.

The proximity of planning target volume (PTV) to organs at risk (OAR) in the brain limits the ability of three-dimensional conformal radiotherapy (3-D CRT) plans to deliver a prescribed dose to PTV while sparing OAR (Jillian et al , 2011). In addition, in treatment, the median volume of gross target tumor (GTV), clinical tumor volume (CTV) and planning target volume (PTV) covered by the 95% isodose were 99, 96 and 72%,

respectively. Even though the dose coverage of the (PTV) in both phases of treatment were unsatisfactory, radiotherapy with the original higher-order technique had produced good local control. The median volume of the target is covered by the 95% isodose; wherever, required and achievable, the constraints were changed to obtain possible minimum doses to critical organs without compromising the PTV coverage of at least 95% dose to 95% of PTV volume (Hitchen, 2112). Furthermore, satisfactory CTV dosimetric criteria were selected to be a minimum CTV dose of 95% of the PTV dose and at least 95% of the CTV receiving 100% of the PTV dose (Brent et al, 2002).

The pituitary adenomas incidence vary widely, suggesting that incidence rates generally increased with age and were higher in females in early life and higher in males in later life. Males are diagnosed with larger tumors on average than females. Diagnosis may be delayed for males, giving tumors a chance to grow larger before clinical detection (McDowell etal, 2011c).

Simultaneously, the two dimension technique was associated with an increased risk of locoregional recurrence (Zhang et al, 2000). Because the two dimension dose distribution in the target volume is represented as a function of two coordinates of the target depth (axis X) and the target width along scan direction (axis Y) for each product to be treated in the irradiation facility, there will usually be a minimum dose limit to obtain the desired

effect and a maximum dose limit that the product can tolerate without degradation in quality (Kaluska et al, 2004b).

The pituitary gland on coronal post-contrast CT scan in 251 patients demonstrated that the pituitary gland is somewhat larger in females than in males. In males, glands measuring greater than 7.7 mm should be considered abnormal; in females, a statistically significant decline of gland height occurs with increasing age, the upper limit of normal for female gland height decreasing from 9.2 cm for a 20-year-old to 6.0 cm for a 90-year-old. Focal low densities greater than 3 mm are rare in males and probably should be considered abnormal (Peysteret al., 1986).Coronal computed tomographic scans of the pituitary gland in 27 normal children, adolescents, and young adults (ages, 8-21 years) and in a comparison group of adults (ages, 24-91 years) were evaluated retrospectively to test the applicability of published criteria for size and configuration of normal adult pituitary glands to younger patients. Statistically significant differences were found between the two groups, indicating that the pituitary gland in adolescents, particularly girls, is larger than in younger or older patients (Peysteret al., 1983).

The size and frequency of visualization of the normal pituitary stalk on high-resolution computed tomography (CT). The normal pituitary stalk can be seen on the vast majority of high-resolution scans obtained with thin sections and intravenous contrast material.

The upper size limit of the normal pituitary stalk is 4 mm at the level of the dorsum sellae and 4.5 mm above the dorsum. Stalks larger than this should be viewed with suspicion. Comparison of the size of the pituitary stalk with that of the nearby basilar artery is possible on most CT scans, providing a convenient and reliable visual check of the size of the stalk (Peyster, 1984). Pituitary microadenomas may present with subtle or no mass effect. They may appear lucent, dense, or heterogeneous on computed tomographic (CT) images. The normal pituitary gland may also have a nonhomogeneous CT appearance with intermingled lucent and dense areas. This heterogeneity is related in part to microscopic variation within the anterior and posterior lobes (Roppolo, 1983).

The height of the pituitary gland in women increased again in the 50- to 59-year-old age group. The changes in the endocrine milieu may be reflected in pituitary morphology. The increase in pituitary height during puberty may be related to the hypersecretion of luteinizing hormone during this period. The greater pituitary height in young subjects, both male and female, may reflect physiological neuroendocrine differences between younger and older subjects. The decline in pituitary height with age may also reflect the endocrinology of aging and a physiological pituitary atrophy. The basal serum concentrations of gonadotropic hormones (luteinizing hormone, follicle-stimulating hormone) decline after puberty up to the fifth decade. In women, however, concentrations of these hormones begin to increase dramatically in the fifth and sixth decades,

apparently due to an age-related decline in circulating gonadal steroids and an increased "drive" from gonadotropin-releasing hormones. If it is true that the endocrine milieu is reflected in a person's pituitary height, it seems reasonable to assume that women have greater pituitary height in this period (Tsunoda et al., 1997).

3.2 Population and Sample

The study population was randomly selected from the age groups (youngers, adults, and olds) starting from 17 up to 57 years old according to the availability as a sample of pituitary adenoma cases. Meanwhile, the samples of the study after the data collection they were (female 178, and male 122). Furthermore, 209 of sample of the study were noticed as married, and the rest 91 were not married. On the other hand , the number of the sample collected were related to the tumor size that , it was noticed that (51% , SD± 0.09 for microadenomas , and 49% , SD± 0.15 for macroadenomas). As the importance of research problem the study was conducted from 2010 up to 2013, and the total number of samples were also randomly collected which lead to these 300 of pituitary adenomas patients.

The symptoms of a pituitary tumor can range from simple common complaints such as listlessness or restlessness to more severe symptoms such as: headaches, vomiting or dizziness. In older children or adolescents, other signs may be seen including problems with normal growth and development. For instance, sometimes young girls or boys,

under age 9, experience a very early puberty, referred to as precocious puberty; this is caused by tumors that secrete luteinizing hormone (LH). Girls may develop breasts, have pubic hair, and begin menstruation. Boys may find their genitals enlarging and facial and pubic hair beginning to grow. Tumors that secrete follicle stimulating hormone (FSH), in contrast, can retard sexual development in both sexes and stunt growth (Related Articled, 2013). However, pituitary adenomas may occur in children and that these tumors when present in the pubertal period may be more likely to exhibit extrasellar extension or invasiveness (Lee et al., 1988).

3.3 Instrumentation

The CT simulator was used to radiograph patients ; in accordance all patients were CT simulated after properly positioning and immobilization for2D and 3D plans inside the pituitary adenoma, and its structures were delineated; including the target volume gross target volume (GTV), clinical target volume (CTV), and planning target volume (PTV)], as well as organs at risk. Conformal beams were designed with the aid of beam's eye view. Dose distribution analysis was edited to provide 3D dose coverage to the target while sparing organs at risk. Plans were evaluated by comparison of dose distributions for the PTV and OARs. The size of tumors was evaluated under the CT Simulator planning on each step the data were recorded on the data recorded sheet for analysis. Then , the CT radiographs has been taken to physics department for dose distribution and evaluate their

distribution in normal tissues as well as organs at risks in both techniques 2D, and 3 D. and finally, high energy Linear Accelerator Clinac 2300 CD (Varian Ag, KSA) having 120 leaf millennium MLC was used for the delivery of treatments.

3.4 Treatment Techniques

The dose distribution was calculated in a single plane through the patient using 2D treatment planning. In this 2D planning technique, the anatomical part is defined in a single axial slice and only coplanar beams are used for planning, the inhomogeneity inside the body is not taken into account for dose calculation. This planning method has its own limitations, as variations in the shape and density of the anatomical structures throughout the patient are not fully accounted for. Furthermore; 2D radiotherapy has long been used to control growth in pituitary tumors. Nevertheless, there is still a controversy, because several potentially significant side effects including Hypopituitarism may develop (Purdy, 1997c). In the same way, (Anderson et al, 1999b) studied that, traditional isodose curve in 2D representation of how dose varies with point dose, and within a beam along direction, because the treatment planning attempts dose distribution optimization for a given clinical goal in a given clinical situation.

The aspect of conventional 2D margin methods is still widely used; therefore, it is important to be aware of the possible deficiencies described. In this manner, beam apertures for radiotherapy treatment should be designed by adding a two dimension (2D)

margin to the gross tumor volume outline in the beam eye view rather than by growing a 2D margin in the transaxial plane only, then creating the beam profiles are correct; it does not ultimately provide an accurate planning treatment volume against which the calculated dose distribution can be assessed. Simultaneously, the 2D technique was associated with an increased risk of locoregional recurrence (Zhang et al, 2000b). In 3D technique Purdy et al., (1988c) claimed that 3D radiation treatment planning systems are rapidly being implemented in clinics around the world so that to produce a precise shaping of dose distributions , improving the quality of radiotherapy, and the efficiency with which radiation therapy can be planned and delivered. Furthermore, 3D conformal radiation therapy conform the prescription dose close to the target volume while limiting dose to organ-at-risk. However, CT images with three dimensional (3D) planning software help in displaying the 3D-dose distribution at different levels in the PTV (Murthy et al., 2010).

3.5 Data Collection

The sample has being collected by formulating the data collection form from the continuous and perseverance of my supervisor and co-supervisor at end we got the mentioned below which include the basic requirement for data collections such as: (gender, age, marital status, tumor size in cm, pituitary size in cm, given dose in Gy, treatment line in 3D versus in 2D, PTV95%, PTV107%, and vital organs including optic chiasm, temporal lobe, and eye). On the other hand, the data were collected and filled the form and processed in order to be understood statistically. Furthermore, CT radiograph of 300 pituitary adenoma patients (179 female, 121 male) were randomly collected from different imaging sections, and then to the treatment planning section room in order to evaluate them in both conventional 2D and 3D dose distribution inside the tumor bed as well as organs at risks (optic chiasm, temporal lobe, and eye) from the isodose curve presentation within the Planning Target Volume (PTV).

3.6 Procedures

1. The CT simulator radiographs were collected after observing the position of organ
2. Record the following (gender, age, and marital status) of patient in the data collection form
3. Record the tumor size from the CT simulator radiograph of the lesion relative to actual size of pituitary gland
4. Record the total tumor dose so that to differentiate between (45, 55, and 60 Gy) in Pituitary adenoma
5. Record a required and achievable treatment line; the constraints were changed to obtain possible minimum doses to critical organs without compromising the PTV coverage of at least 95% dose to 95% of PTV volume by using both techniques 2D and 3D dose distribution.
6. Record the isodose line of dose distribution in both 2D and 3D to evaluate more dose exposure to organ at risks (optic chiasma, temporal lobe, and eye).

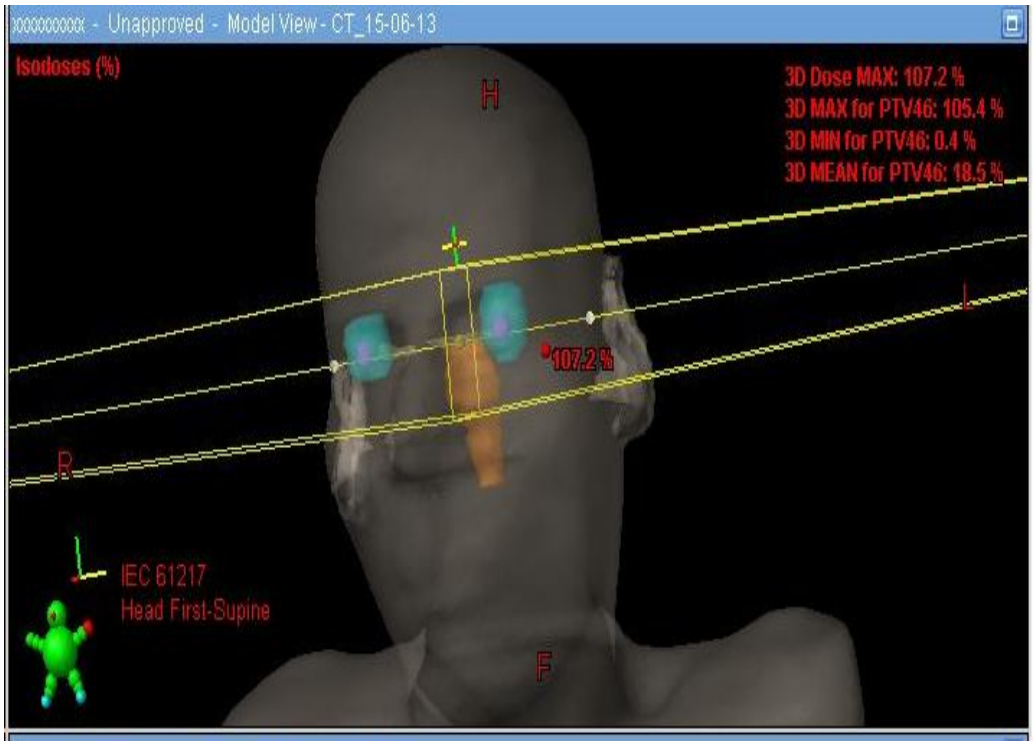


Figure 3.1 pituitary adenoma tomogram planning view in two opposing field

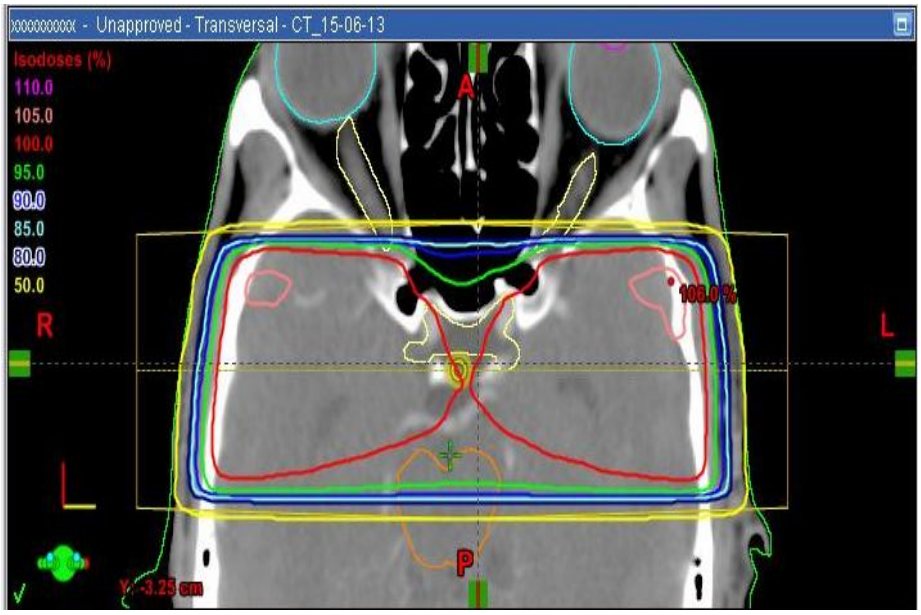


Figure.3.2 dose distribution inside the pituitary adenoma in relation with the treatment line in the adjacent healthy and normal tissue

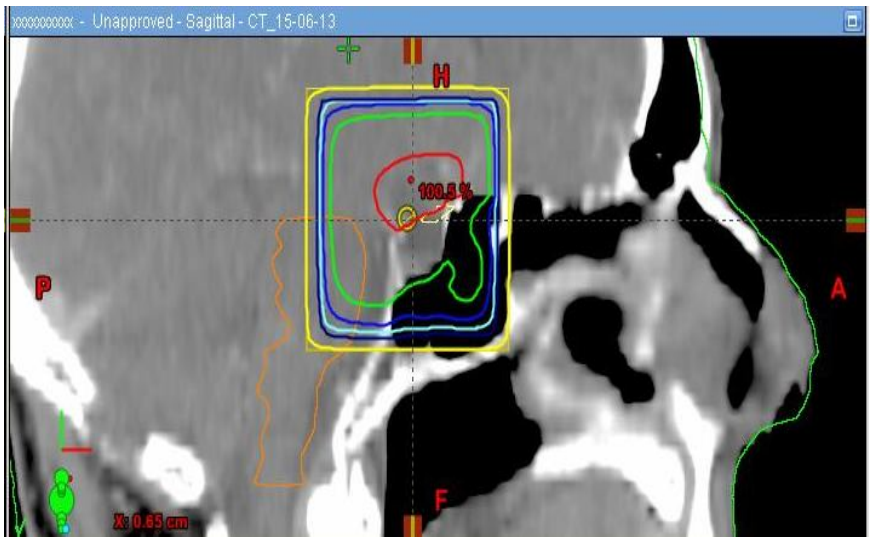


Figure 3.3 planning target volume in the pituitary adenoma in relation with the given dose confined in the bed of tumor sparing the organ at risk.

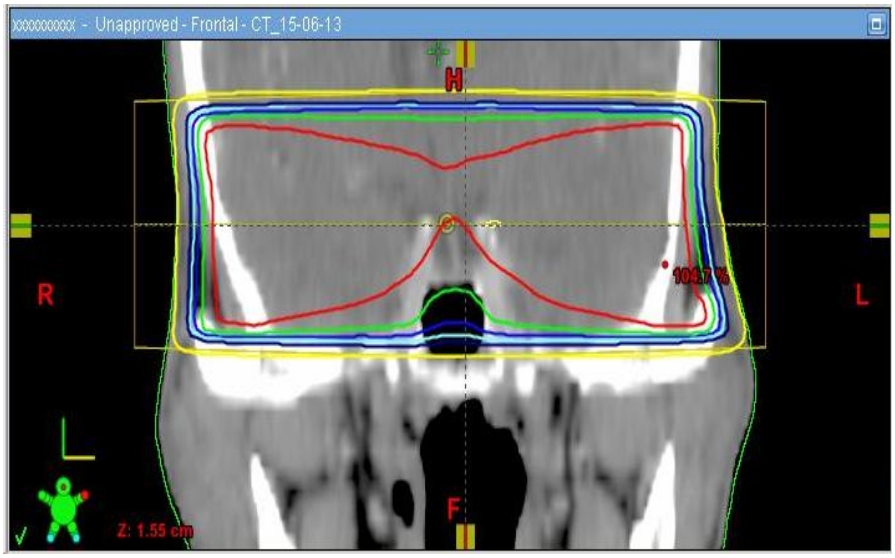


Figure 3.4 the discrepancies of dose distribution in the pituitary adenoma according to treatment line with the two opposing fields.

3.8 Data Analysis

Using statistical program, numerical data were summarized using means, standard deviations, and ranges. Comparisons between 2D and 3D plans were performed using the Wilcoxon Signed Ranks test, a nonparametric test equivalent to the paired test to be used for small sample size. All *p*-values are two-sided. *P-values*<0.05 were considered significant.

Chapter Four

Results

The results of this study displayed using tables and figures. The tables show the mean and standard deviation of PTV95%, dose received by temporal lobe, eye and optic chiasma using 3D and 2D dose distributions, as well as significant test results between 3D and 2D. The figures consist of histogram and scatter-plots; the histogram shows the distribution of the variable included in this study is 300 patients. The scatter plot depicted the association between the tumor doses and the dose received by the critical organs; as well as the effects of tumor size on tumor dose.

Table 01 shows the distribution of mean for PTV 95% and dose received by critical organs for 2D and 3D dose distribution.

Variable	3D	2D
	Mean±SD	Mean±SD
PTV95%	94.2 0±0.75	91.28±0.69
Temporal lobe	0.23±0.01	0.46±0.04
Eye	0.22±0.01	0.33±0.02
Optic chiasma	0.20±0.02	0.42±0.02

Table4. 2 a paired *t*-test between the 2D and 3D dose distribution with *t* and *p*-value

Paired *t*-test	*t*	sig (2 tailed)*p*
PTV95%	49.7	.000
Temporal lobe	95.3	.000
Eye	87.9	.000
Optic chiasma	121.6	.000

The tables above show that there are differences between variables when using 3D and 2D as shown in Table 4-1. These differences were significant at $p = 0.05$ between the dose distribution using 3D and 2D in favor of 3D using paired *t*-test concerning the PTV95%, temporal lobe, eye and optic chiasma received dose, with $t = 49.664$, 95.322, 87.961 and 121.581 respectively and $p<0.0001$.

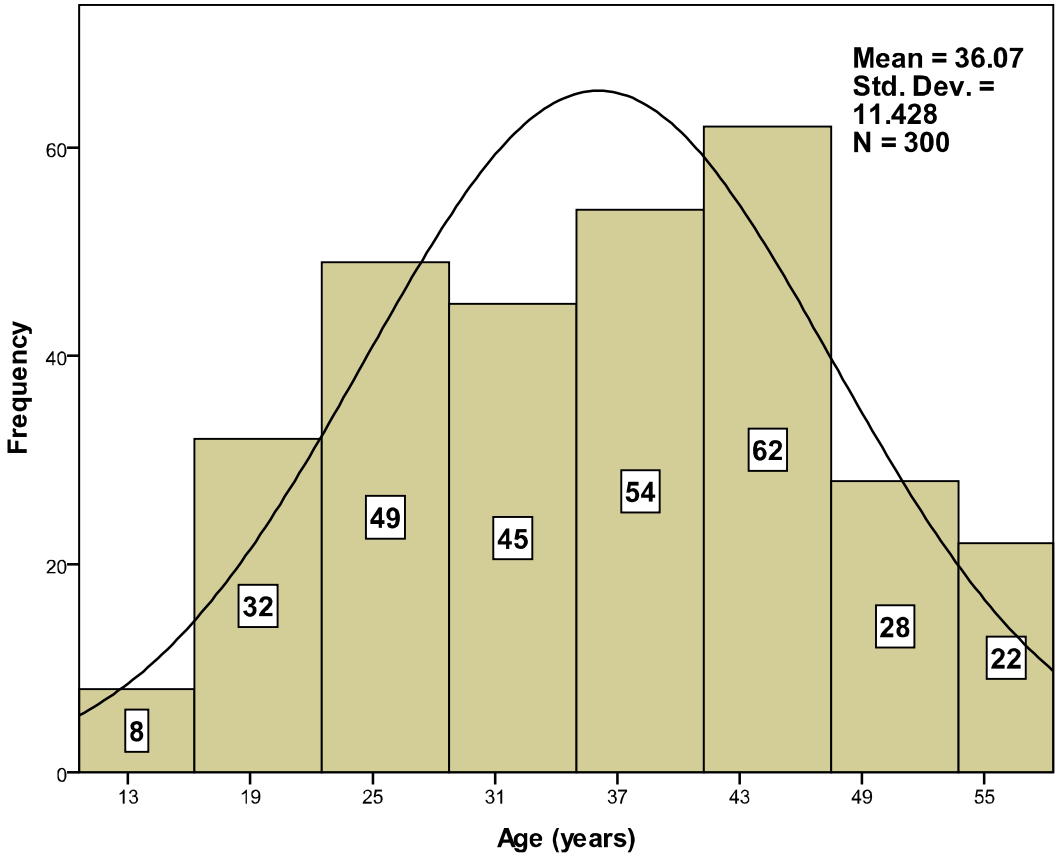


Figure.4.1 (a bar chart or histogram) shows the frequency distribution of age; with a normal curve over-plotted as well as the mean and standard deviations.

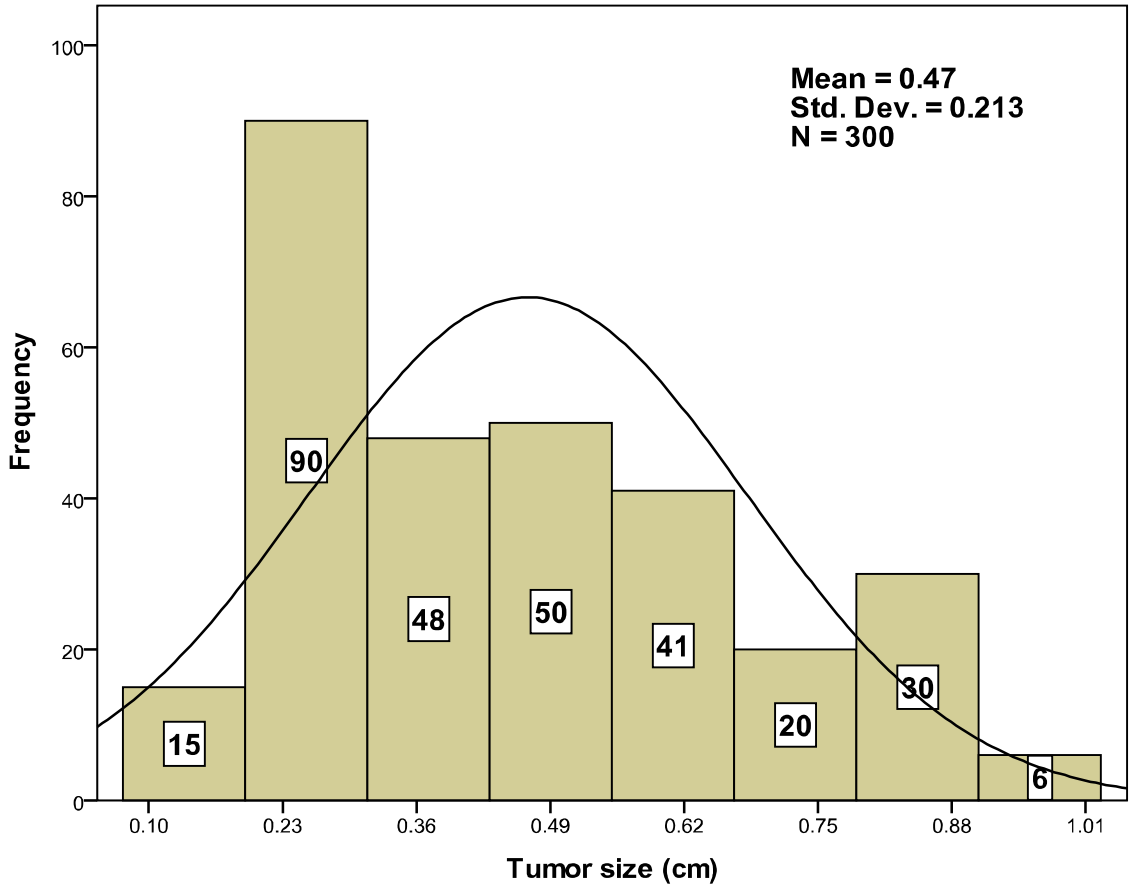


Figure4.2 (a bar chart or histogram) shows the frequency distribution of the tumor size; with a normal curve over-plotted as well as the mean and standard deviations.

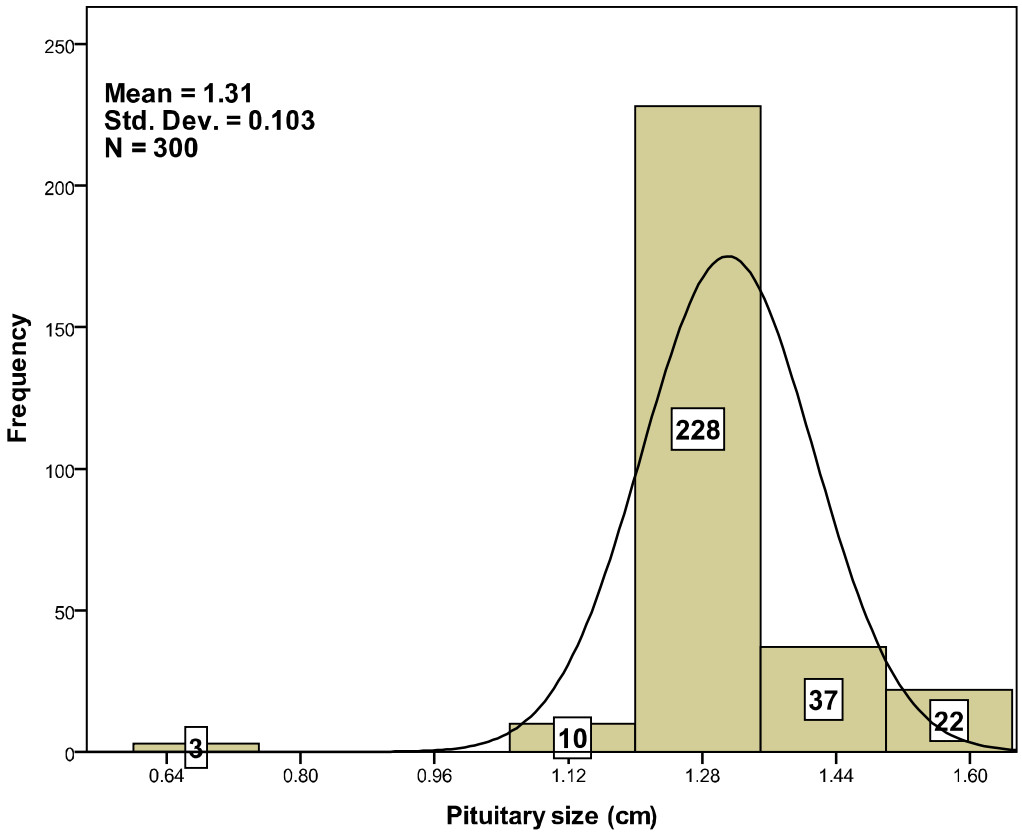


Figure 4.3 (a bar chart or histogram) shows the frequency distribution of the pituitary size in cm; with a normal curve distribution over-plotted as well as the mean and standard deviations.

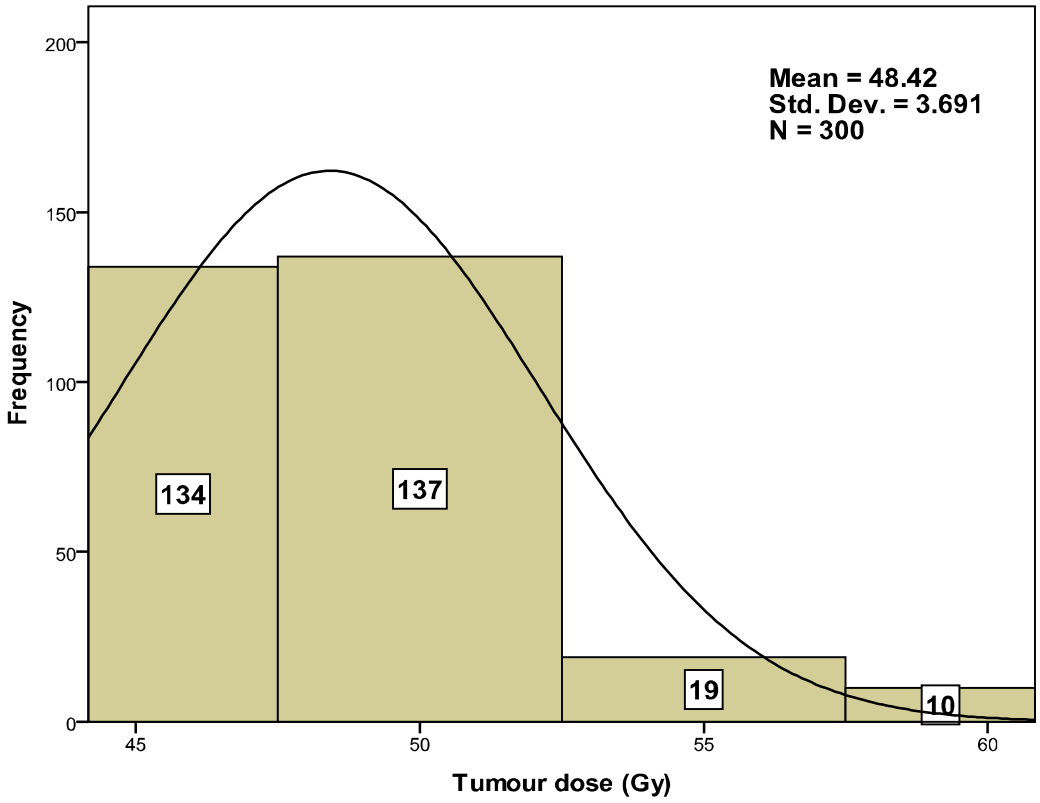


Figure 4.4 (a bar or histogram) shows the frequency distribution of the pituitary adenoma tumor dose in Gray.

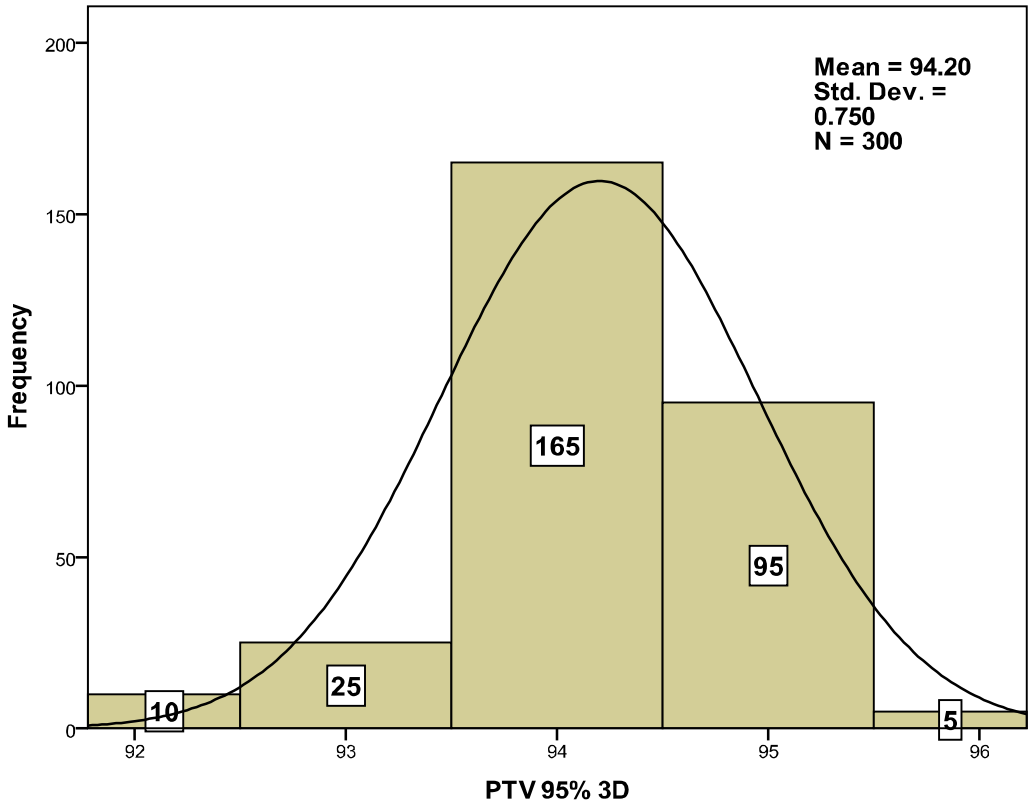


Figure 4.5 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on PTV 95% in 3D.

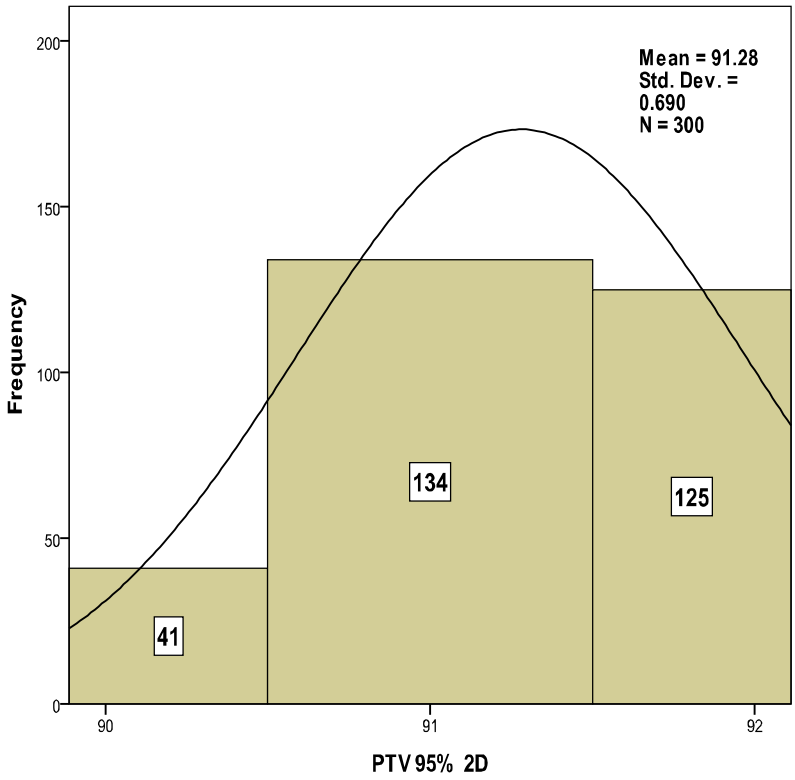


Figure 4.6 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on PTV 95% in 2D.

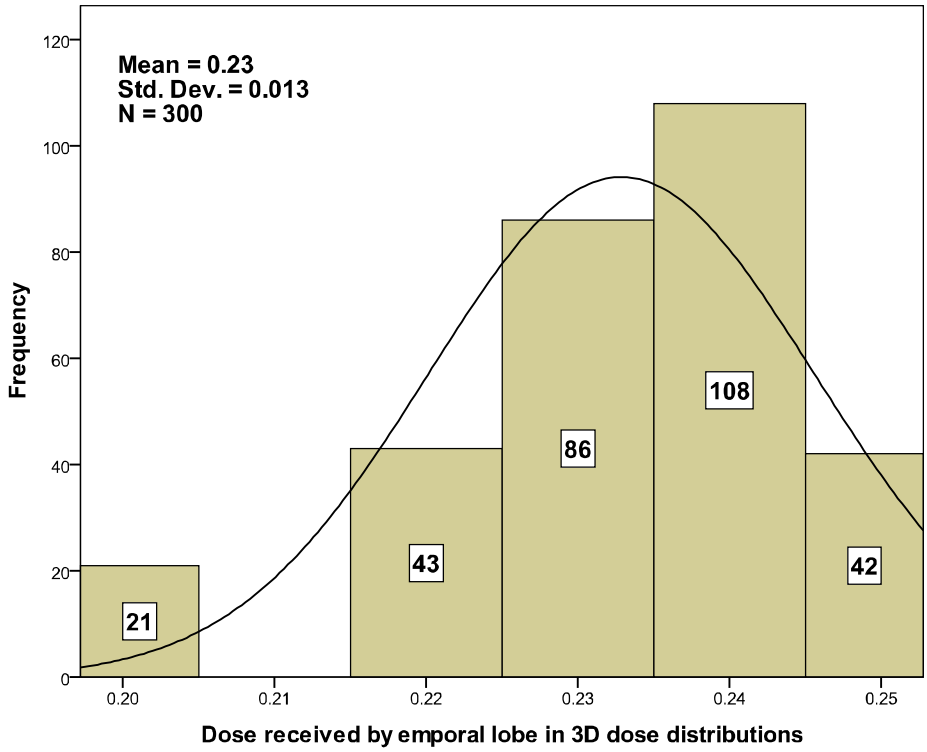


Figure 07 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on dose received by temporal lobe in 3D dose distribution.

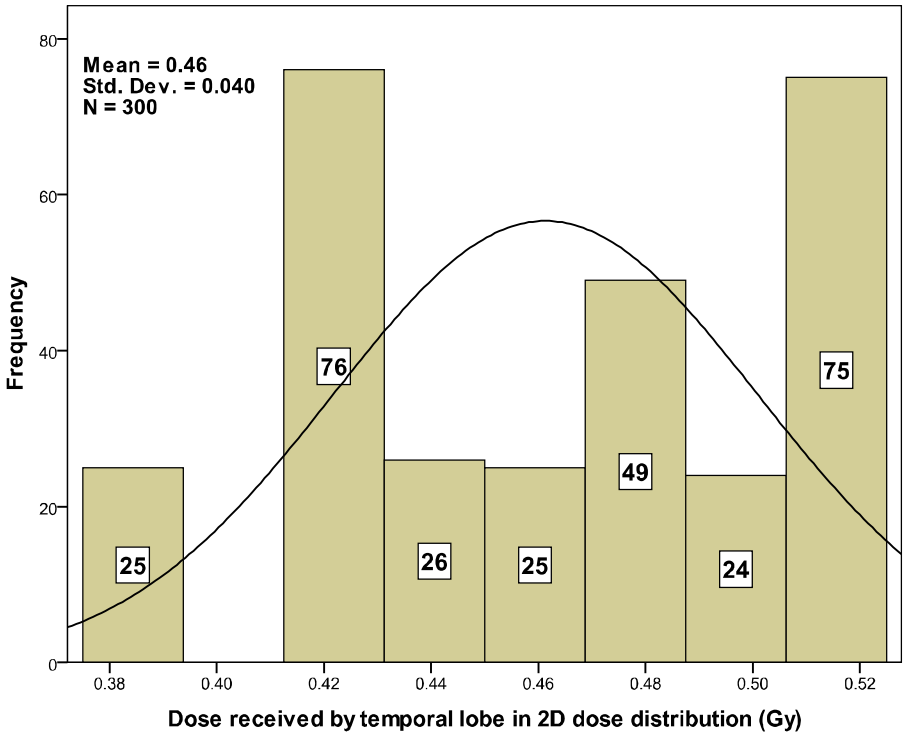


Figure .4-8 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on dose received by temporal lobe in 2D dose distribution.

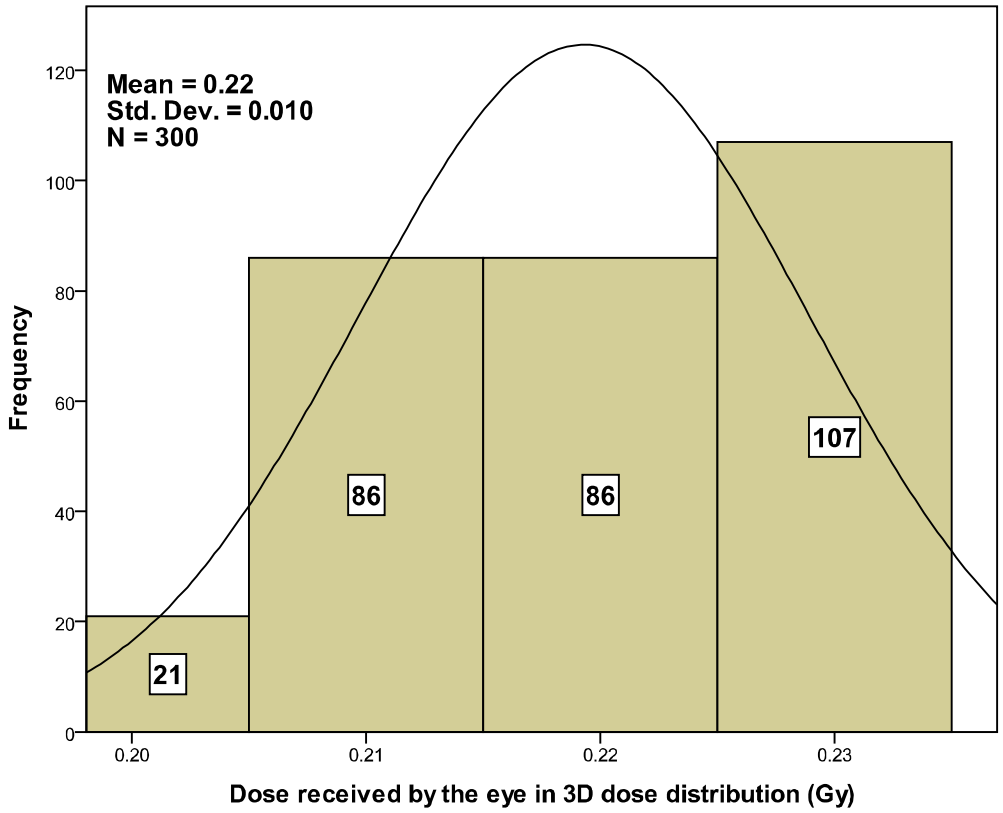


Figure4.9 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on dose received by eye in 3D dose distribution.

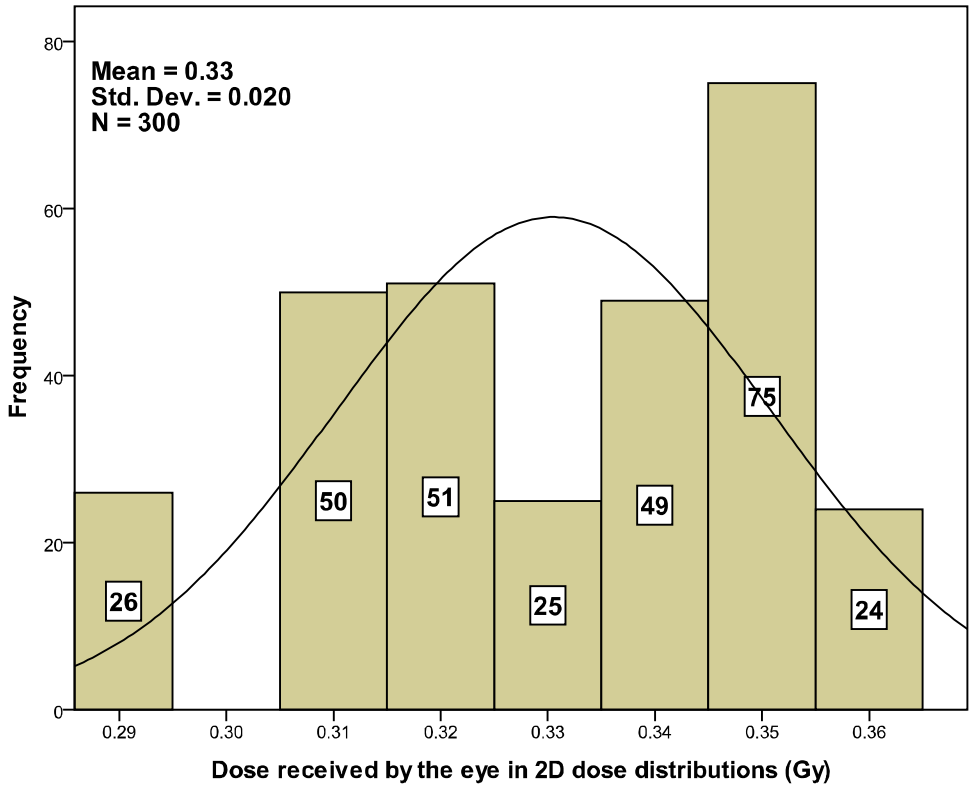


Figure 4.10 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on dose received by eye in 2D dose distribution.

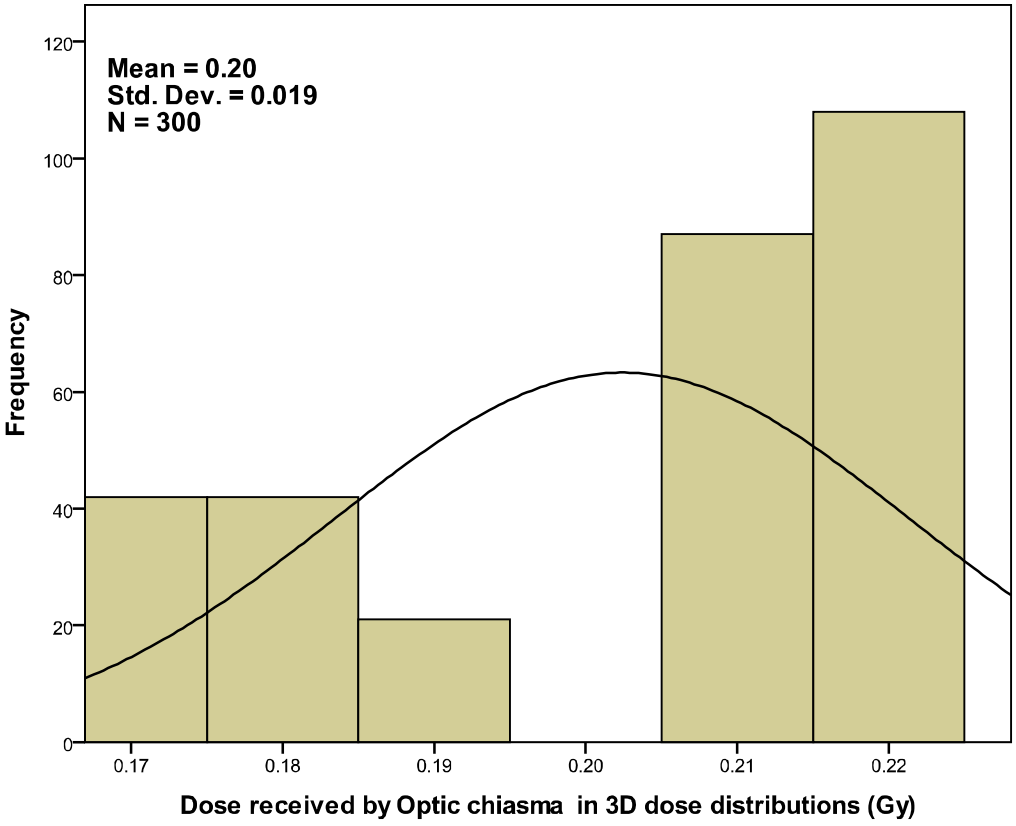


Figure 4.11 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on dose received by optic chiasma in 3D dose distribution.

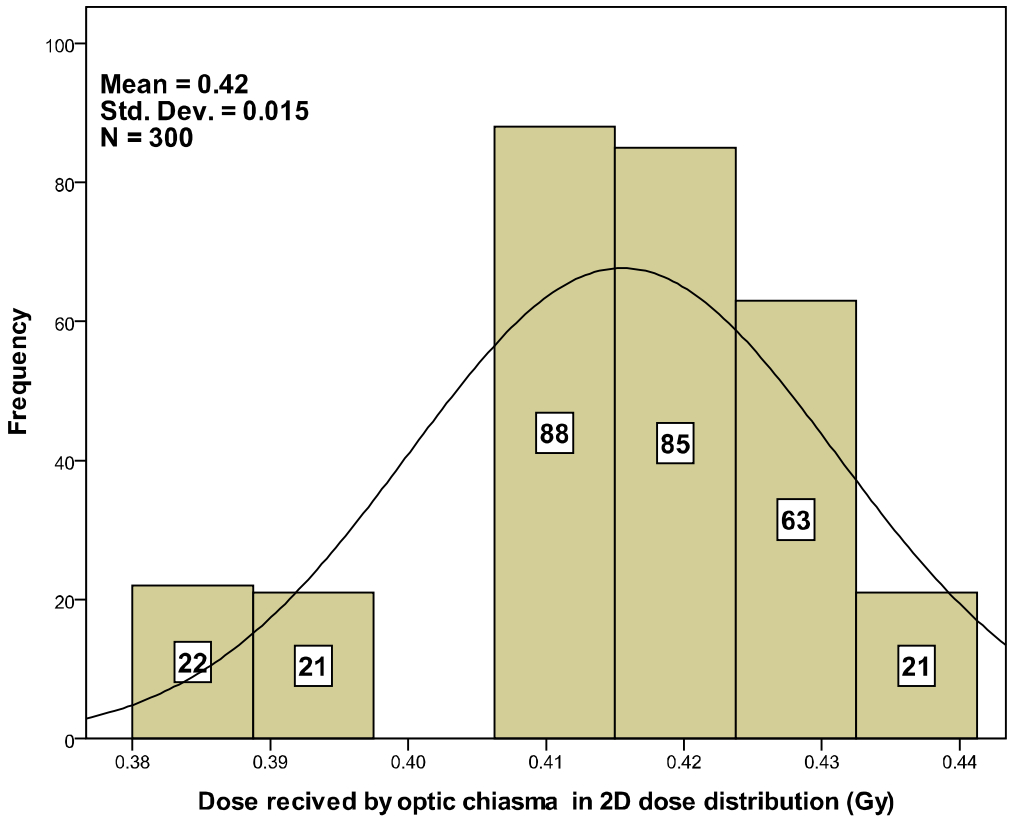


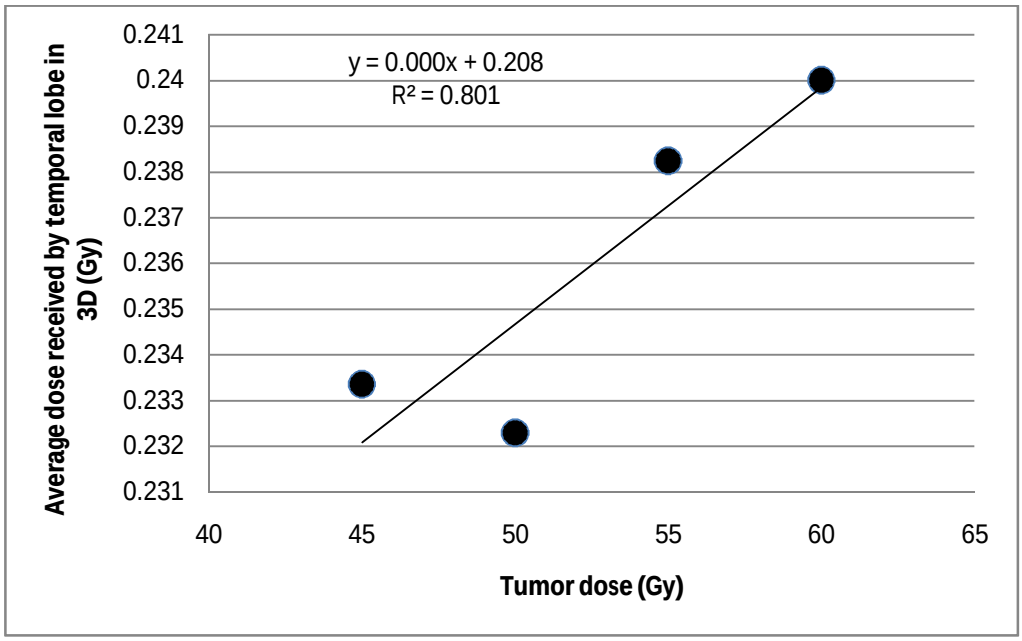
Figure 4.12 (a bar or histogram) shows the frequency distribution of the pituitary adenoma based on dose received by optic chiasma in 2D dose distribution.

In these histograms plot show the distributions of patient's age, tumor size, pituitary size, tumor dose, PTV95%, in the figure 4.3, we observe that (3.3% , 76% , 12.3%) of patients' tumor size represent (1.12 cm; 1.28 cm , and 1.44 cm respectively) , and 7.3% patients' tumor size was about 1.6 cm while 1% patients' tumor size is 0.6 cm . However, the tumor size (1.28 cm) represents about 76% of study sample. While , figure 4.4 shows tumor doses were (44 %- 45 Gy, and 45.6%- 50 Gy respectively), but 6.3% of patients were treated with 55 Gy, and 3.3% patients tumor dose is 60Gy . On the other

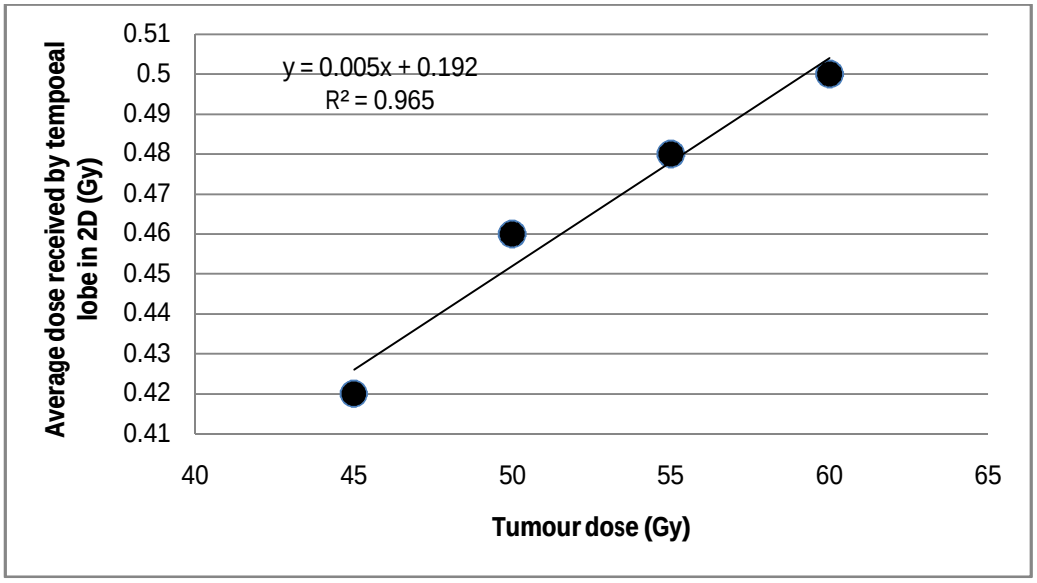
hand , figure 4.5 presents PTV95% of patients receiving isodose line that fluctuating among (93 %, 94%, and 95% respectively) in using 3D technique, while 1.6 % of patients received the isodose line at the level of 96%; and 3.3% of patients received at the level of 92% . In contrast, figure 4.6 describes the PTV95% when 2D technique is used we observe isodose line distribution in tumor bed are (90%, 91%, and 92% respectively) against patients percentages (13.6%, 44.6%, and 41.6% respectively).

In this case , figure 4.7 shows the usage of 3D technique (79 %) patients of temporal lobe will receive the average of escalating doses to surrounding healthy tissues is about (0.47Gy). But, when 2D technique is used, as shown in figure 4.8, (41.3%) of patients will receive unnecessary dose(1.62 Gy) during the treatment session. The critical organs in figure4.9, 3Dtechnique dose distribution technique (57.3 %) of patients have average doses receiving the eye is (0.22 Gy). Comparing 2D technique dose distribution as in figure 4.10, (58.3%) of patients will receive (1.62 Gy) from prescribed dose as unnecessary dose during treatment. Meanwhile, in figure 4.11, when 3D dose distribution technique is used (37.3 %) patients of optic chiasma receives average doses of (0.2 Gy), while in figure 4.12, the 2D dose distribution technique, I noticed the unnecessary dose reaching the optic chiasma is (0.825 Gy) from the prescribed dose.

In generally speaking, 3D and 2D dose distribution as well as the distribution of the dose received by critical organs (temporal lobe, eye and optic chiasma) in 3D and 2D dose distributions; the results mainly confirm that 3D dose distribution enhance the results of treatment; by delivering a lower dose to the critical organs regardless the variability of the tumor dose and tumor sizes.

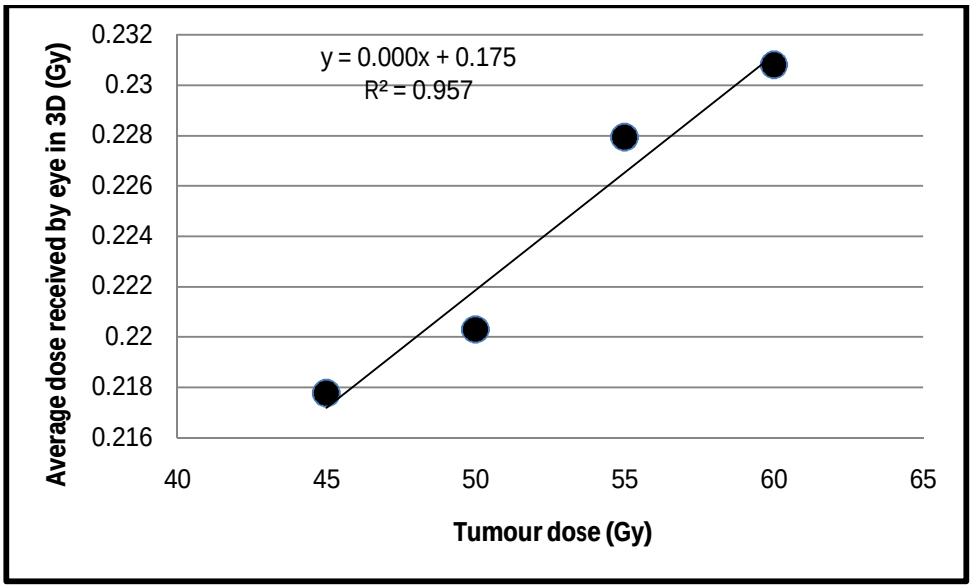


(a)

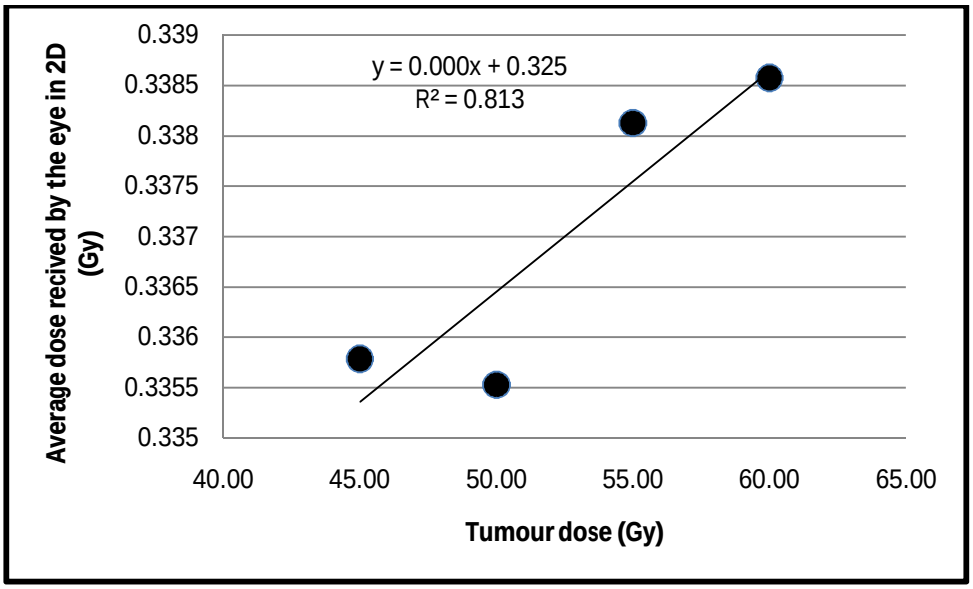


(b)

Figure 4.13 scatter plot shows a direct linear relationship between the dose received by eye versus tumor dose (a) using 3D dose distribution and (b) using 2D dose distribution.

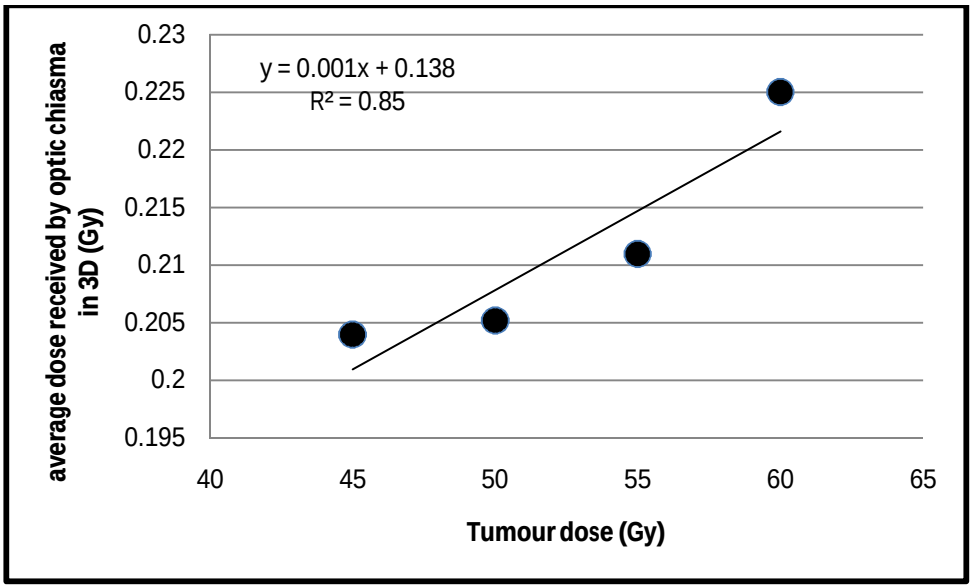


(a)

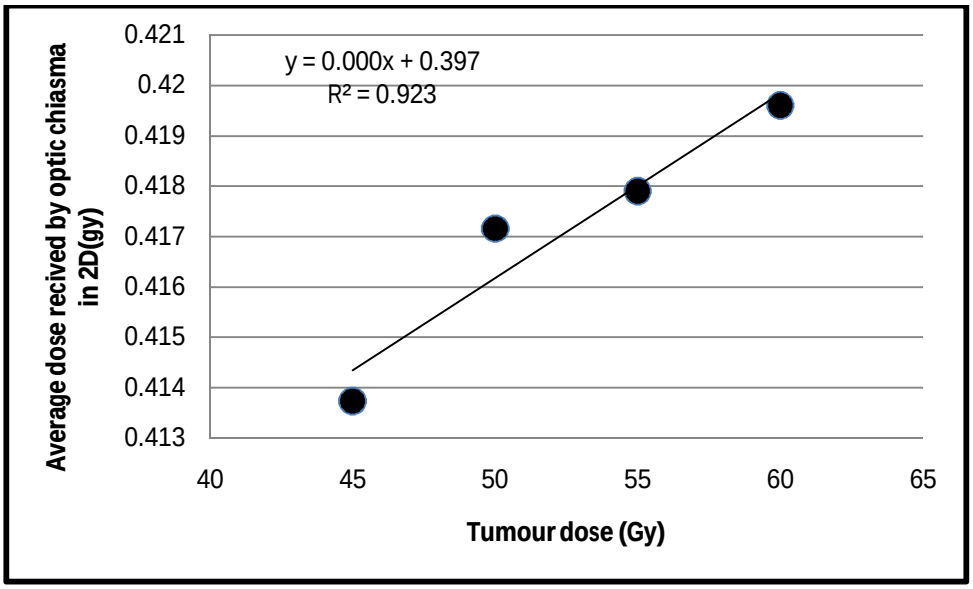


(b)

Figure 4.14 scatter plots shows a direct linear relationship between the dose received by eye versus tumor dose (a) using 3D dose distribution and (b) using 2D dose distribution.



(a)



(b)

Figure 4.15 scatter plot shows a direct linear relationship between the dose received by optic chiasma versus tumor dose (a) using 3D dose distribution and (b) using 2D dose distribution.

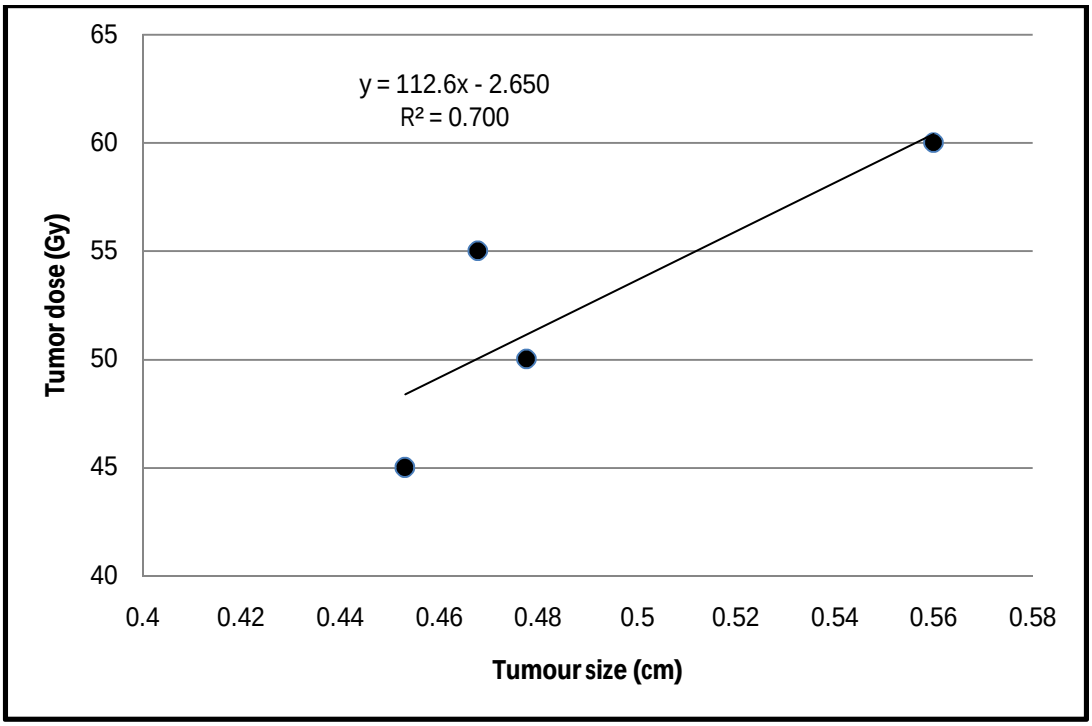


Figure 4.16 scatter plot show the relationship between the tumor size and the tumor dose where the tumor dose increase linearly with the increase of the tumor size.

In these figures portrayed scatter plot between the tumor dose and the average dose received by temporal lobe, eye and optic chaisma, I observed in the figure 4.13 the temporal lobe received dose in a linearly manner with (0.0005 Gy ,in 3D , and 0.00052 Gy in 2D) according to their total tumor dose . However, in figure 4.14, the unnecessary dose reaching the eye is linearly increased by (0.0009 Gy in 3D, and 0.0002 Gy in 2D). Moreover, in figure 4.15 the optic chiasma the linearly increment of its dose during treatment is (0.0014 Gy in 3D, and 0.00043 Gy in 2D). In generally speaking, 3D and 2D dose distribution as well as the distribution of the dose received by critical organs (temporal lobe, eye and optic chiasma) in both 3D and 2D dose distributions; the results mainly confirm that 3D dose distribution enhance the results of treatment; by delivering a lower dose to the critical organs regardless the variability of the tumor dose and tumor sizes.

Chapter Five

Discussions

The data of this study were collected from 300 patients suffering from pituitary adenomas treated by external radiation therapy using 2D dose distributions and hence 3D dose distributions were assimilated by the researchers for comparative purpose as the objective of the study implies. The mean age of the patients contributed in this study was 36.1±11.4 years ranged from 13 to 56 years as shown in Figure (4-1). The patient in this study suffers from a tumor of variables sizes that range from 0.1 to 1 cm with a mean tumor size of 0.47±0.21 cm (Figure 4.2), where the pituitary size ranged from 0.6 to 1.6 cm with average size of 1.3±0.1 cm (Figure 4.3). The pituitary tumor received a variable tumor doses range from 40 to 60 Grays (Figure 4.4), which resulted in a variable PTV95%, which ranged from 92% to 96% for 3D dose distributions (Figure 4-5) versus 90% to 92% for 2D dose distributions (Figure 4.6). These differences in tumor doses, PTV95%, pituitary sizes and tumor lead to a variable doses that received by the critical organs (temporal lobe, eyes and optic Chiasma) in 2D and 3D dose distributions.

5.1 Temporal Lobe

The dose received by temporal lobe in average was 0.47±0.03 Gy using 2D dose distributions and it was 0.24±0.01 Gy when using 3D dose distributions. The results showed that the dose received by temporal lobe was higher in 2D distribution relative to 3D; this increment was obvious in respect to tumor dose where the dose in temporal lobe is linearly increased by 0.0052 Gy per unit of a tumor dose starting 0.2 Gy in 2D as shown in figure 4.13 (b) versus the 3D dose distribution where the dose received by temporal lobe increase by 0.0005 Gy per each Gray of tumor dose starting at 0.2 Gy as presented in Figure 4.13 (a). Therefore this result prove that 3D dose distribution will reduce the amount of radiation received by temporal lobe substantially even if the total tumor dose increases from 45 Gy to 60 Gy; where in case of 60 Gy the dose for temporal lobe increased to 0.31 Gy for 2D versus 0.03 Gy for 3D. In particular, the findings relating to this study were illuminated in previous research by Chau et al. (2001) qualified that, 3D customization of the treatment portals reduced the maximum dose to the temporal lobes by 12 %. Temporal lobe necrosis is the most late-stage complication after radiation therapy. However, Chen et al. (2011) go beyond that; mentioning hearing loss and facial weakness is a function of cranial nerve damage due to radiation dose escalation to the surrounding tissues. Nevertheless Linskey, (2003b) agreed that temporal lobe contain rich networks of other sensitive structures that are at risk after radiotherapy

and that may contribute to toxicity afterward. Therefore, this result dictates the following: since the tumor dose ranges from 45 to 60 Gy, 3D technique is the suitable treatment for pituitary adenoma which will provide safe and healthy environment without escalating –unnecessary- dose to adjacent tissues. In addition, these findings can be used clinically in order to avoid dose escalation to the healthy and normal tissue surrounding the bed of tumor, and confined the dose of the treatment line and total given dose to the bed of pituitary adenoma.

5.2 Eye

Concerning the dose received by eye in average was 0.34±0.002 Gy using 2Ddose distributions and it was 0.22±0.006Gywhen using 3D dose distributions. The results show that the dose received by eye was higher in 2D distribution relative to 3D; this increment was obvious in respect to tumor dose where the dose in eye is linearly increased by 0.0002 Gy per unit of the tumor dose starting from 0.2 Gy in 2D as shown in Figure 4.14(b) versus the 3D dose distribution when the dose is received by eye it increases by0.0009 Gy per unit of tumor dose starting from 0.2 Gy in 3D as shown in Figure 4.14 (a). Therefore, this result also proves that 3D dose distribution will reduce the amount of radiation to the eye substantially even when the total tumor dose increases from 45 Gy to 60 Gy , where in case of 60 Gy the unnecessary dose reaching the eye will be 0.34 Gy for

2D versus 0.23 Gy for 3D. In the scholarly studies; Minniti et al. (2011) stated that risk of late normal central nervous system toxicity to doses less than 50 Gy at 2 Gy per fraction is low, with a reported incidence of optic neuropathy resulting in visual deficits of 1-5%, and a risk of necrosis of normal brain structures of 0-2%. However, Jonathan,(2013b) qualified that visual loss is associated with a mass lesion; the cause may interfere with the function of the optic apparatus. Such interference may be the result of abnormalities in the vasculature to the apparatus as a result of the tumor. Generally the dose reaching the eye should be less than 2 Gy. Thus, 3D techniques accomplish the aim of avoiding irradiating the eye by unnecessary radiation. These findings can be used in treatment of pituitary adenoma as a new method of treatment because it avoids the surrounding tissues from unnecessary radiation.

5.3 Optic Chiasma

The statement of study findings shows that, the dose received by optic chiasma in average was 0.42±0.002Gywhen using 2Ddose distributions and it was 0.21±0.01Gywhen using 3D dose distributions. The results shows that the dose received by optic chiasma was higher in 2D distribution in comparison with 3D; this increment was obvious in respect to tumor dose when the dose in optic chiasm is linearly increased by 0.0014 Gy per unit of the tumor dose starting from 0.2 Gy in 3D as shown in Figure 4.5 (a) versus the 2D dose distribution when the dose is received by eye increases by 0.0004 Gy per unit of tumor dose starting from 0.4 Gy in 2D as shown in 4.15 (b). Therefore, this result proves that 3D dose distribution will reduce the amount of radiation to the optic chiasma substantially even if the total tumor dose increases from 45 Gy to 60 Gy, where in case of 60 Gy the dose for optic chiasma was 0.4196Gy for 2D versus 0.23Gy for 3D.Recent research on this processed by Charles et al., (2010)have clearly demonstrated that; radiation toxicity in the optic chiasm attributed to dose received by the optic chiasma where the risk of toxicity is markedly increased at doses less than 60 Gy at 1.8 Gy/fraction as well as at less than 12 Gy for single-fraction. The evidence is strong that radiation tolerance is increased with a reduction in the dose per fraction. While, the maximum radiation dose to the optic nerve was 10 Gy range from 0.4 to 16.0 Gy (Stafford et al. 2003b), the 2D dose distribution was associated with an increased risk of

locoregional recurrence (Zhang, 2000).Therefore, (ICRU report No 62) the 2D planning dose distribution calculation is faster and easier and can be performed by hand moreover is much less accurate. Interestingly, 3D planning provides more accurate visualization of dose distribution as compared with 2D planning, with the option of giving a more homogeneous dose within the target and lower dose to the organs at risk of radiation toxicity. This result in a greater dose differential between the target and normal brain tissue and the total dose of 45-55 Gy is achieved by daily doses of 1.8-2.0 Gy (Minniti et al., 2011b).Furthermore, radiation toxicity of the optic nerves and chiasm to dose and dose-volume measures were markedly increased at doses higher than 60 Gy. The strong evidence shows that radiation tolerance increases with a reduction in dose per fraction (Mayo et al., 2009).

In summary, using 3D will reduce the dose to the critical organs and peripheral tissues substantially as well as the result of this study shows that, differences between the dose distribution using 3D and 2D was significant at $p = 0.05$ in favor for 3D using paired *t*-test concerning the PTV95%, temporal lobe, eye and optic chiasma with $t= 49.7$, 95.3, 87.9 and 121.6 respectively with $p<0.0001$.

Conclusions

The main objectives of this study is to evaluate the target volume and estimate the dose received by critical organs in an external irradiation of pituitary adenoma using 2D and 3D radiation dose distribution , in order to quantify the difference between the two techniques as well as to evaluate their impact on the temporal lobe , optic chiasm , and eye .

The three-dimensional technique is the standard of practice in clinics around the world. Because three-dimensional dose distribution provides target coverage with a full given dose and lower doses to surrounding normal tissues such as: temporal lobe, eye, and optic chiasm. The 3D dose distribution inside the pituitary adenoma reduces the linearly increment of unnecessary dose receiving by optic chiasm, eye, and temporal lobe with each unit of tumor dose starting from 0.2 Gy; the suitable tumor dose for pituitary adenoma is 50 Gy as a protocol due to its reasonability of its dose increment in the surrounding organs at risk with each unit of tumor dose.

The studies sample consists of 300 of pituitary adenoma with the evaluation of tumor size ranging from 0.10 up to 1.01 cm (51%, SD± 0.09 for microadenomas, and 49%, SD± 0.15 for macroadenomas). The three-dimension technique (3D) conforms the treatment dose to the target volume while limiting unnecessary dose to organ-at-risk. Therefore, the 3D technique is safe and effective treatment to an organ-at-risk and gives a satisfactory long-term tumor control, and good functional outcome

This study concluded that the assessment of the local-control and compare it between 2D and 3D dose distribution in target localization to the PTV definition in the treatment

planning for CRT of pituitary adenoma case. The results shows that, 3D dose distribution enhances the results of treatment; by lowering dose to the critical organs regardless the fluctuation between tumor dose and tumor sizes.

References

[1]. Amar AP, Weiss, MH 2003, 'Pituitary anatomy and physiology', *Neurosurg Clin N Am*, vol.14, no.1, pp.11-23.

[2]. Anderson JR, Antoun N, Burnet N, Chatterjee K, Edwards O, Pickard JD,Sarkies, N 1999, 'Neurology of the pituitary gland', *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 66, no. 6, pp.703-19.

[3]. Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, Neelis KJ, Biermasz NR, Romijn JA, Smit JW, and Pereira AM,(2011), 'Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis'. *J Clin Endocrinol Metab, pp*. 36-45

[4]. Becker G, Kocher M, Kortmann RD, Paulsen F, Jeremic B, Müller RP, Bamberg,M 2002, 'Radiation therapy in the multimodal treatmentapproach of pituitary adenoma'. *Strahlenther Onkol*, vol. 178, no.4, pp.173-86.

[5]. Bokstein F, Kovner F, Blumenthal DT, Ram Z, Templehoff H, Kanner AA, Corn BW, (2008), "A common sense approach to radiotherapy planning of glioblastoma multiforme situated in the temporal lobe". Int J Radiat Oncol Biol Phys, Vol 72, no.(3), pp. 900-4.

[6]. Bokstein,F, F. Kovner, Z. Ram, H. Templehoff, A. A. Kanner, D. T. Blumenthal and B. Corn , (2007), "A common sense approach to radiation treatment planning of temporal lobe GBM", Journal of Clinical Oncology, Vol 25, No 18S , PP. 2044

[7]. Bonneville JF, Bonneville F, Cattin, F 2005, 'MRI of the pituitary gland: indications and results in gynecology and in obstetrics', *Gynecol Obstet Fertil*, vol. 33 no. 3, pp.147-53.

[8]. Boyer AL, Geis P, Grant W, Carol, M 1997, 'Modulated beam conformaltherapy for head and neck tumors'. *Int J Radiat Oncol Biol Phys*, vol. 39, no.1, pp. 227-36.

[9]. Brizel DM, Light K, Zhou SM, Marks LB, (1999),"Conformal radiation therapy treatment planning reduces the dose to the optic structures for patients with tumors of the paranasal sinuses", Radiother Oncol, Vol 51, no (3) , pp. 215-8.

[10]. Brent C. Parker, Almon S. Shiu, Moshe H. Maor, Frederick F. Lang, H. Helen Liu,i R. Allen White, and. Antolak.,John, A 2002,'PTV margin determination in conformal SRT of intracranial lesions', Journal of Applied Clinical Medical Physics, Vol. 3, No. 3, pp.34-36

[11]. Buatti JM, Marcus, RBJr, 1997, 'Pituitary adenomas: current methods of diagnosis and treatment', *Oncology (Williston Park)*, vol.11, no. 6, pp.791-6.

[12]. Chand-Fouché ME, Colin P, Bondiau PY, (2012), "Pituitary adenomas: Multimodal management and modern irradiation techniques", Cancer Radiother. vol.16, no.90, pp.100.

[13]. Chau RM, Teo PM, Choi PH, Cheung KY, Lee WY, (2001), "Three-Dimensionaldosimetric evaluation of a conventional radiotherapy technique for treatment of nasopharyngeal carcinoma", Radiother Oncol, vol.58, no. 2, pp.143-53.

[14]. Charles Mayo, Mary K. Martel, , Lawrence B. Marks., JohnFlickinger,, Jiho Nam, , John Kirkpatrick, (2010), Radiation Dose–Volume Effects of Optic Nerves and Chiasm Next , International Journal of Radiation Oncology , Biology Physics, Vol 76, no. 3, pp.28-35.

[17]. Chen J, Dassarath M, Yin Z, Liu H, Yang K, Wu G, (2011), "Radiation induced temporal lobe necrosis in patients with nasopharyngeal carcinoma: a review of new avenues in its management".Radiat Oncol, Vol6, no 128, pp. 6-128.

[18]. Childs, GV *2009*, "Pituitary gland cell types, mediators, development"*Encyclopedia of Neuroscience*, pp.719-726.

[19]. Colao, A., Vitale, G., Cappabianca, P., Briganti, F., Ciccarelli, A., De, R.M., et al. (2004) Outcome of cabergoline treatment in men with prolactinoma: Effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. *J. Clin. Endocrinol. Metab.*,89: 1704–11.

[20]. Colao, A., Loche, S., Cappa, M., Di, S.A., Landi, M.L., Sarnacchiaro, F., et al. (1998) Prolactinomas in children and adolescents. Clinical presentation and long-term follow-up. *J. Clin. Endocrinol. Metab, Vol.*83, pp. 2777–80.

[21]. Colao A, Ochoa AS, Auriemma RS, Faggiano A, Pivonello R, Lombardi, G (2010), 'Pituitary carcinomas'.*FrontHorm Res,* vol.38, pp.94-108.

[22]. Cox JD, Schechter NR, Lee AK, Forster K, Stevens CW, Ang KK, Komaki R, Liao Z, Milas L,(2003). "Uncertainties in physical and biological targetingwith radiation therapy". Vol.28, no (3), pp.211-5.

[23]. Das IJ, Cheng CW, Fein DA, Coia LR, Curran WJ Jr, Fowble, B 1997, 'Dose estimation to critical organs from vertex field treatment of brain tumors'.*Int J Radiat Oncol Biol Phys,* vol.15; 37, no. 5, pp.1023-9.

[24]. De Menis E, Visentin A, Billeci D, Tramontin P, Agostini S, Marton E, Conte N, (2001), 'Pituitary adenomas in childhood and adolescence. Clinical analysis of 10 cases'.J Endocrinol Invest, Vol.24, no.2 , pp.92-7.

[25]. Dietmar Zierhut, Michael Flentje, Jürgen Adolph, Johannes Erdmann, Friedhelm Raue, Michael Wannenmacher, D.D.S 1995,'External radiotherapy of pituitary adenomas 'International Journal of Radiation OncologyBiologyPhysics,Vol.33, no. 2,pp. 307–314.

[26]. Dorton, AM, 2000, "The pituitary gland: embryology, physiology, andPathophysiology", *Neonatal Netw*, vol.19, no.2, pp. 9-17.

[27]. Emami B, Graham MV, (1997),"Lung, In : Principles and Practice of Radiation Oncology", Parez CA & Brady LW, eds, 3rd edition, Philadelphia, pp. 1181-1220.

[28]. 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. Int. J. Radiat. Oncol. Biol. Phys. 21: 109 –122.

[29]. Feuvret L, Noël G, Nauraye C, Garcia P, J-Mazeron, J 2004, 'Conformal indexandRadiotherapy', *Cancer Radiother*, vol.8, no.2 pp.108-19.

[30]. Feuvret L, Noël G, Mazeron J, Bey P. (2006). "Conformity index: a review",Int J RadiatOncol Biol Phys, vol. 64, no.2, pp.333-42.

[31]. Gambacorta MA, Pasini D, Minsky BD, Arcangeli S, Mannocci A, BarbaMC, Barbaro B, Manfrida S, Balducci M, Valentini V,(2013), "is two-dimensional field definition sufficient for pelvic node coverage in rectal cancer compared to technical three-dimensional definition". Tumori, Vol (2), pp.191-8.

[32]. Harles. C. Mayo, Mary K. Martel, John Flickinger. Jiho Nam. Lawrence B. Marks, And John Kirkpatrick, (2010), "Radiation Dose–Volume Effects of Optic Nerves and Chiasm", Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, pp. S28–S35,

[33]. Hasegawa T, Kobayashi T, Kida Y. Tolerance of the optic apparatus in single-fraction irradiation using stereotactic radiosurgery: evaluation in 100 patients with craniopharyngioma, (2010),Neurosurgery, Vol 66, no (4) pp.688-94.

[34]. Hasegawa Y; Iuchi T; Osato K; Kodama T; Toyama N; Hatano, K,(2011), 'Comparison of intensity modulated radiotherapy and dynamic three-dimensional conformal radiotherapy with regard to dose distribution and sparing of organs at risk', *Neurologia Medico-Chirurgica* , vol.51 , no.5, pp. 349-55

[35]. Hess CF, Christ G, Jany R, Bamberg M, (1993),"Dosage specification at the ICRU reference point: the consequences for clinical practice", Strahlenther Onkol, Vol 169, no (11), pp.660-7.

[36]. Hidetsugu Nakayama, Hiroaki Satoh, Koichi Kurishima Hiroichi Ishikawa, Koichi Tokuuye. (2010),"High-Dose Conformal Radiotherapy for Patients with Stage III Non–Small-Cell Lung Carcinoma", International Journal of Radiation Oncology Biology Physics,Vol78, no.3, pp. 645-650.

[38]. Hitchen CJ, Osa EO, Dewyngaert JK, Chang J, Narayana A 2012, Dose to craniofacial region through portal imaging of pediatric brain tumors, J Appl Clin Med Phys, Vol 13. no1,pp: 3385.

[39]. ICRU 50 Prescribing, Recording and Reporting Photon Beam Therapy Bethesda, MD, International Committee on Radiation Units and Measurements, 1993.

[40]. ICRU 62 Prescribing, Recording and Reporting Photon Beam Therapy, Bethesda, MD, International Committee on Radiation Units and Measurements, 2001.

[41]. 'ICRU Reports 50 and 62', Recommendations, viewed 9 November 2012http://ozradonc.wikidot.com/current-icru-

[42]. ICRU REPORT 50 and 62: Prescribing, Recording, and Reporting Photon Beam Therapy, viewed 27 October 2012,http://www.icru.org/content/ uncategorised/current-program-of-the-icru#therapy.

[43]. International Commission of Radiation Units and Measurements, ICRU 1993, *Prescribing, Recording and Reporting Photon Beam Therapy*, report no 50. Bethesda.

[44]. Jacques DE Villiers, C 2003, 'Pituitary metastases', *African Journal of Neurological Sciences*, vol. 22, no. 1.

[45]. Jason G 2008, 'Volumetric 3d display for radiation therapy planning', *Journal of Display Technology*, vol.4, no.4.

[46]. Jillian Maclean, Christopher Stacey, Naomi Fersht, Ivan Rosenberg, DerekD'Souza, Julia Solano, Nazima Haji and Susan Short, (2011),"Arc Delivered Intensity-Modulated Radiotherapy Achieves Highly Conformal Radiotherapy for Brain Tumor Patients with Minimal Hair Loss", EJCMO,Vol (4).

[47]. John Ayuk, Stewart Paul, M, 2009, 'Mortality following pituitary radiotherapy', *Norwell,* vol.12, no.1, pp.35-5.

[48]. Jonathan A. Borden, (2013), "Treatment of Tumors involving the Optic Nerves and Chiasm", Accessed 7/3/2013onhttp://www.jonathanborden-md.com/OpticTumors.html.

[49]. Joshi R. C., PK Julka, R. Prabhakar, T. K. Rath, Monica Malik, Ganesh, G (2007),'Quantification of shift in isocenter for 2-dimensional and 3-dimensional radiotherapy plans for various treatment sites'. *Internet Journal of Oncology*, Vol4, no1, pp: 33

[50]. Kaluska, V.T. Lazurik, V.M. Lazurik, G.F. Popov, Yu.V. Rogov, Zimek, Z 2004, 'Basic laws of boundaries effects for the absorbed dose distribution of electrons in the heterogeneous materials', *Journal of Kharkiv University* , no. 619, pp. 87-50.

[51]. Kantor G, Loiseau H, Vital A, Mazeron JJ ,(2001),"Gross tumor volume(GTV) and clinical target volume (CTV) in adult gliomas".Cancer Radiother, Vol 5, no (5), pp.571-80.

[52]. Kara Bucci, Alison Bevan, Mack Roach, M (2005), 'Advances inradiation therapy: conventional to 3d, to IMRT, to 4d, and beyond' *Cancer J Clin*; Vol 55, no.117, pp 134.

[53]. Kobayashi T, Mori Y, Tsugawa T, Hashizume C, Takahashi, H(2012), 'Prognostic factors for tumor recurrence after gamma knife radiosurgery of partially resected and recurrent craniopharyngiomas', *Nagoya J Med Sci* , vol.74 , no. 1-2 , pp.141-7.

[54]. Kukołowicz PF, Mijnheer BJ, (1997), "Comparison between dose valuesspecified at the ICRU reference point and the mean dose to the planning target volume", Radiother Oncol. Mar; 42(3):271-7.

[55]. Laurence Masson-Côté, Christian Couture, André Fortin, Anne Dagnault,(2011), "Postoperative Radiotherapy for Lung Cancer: Improvement in Locoregional Control Using Three-Dimensional Compared With Two-Dimensional Technique" , International Journal of Radiation Oncology Biology Physics, Vol. 80, no.3, pp. 686-691

[56]. Lee AG, Sforza PD, Fard AK, Repka MX, Baskin DS, Dauser RC, (1998),Pituitary adenoma in children. J Neuroophthalmol, Vol.8 (2), pp.102-5.

[57]. Linskey ME, Johnstone PA, (2003), "Radiation tolerance of normal temporal bone structures: implications for gamma knife stereotactic radiosurgery", Int J Radiat Oncol Biol Phys, Vol 57, no (1), pp.196-200.

[58]. Loeffler JS, Shih, HA (2011), 'Radiation therapy in the management of pituitary adenomas' *ClinEndocrinolMetab*, vol. 96, no. 7, pp.1992-2003.

[59]. Lucie Abouaf, Nicolas Girard, Thibaud Lefort, Anne D'hombres,(2012).Standard-Fractionated Radiotherapy for Optic Nerve Sheath Meningioma: Visual Outcome Is Predicted by Mean Eye Dose, International Journal of Radiation Oncology Biology Physics, Vol. 82, no.3, pp. 1268-1277.

[60]. Martel MK, Sandler HM, Cornblath WT, Marsh LH, Hazuka MB, Roa WH,Fraass BA, LichterAS, (1997),"Dose-volume complication analysis for visual pathway structures of patients with advanced paranasal sinus tumors", Int J Radiat Oncol Biol Phys, Vol 38, no (2), pp.273-84.

[61]. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J, (2009),"Radiation dose-volume effects of optic nerves and chiasm", Int.J Radiat. Oncol. Biol. Phys, Vol 1, no76, pp. S28-35.

[62]. Mayr NA, Yuh WT, Muhonen, MG (1993), 'Pituitary metastases': *MR findings. J Comput Assist Tomogr*, vol.17 no. 3, pp. 432-7.

[63]. McDowell BD, Wallace RB, Carnahan RM, Chrischilles EA, Lynch CF, Schlechte JA (2011) , 'Demographic differences in incidence for pituitary adenoma', *Pituitary*, vol.14, no. 1, pp.23-30.

[64]. .McNicol, Anne, M (*2007)* , 'Pathology of tumors of the pituitary**,** parathyroid and adrenal glands' . *Surgery (Oxford)*, vol.25, no. 11, pp.453-457.

[65]. Metellus P; Kapoor S; Kharkar S; Batra S; Jackson JF; Kleinberg L; Miller NR; Rigamonti, D (2011), 'Fractionated conformal radiotherapy for management of optic nerve sheath meningiomas: long-term outcomes of tumor control and visual function at a single institution', *International Journal Of Radiation Oncology, Biology, Physics*, vol.80, no.1, pp. 185-92.

[66]. McGowan SE, Burnet NG, Lomax AJ,(2013),"Treatment planningoptimization in proton therapy", Br J Radiol, Vol86, no(1021) , pp.288.

[67]. Mellstedt H, (2006),"Cancer initiatives in developing countries", AnnOncol, no.8, pp.24-31.

[68]. Mezosi E, Nemes, O (2009), 'Treatment of pituitary adenomas',Orv Hetil.Vol.150, no.39, pp.1803-10.

[69]. Michalski JM, Purdy, JA (1998) , 'Innovations in three-dimensional treatment planning and quality assurance', *Tumori*, vol.84, no.2 , pp. 127-39.

[70]. Millunchick CH, (2013), "Treating benign optic nerve tumors with 3-D conformal plan". Med Dosim. Vol1, no (12) pp184-7.

[71]. Mindermann T, Wilson C, B (1994) , 'Hormonal Relation to Pituitary Adenoma Incidence, Age-related and gender-related occurrence of pituitary adenomas'.Clin Endocrinol (Oxf), Vol.41, no.3, pp.359-64.

[72]. Munir Ahmed Elias , Benign Pituitary Cysts, accessed on 23 July 2011http://www.pituitaryadenomas.com/benignpituitarycyst.htm.

[73]. Minniti et al. Radiation Oncology 2011, 6:167 http://www.ro-journal.com/content/6/1/167

[74]. Moghaddasi L, Bezak E, Marcu, LG (2012), "Current challenges in clinical target volume definition: tumor margins and microscopic extensions". *Acta Oncol,* vol.51, no.8, pp.984-95.

[75]. Mika Kapanen, (2011), "How can a cost/benefit ratio be optimized for anoutput measurement program of external photon radiotherapy beams?"Phys. Med. Biol.*No.**56,*** pp**.** 2119.

[76]. Murthy,KK, KA Shukeili, SS Kumar, CA Davis, RR Chandran, and S,(2010), "Namrata. Evaluation of dose coverage to target volume and normal tissue sparing in the adjuvant radiotherapy of gastric cancers: 3D-CRT compared with dynamic IMRT". Biomed Imaging Interv J, Vol.6, no.3, pp.29.

[77]. Noda SE, Lautenschlaeger T, Siedow MR, Patel DR, El-Jawahri A, SuzukiY, Loeffler JS, Bussiere MR, Chakravarti A, (2009),"Technological advances in radiation oncology for central nervous system tumors", Semin Radiat Oncol, vol.19, no.3, pp.179-86.

[78]. Oh MC, Tihan T, Kunwar S, Blevins L, Aghi, MK (2012), 'Clinical management of pituitary carcinomas', *Neurosurg Clin N Am* , vol.23, no.4, pp.595-606.

[79]. Ooi GT, Tawadros N, Escalona, RM (2004) , 'Pituitary cell lines and their endocrine applications', *Mol Cell Endocrinol,*vol.228 , no.1-2, pp.1-21.

[80]. Ostrom QT, McCulloh C, Chen Y, Devine K, Wolinsky Y, Davitkov P, Robbins S,Cherukuri R, Patel A, Gupta R, Cohen M, Barrios JV, Brewer C, Schilero C, Smolenski K, McGraw M, Denk B, Naska T, Laube F, Steele R, Greene D, Kastl A, Bell S, Aziz D, Chiocca EA, McPherson C, Warnick R, Barnett GH, Sloan AE,

Barnholtz-Sloan ,JS (2012), 'Family history of cancer in benign brain tumor subtypes versus gliomas', *Front Oncol*, vol.2, no.19.

[81]. Parker W, Patrocinio, H (2005), 'Clinical treatment planning in external photon beam radiotherapy',*IAEA in Austria*, PP 219-220.

[82]. Pehlivan B, Ares C, Lomax AJ, Stadelmann O, Goitein G, Timmermann B,Schneider RA, Hug EB (2012), "Temporal lobe toxicity analysis after proton radiation therapy for skull base tumors", Int J Radiat Oncol BiolPhys, vol. 1, no.83, pp.1432-40.

[83]. Peyster RG, Adler LP, Viscarello RR, Hoover ED, Skarzynski J, (1986) "CT of the normal pituitary gland", Neuroradiology, Vol.28 (2), Pp.161-5.

[84]. Peyster RG, Hoover ED, Viscarello RR, Moshang T, Haskin ME, (1983),"CT appearance of the adolescent and preadolescent pituitary gland",Am J Neuroradiol, Vol 4(3), pp. 411-4.

[85]. Prabhakar R, Rath, G K (2009), 'Slice-based plan evaluation methods for Three dimensional conformal radiotherapy treatment planning', *Australasian Physical & Engineering Sciences in Medicine Adelaide*, vol. 32,no.4, pp.233-7.

[86]. Purdy JA, Harms, WB (1998), 'Quality assurance for 3D conformal radiation therapy', *Strahlenther Onkol*, vol.174, no.2, pp.2-7.

[87]. Purdy, JA (2008), 'Dose to normal tissues outside the radiation therapy patients Treated volume: a review of different radiation therapy techniques', *Health Phys*, vol.95, no.5, and pp.666-76.

[88]. Purdy, JA (1997), 'Advances in three-dimensional treatment planning and conformal dose delivery, *Semin Oncol* , vol. 24, no. 6, pp.655-71.

[89]. Related Articled. (2013), Pituitary Tumors in Children Available From:http://www.kidneeds.com/diagnostic_categories/articles/pituitarytumorsinchild.htm. Accessed on 15/6/2013

[90]. Rostad, S (2012), 'Pituitary adenoma pathogenesis: an update', CurrOpinEndocrinol *Diabetes Obes*. Pp. 4

[91]. 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.

[92]. Roppolo HM, Latchaw RE, (1983), "Normal pituitary gland: 2. Microscopic anatomy-CT correlation", AJNR Am J Neuroradiol, Vol.4, no.4, pp.937-44.

[93]. Saeger, W., Ludecke, D.K., Buchfelder, M., Fahlbusch, R., Quabbe, H.J. and Petersenn, S. (2007) Path histological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur. J. Endocrinol.,* 156: 203–16.

[94]. Seegenschmiedt MH, Zehe M, Fehlauer F, Barzen G., (2012). “Possibilitiesand Perspectives of Quality Management in Radiation Oncology”, Urologe A. pp.24-26

[95]. Shah C, Wilkinson JB, Lanni T, Jawad M, Wobb J, Fowler A, Wallace M, Chen P, Grills IS, Vicini, F (2012), ‘Five-year outcomes and toxicities using 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation’, *Clin Breast Cancer*, vol.1526-8209, no.12, pp. 224-8.

[96]. Srinivasan Vijayakumar, George Chen, (1995), *IJROBP*, vol.33, no. 5, pp.979-983.

[97]. Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ,Gorman DA, Schomberg PJ, (2003), “A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery”, Int J Radiat Oncol Biol Phys. Vol 55, no (5), pp.1177-81.

[98]. Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, Gorman DA, Tao Y, Lian D, Hui-juan Z, Hui P, Zi-meng J (2011), ‘Value of brain magnetic resonance imaging and tumor markers in the diagnosis and treatment of intracranial germinoma in children’, *Zhongguo Yi Xue Ke Xue Yuan Xue Bao,* vol.33, no.2, pp.111-5.

[99]. Steele CA, MacFarlane IA, Blair J, Cuthbertson DJ, Didi M, Mallucci C, Javadpour M, Daousi C (2010) , 'Pituitary adenomas in childhood, adolescence and young adulthood: presentation, management, endocrine and metabolic outcomes'.Eur J Endocrinol. vol.163, no.4 pp.515-22.

[100]. Sylvia L. Asa (*2008*) Practical Pituitary Pathology: What Does the Pathologist Need to Know?. Archives of Pathology & Laboratory Medicine: August 2008, Vol. 132, No. 8, pp. 1231-1240.

[101]. Tammy Newel, Robert D, Adams, Charles, M 2004, Endocrine system,*Principles and Practice of Radiation Therapy*, 2ed, Mosby, St. LouisMissouri, pp.505:507.

[102]. Thwaites D, Scalliet P, Leer JW, Overgaard J, (1995),"Quality assurance in Radiotherapy, European Society for Therapeutic Radiology andOncology Advisory Report to the Commission of the European Union for the 'Europe Against Cancer Programme'. Radiother Oncol, vol.35, no.1, pp.61-73.

[103]. Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E 3rd, KooyHM, Flickinger JC , (1993),"Tolerance of cranial nerves of the cavernous sinus to radiosurgery", Int J Radiat Oncol Biol Phys, Vol 27, no (2), pp. 215-21.

[104]. Tsunoda. A., O. Okuda, and K. Sato, (1997),"MR Height of the Pituitary Gland as a Function of Age and Sex: Especially Physiological Hypertrophy in Adolescence and in Climacterium", *AJNR Am J Neuroradiol, Vol.*18, pp.551–554.

[105]. Turaka A, Parsons RB, Buyyounouski MK, (2012),"Radiation therapy for pituitary metastasis: report of four cases", Tumori, vol.98, no.1, pp.1-6.

[106]. Ulrike Mock, Dietmar Georg, Joachim Bogner, Thomas Auberger, Richard Pötter, ,(2004), 'Treatment planning comparison of conventional, 3D conformal, and intensity-modulated photon (IMRT) and proton therapy for paranasal sinus carcinoma',International Journal of Radiation Oncology*Biology*Physics, vol.58, no. 1, pp. 147–154

[107]. Uy NW, Woo SY, Teh , BS (2002), 'Intensity-modulated radiation therapy (IMRT) for meningioma', *Int J Radiat Oncol Biol Phys*, vol. 53, pp.1265-70.

[108]. Verhey, LJ (1999), 'Comparison of three-dimensional conformal radiation therapy and intensity-modulated radiation therapy systems', *Semin Radiat Oncol* vol. 9, no.1, pp. 78-98.

[109]. Waldron J, Tin MM, Keller A, Lum C, Japp B, Sellmann S, van Prooijen M,Gitterman L, Blend R, Payne D, Liu FF, Warde P, Cummings B, Pintilie M, O'Sullivan B , (2003), "Limitation of conventional two dimensional radiation

therapy planning in nasopharyngeal carcinoma", Radiother Oncol, vol. 68, no2, pp.153-61.

[110]. William Parker, Horacio Patrocinio., (2005). Clinical Treatment Planning InExternal Photon Beam Radiotherapy 2005 Printed By the IAEA in Austria, Pp 219-264.

[111]. Wu VW, Kwong DL, Sham, JS (2004), Target dose conformity in 3-dimensional conformal radiotherapy and intensity modulated radiotherapy', *Radiother Oncol*, vol.71, no.2, pp.201-6.

[112]. Yeung CM, Chan CB, Leung PS, Cheng, CH (2006), 'Cells of the anteriorpituitary', *Int J Biochem Cell Biol*, vol.38, no.9, pp.1441-9.

[113]. Zhang F; Zheng, M (2011), 'Dosimetric evaluation of conventional radiotherapy, three dimensional conformal radiotherapy and direct machine parameter optimization intensity-modulated radiotherapy for breast cancer after conservative surgery', *Journal of Medical Imaging and Radiation Oncology*, vol. 55, no.6, pp.595-602.

Appendix

Data Collection Form

No	Gender	Age	Marital Status	Tumor Size cm	Pituitary Size cm	Given Dose	Treatment Line				Vital Organs Doses					
							3D		2D		3D			2D		
							PTV 95-≤107%	Adj.NT%	PTV 95-≤107%	Adj.NT%	Temporal Lobe	Eye	Optic Chiasma	Temporal Lobe	Eye	Optic Chiasma

Appendix

Master Data Collection Sheet

Number	age	tumor size	pit size	3D tumor size%	GD	PTV95 3D	PTV95 2D	Temporal lobe 3D	Eye 3D	Optic 3D	Temporal lobe 2D	Eye 2D	Optic 2D
1	17	0.2	1.4	51	50	92	92	0.24	0.23	0.18	0.43	0.31	0.43
2	20	0.3	1.6	50	45	94	91	0.23	0.22	0.21	0.43	0.3.2	0.41
3	23	0.7	1.2	51	50	92	91	0.24	0.23	0.22	0.51	0.35	0.41
4	24	0.9	0.6	49	45	95	90	0.25	0.22	0.19	0.51	0.2.9	0.39
5	18	0.6	1.4	51	50	92	92	0.22	0.23	0.21	0.42	0.35	0.41
6	14	0.8	1.5	51	50	92	91	0.24	0.23	0.22	0.51	0.35	0.41
7	20	0.5	1.4	50	45	94	92	0.22	0.23	0.21	0.45	0.35	0.41
8	18	0.3	1.5	52	45	93	92	0,23	0.22	0.22	0.44	0.32	0.42
9	18	0.1	1.4	51	50	92	92	0.25	0.22	0.17	0.52	0.36	0.44
10	18	0.25	1.5	52	50	92	92	0.23	0.22	0.21	0.39	0.34	0.41
11	13	0.75	1.4	51	45	93	92	0.23	0.23	0.17	0.51	0.35	0.43
12	20	0.3	1.3	50	45	94	91	0.24	0.21	0.22	0.39	0.34	0.41
13	23	0.5	1.4	50	50	92	91	0,23	0.22	0.22	0.43	0.3.2	0.42
14	25	0.4	1.4	51	45	94	92	0.24	0.21	0.22	0.43	0.3.2	0.38
15	27	0.5	1.3	50	50	93	92	0.24	0.23	0.22	0.42	0.35	0.41
16	29	0.6	1.3	51	45	96	92	0.23	0.22	0.21	0.51	0.2.9	0.41
17	32	0.6	1.3	49	50	93	92	0.20	0.21	0.22	0.49	0.34	0.42
18	34	0.4	1.3	51	45	94	91	0.25	0.22	0.19	0.49	0.34	0.39
19	36	0.3	1.3	51	50	93	90	0.22	0.23	0.21	0.47	0.31	0.41
20	39	1	1.3	50	50	93	91	0.24	0.21	0.22	0.44	0.32	0.41

21	33	0.7	1.3	52	45	95	91	0.22	0.23	0.21	0.43	0.31	0.41
22	34	0.4	1.3	51	45	95	91	0.23	0.22	0.22	0.52	0.36	0.42
23	31	0.5	1.3	52	50	93	91	0.23	0.2	0.21	0.48	0.33	0.42
24	38	0.6	1.3	51	50	93	91	0.25	0.22	0.19	0.52	0.36	0.39
25	40	1	1.3	50	45	94	90	0.23	0.23	0.17	0.42	0.35	0.43
26	42	0.3	1.3	50	45	94	90	0.24	0.21	0.22	0.43	0.3.2	0.41
27	44	0.4	1.3	51	50	93	90	0.22	0.21	0.21	0.47	0.31	0.42
28	45	0.5	1.3	50	45	94	92	0.24	0.21	0.22	0.51	0.2.9	0.38
29	47	0.2	1.3	51	50	93	91	0.24	0.23	0.18	0.48	0.33	0.43
30	46	0.3	1.3	49	45	94	92	0.23	0.22	0.21	0.49	0.34	0.41
31	34	0.1	1.3	51	50	93	91	0.24	0.23	0.22	0.45	0.35	0.41
32	23	0.2	1.3	51	45	94	92	0.25	0.22	0.19	0.44	0.32	0.39
33	28	0.3	1.3	50	50	93	90	0.22	0.21	0.21	0.47	0.31	0.42
34	34	0.3	1.3	52	50	93	91	0.24	0.23	0.18	0.48	0.33	0.43
35	36	0.8	1.3	51	45	95	91	0.22	0.23	0.21	0.51	0.35	0.41
36	55	1	1.3	52	45	95	92	0,23	0.22	0.22	0.39	0.34	0.42
37	51	1	1.25	51	50	93	90	0.24	0.21	0.22	0.52	0.36	0.38
38	50	0.4	1.25	50	50	94	91	0.24	0.23	0.18	0.48	0.33	0.43
39	48	0.5	1.3	50	45	94	91	0.23	0.23	0.17	0.47	0.31	0.43
40	47	0.6	1.3	51	45	94	91	0.24	0.21	0.22	0.51	0.2.9	0.41
41	46	0.3	1.3	50	50	94	92	0.23	0.23	0.17	0.45	0.35	0.43
42	39	0.2	1.3	51	45	95	91	0.24	0.21	0.22	0.49	0.34	0.38
43	37	0.3	1.3	49	50	94	90	0.22	0.21	0.21	0.43	0.31	0.42
44	24	0.3	1.4	51	50	94	92	0.23	0.23	0.17	0.45	0.35	0.43
45	23	0.2	1.3	51	45	95	92	0.22	0.21	0.21	0.43	0.31	0.42
46	28	0.3	1.3	50	45	95	91	0.25	0.22	0.19	0.52	0.36	0.39
47	56	0.4	1.25	52	50	94	92	0.22	0.21	0.21	0.45	0.35	0.42

48	54	0.3	1.26	51	50	94	91	0.24	0.23	0.18	0.43	0.31	0.43
49	46	0.4	1.27	52	45	94	91	0.22	0.23	0.21	0.42	0.35	0.41
50	48	0.5	1.25	51	45	94	92	0,23	0.22	0.22	0.43	0.3.2	0.42
51	49	0.3	1.25	50	50	94	92	0.24	0.23	0.22	0.51	0.35	0.41
52	43	0.1	1.25	50	45	95	92	0.25	0.22	0.17	0.51	0.2.9	0.44
53	45	0.6	1.25	51	50	94	92	0.22	0.23	0.21	0.45	0.35	0.41
54	47	0.5	1.25	50	50	94	92	0.22	0.21	0.21	0.45	0.35	0.42
55	34	0.5	1.3	51	45	94	92	0.23	0.20	0.21	0.45	0.35	0.42
56	33	0.9	1.3	49	45	95	91	0.24	0.21	0.22	0.44	0.32	0.38
57	32	0.4	1.3	51	50	94	90	0,23	0.22	0.22	0.44	0.32	0.42
58	35	0.3	1.3	51	50	94	92	0.24	0.23	0.22	0.48	0.33	0.41
59	37	0.4	1.3	50	45	94	91	0.22	0.21	0.21	0.51	0.35	0.42
60	39	0.3	1.3	52	45	94	92	0.25	0.22	0.19	0.39	0.34	0.39
61	40	0.6	1.3	51	50	94	90	0.22	0.23	0.21	0.45	0.35	0.41
62	43	0.8	1.3	52	45	94	91	0.20	0.21	0.22	0.43	0.3.2	0.42
63	17	0.6	1.4	51	50	94	91	0.23	0.2	0.21	0.43	0.31	0.42
64	20	0.1	1.4	50	45	94	91	0,23	0.22	0.22	0.51	0.2.9	0.42
65	23	0.3	1.5	50	50	94	91	0.23	0.22	0.21	0.43	0.3.2	0.41
66	24	0.3	1.4	51	45	95	91	0.25	0.22	0.17	0.49	0.34	0.44
67	18	0.4	1.4	50	50	94	91	0.22	0.21	0.21	0.51	0.35	0.42
68	14	0.6	1.5	51	50	94	91	0.20	0.21	0.22	0.44	0.32	0.42
69	20	0.7	1.4	49	45	94	90	0.23	0.20	0.21	0.43	0.31	0.42
70	18	0.6	1.4	51	45	93	90	0.24	0.21	0.22	0.52	0.36	0.38
71	18	0.4	1.5	51	50	94	90	0.24	0.23	0.18	0.51	0.35	0.43
72	18	0.5	1.5	50	50	94	92	0.24	0.21	0.22	0.52	0.36	0.41
73	13	0.4	1.6	52	45	93	92	0.22	0.21	0.21	0.42	0.35	0.42
74	20	0.3	1.3	51	45	94	92	0.25	0.22	0.19	0.43	0.3.2	0.39

75	23	0.8	1.3	52	50	94	91	0.23	0.23	0.17	0.42	0.35	0.43
76	25	0.5	1.3	51	45	94	92	0.20	0.21	0.22	0.51	0.2.9	0.42
77	27	0.4	1.3	50	50	94	91	0.25	0.22	0.19	0.39	0.34	0.39
78	29	0.2	1.3	50	45	96	91	0,23	0.22	0.22	0.49	0.34	0.42
79	32	0.6	1.3	51	50	94	91	0.22	0.21	0.21	0.47	0.31	0.42
80	34	0.8	1.3	50	45	94	92	0.25	0.22	0.17	0.44	0.32	0.44
81	36	0.9	1.3	51	50	94	91	0.24	0.23	0.18	0.42	0.35	0.43
82	39	0.2	1.3	49	50	94	91	0.23	0.23	0.17	0.47	0.31	0.43
83	33	0.3	1.3	51	45	95	91	0.23	0.20	0.21	0.51	0.35	0.42
84	34	0.5	1.3	51	45	95	91	0.24	0.21	0.22	0.39	0.34	0.38
85	31	0.3	1.3	50	50	94	92	0.22	0.21	0.21	0.48	0.33	0.42
86	38	0.4	1.3	52	50	94	91	0.24	0.21	0.22	0.52	0.2.9	0.38
87	40	0.7	1.3	51	45	94	91	0.22	0.21	0.21	0.47	0.31	0.42
88	42	0.3	1.3	52	45	94	91	0.25	0.22	0.19	0.51	0.2.9	0.39
89	44	0.5	1.3	51	50	94	90	0.2	0.21	0.22	0.39	0.34	0.42
90	45	0.5	1.3	50	45	94	91	0.2	0.21	0.22	0.49	0.34	0.42
91	47	0.7	1.3	50	50	94	91	0.24	0.21	0.22	0.43	0.3.2	0.41
92	46	0.9	1.3	51	45	94	90	0,23	0.22	0.22	0.44	0.32	0.42
93	34	0.5	1.3	50	50	94	91	0.25	0.22	0.19	0.51	0.2.9	0.39
94	23	0.6	1.3	51	45	94	92	0.25	0.22	0.17	0.52	0.36	0.44
95	28	0.5	1.3	49	50	94	91	0.23	0.23	0.17	0.47	0.31	0.43
96	34	0.6	1.3	51	50	94	90	0.2	0.21	0.22	0.39	0.34	0.42
97	36	0.8	1.3	51	45	95	92	0.23	0.2	0.21	0.42	0.35	0.42
98	55	0.4	1.25	50	45	95	92	0.24	0.21	0.22	0.43	0.3.2	0.38
99	51	0.4	1.26	52	50	94	92	0.25	0.22	0.17	0.43	0.3.2	0.44
100	50	0.1	1.27	51	50	94	91	0.23	0.22	0.21	0.51	0.2.9	0.41
101	48	0.2	1.25	52	45	94	91	0.22	0.21	0.21	0.48	0.33	0.42

102	47	0.3	1.25	51	45	94	92	0.25	0.22	0.19	0.49	0.34	0.39
103	46	0.7	1.25	50	50	94	92	0,23	0.22	0.22	0.49	0.34	0.42
104	39	0.9	1.25	50	45	95	92	0.2	0.21	0.22	0.44	0.32	0.42
105	37	0.6	1.25	51	50	94	92	0.25	0.22	0.17	0.43	0.3.2	0.44
106	24	0.8	1.3	50	50	94	91	0.22	0.23	0.21	0.42	0.35	0.41
107	23	0.5	1.3	51	45	95	90	0.24	0.23	0.18	0.51	0.35	0.43
108	28	0.3	1.3	49	45	95	91	0.25	0.22	0.17	0.39	0.34	0.44
109	56	0.1	1.25	51	50	94	90	0.24	0.23	0.18	0.45	0.35	0.43
110	54	0.25	1.26	51	50	94	91	0.23	0.23	0.17	0.43	0.31	0.43
111	46	0.75	1.27	50	45	94	92	0.23	0.2	0.21	0.47	0.31	0.42
112	48	0.3	1.25	52	45	94	91	0.24	0.21	0.22	0.51	0.2.9	0.38
113	49	0.5	1.25	51	50	94	92	0.22	0.21	0.21	0.51	0.35	0.42
114	43	0.4	1.25	52	45	95	90	0.23	0.22	0.21	0.49	0.34	0.41
115	45	0.5	1.25	51	50	94	90	0.24	0.23	0.18	0.45	0.35	0.43
116	47	0.6	1.25	50	50	94	91	0.25	0.22	0.17	0.39	0.34	0.44
117	34	0.6	1.2	50	45	94	92	0.24	0.23	0.18	0.43	0.31	0.43
118	33	0.4	1.2	51	45	95	92	0.2	0.21	0.22	0.52	0.36	0.42
119	32	0.3	1.3	50	50	94	92	0.24	0.23	0.18	0.43	0.31	0.43
120	35	1	1.3	51	50	94	91	0.23	0.22	0.21	0.43	0.3.2	0.41
121	37	0.7	1.3	49	45	94	92	0.24	0.23	0.18	0.42	0.35	0.43
122	39	0.4	1.3	51	45	94	91	0.25	0.22	0.17	0.43	0.3.2	0.44
123	40	0.5	1.3	51	50	94	92	0.23	0.23	0.17	0.51	0.35	0.43
124	43	0.6	1.3	50	45	94	92	0.24	0.21	0.22	0.51	0.2.9	0.41
125	17	0.7	1.4	52	50	94	92	0,23	0.22	0.22	0.51	0.2.9	0.42
126	20	0.3	1.6	51	45	94	92	0.24	0.21	0.22	0.49	0.34	0.38
127	23	0.4	1.2	52	50	94	90	0.22	0.21	0.21	0.42	0.35	0.42
128	24	0.5	0.6	51	45	95	91	0.23	0.22	0.21	0.44	0.32	0.41

129	18	0.2	1.4	50	50	94	91	0.25	0.22	0.17	0.39	0.34	0.44
130	14	0.3	1.5	50	50	94	92	0.23	0.23	0.17	0.51	0.35	0.43
131	20	0.1	1.4	51	45	94	91	0.24	0.23	0.18	0.51	0.35	0.43
132	18	0.2	1.5	50	45	93	91	0.2	0.21	0.22	0.39	0.34	0.42
133	18	0.3	1.4	51	50	94	92	0.24	0.21	0.22	0.49	0.34	0.41
134	18	0.3	1.5	49	50	94	92	0.25	0.22	0.19	0.44	0.32	0.39
135	13	0.8	1.4	51	45	93	90	0.24	0.23	0.18	0.47	0.31	0.43
136	20	0.6	1.3	51	45	94	90	0.25	0.22	0.17	0.51	0.2.9	0.44
137	23	0.5	1.4	50	50	94	91	0.25	0.22	0.17	0.52	0.36	0.44
138	25	0.4	1.4	52	45	94	92	0.24	0.21	0.22	0.49	0.34	0.41
139	27	0.5	1.3	51	50	94	91	0.22	0.23	0.21	0.43	0.31	0.41
140	29	0.6	1.3	52	45	96	92	0.24	0.21	0.22	0.44	0.32	0.38
141	32	0.3	1.3	51	50	94	92	0.23	0.22	0.21	0.44	0.35	0.41
142	34	0.2	1.3	50	45	94	92	0.23	0.22	0.21	0.52	0.36	0.41
143	36	0.3	1.3	50	50	94	92	0.24	0.23	0.18	0.51	0.35	0.43
144	39	0.3	1.3	51	50	94	90	0.24	0.23	0.22	0.42	0.35	0.41
145	33	0.2	1.3	50	45	95	91	0.24	0.23	0.18	0.42	0.35	0.43
146	34	0.3	1.3	51	45	95	92	0.2	0.21	0.22	0.43	0.3.2	0.42
147	31	0.4	1.3	49	50	94	91	0.22	0.23	0.21	0.47	0.31	0.41
148	38	0.3	1.3	51	50	94	92	0.24	0.23	0.18	0.51	0.35	0.43
149	40	0.4	1.3	51	45	94	91	0.24	0.23	0.18	0.48	0.33	0.43
150	42	0.5	1.3	50	45	94	91	0.25	0.22	0.17	0.49	0.34	0.44
151	44	0.3	1.3	52	50	94	90	0.24	0.23	0.22	0.42	0.35	0.41
152	45	0.1	1.3	51	45	94	91	0.24	0.21	0.22	0.44	0.32	0.41
153	47	0.6	1.3	52	50	94	92	0.23	0.22	0.21	0.52	0.36	0.41
154	46	0.5	1.3	51	45	94	91	0.24	0.21	0.22	0.52	0.36	0.38
155	34	0.5	1.3	50	50	94	92	0,23	0.22	0.22	0.39	0.34	0.42

156	23	0.9	1.3	50	45	94	91	0.23	0.22	0.21	0.39	0.34	0.41
157	28	0.4	1.3	51	50	94	92	0.24	0.21	0.22	0.43	0.3.2	0.38
158	34	0.3	1.3	50	50	94	91	0.23	0.23	0.17	0.45	0.35	0.43
159	36	0.4	1.3	51	45	95	91	0.24	0.23	0.18	0.47	0.31	0.43
160	55	0.3	1.3	49	45	95	92	0.2	0.21	0.22	0.51	0.2.9	0.42
161	51	0.6	1.25	51	50	94	91	0.25	0.22	0.19	0.51	0.2.9	0.39
162	50	0.8	1.25	51	50	94	91	0.23	0.2	0.21	0.47	0.31	0.42
163	48	0.6	1.3	50	45	94	92	0.24	0.23	0.18	0.45	0.35	0.43
164	47	0.1	1.3	52	45	94	92	0.25	0.22	0.17	0.44	0.32	0.44
165	46	0.3	1.3	51	50	94	92	0.24	0.23	0.18	0.48	0.33	0.43
166	39	0.3	1.3	52	45	95	91	0.24	0.21	0.22	0.52	0.36	0.41
167	37	0.4	1.3	51	50	94	90	0.23	0.23	0.17	0.45	0.35	0.43
168	24	0.6	1.4	50	50	94	91	0.23	0.2	0.21	0.47	0.31	0.42
169	23	0.7	1.3	50	45	95	91	0.24	0.23	0.22	0.42	0.35	0.41
170	28	0.6	1.3	51	45	95	92	0.23	0.22	0.21	0.43	0.3.2	0.41
171	56	0.4	1.25	50	50	94	92	0.24	0.23	0.18	0.48	0.33	0.43
172	54	0.5	1.26	51	50	94	92	0.24	0.21	0.22	0.51	0.2.9	0.38
173	46	0.4	1.27	49	45	94	90	0.24	0.23	0.18	0.48	0.33	0.43
174	48	0.3	1.25	51	45	94	91	0.2	0.21	0.22	0.49	0.34	0.42
175	49	0.8	1.25	51	50	94	90	0.23	0.20	0.21	0.48	0.33	0.42
176	43	0.5	1.25	50	45	95	91	0,23	0.22	0.22	0.44	0.32	0.42
177	45	0.4	1.25	52	50	94	91	0.24	0.23	0.18	0.45	0.35	0.43
178	47	0.2	1.25	51	50	94	92	0.23	0.23	0.17	0.43	0.31	0.43
179	34	0.6	1.3	52	45	94	90	0.23	0.23	0.17	0.51	0.35	0.43
180	33	0.8	1.3	51	45	95	90	0.24	0.21	0.22	0.39	0.34	0.41
181	32	0.9	1.3	50	50	95	92	0.23	0.23	0.17	0.48	0.33	0.43
182	35	0.2	1.3	50	50	95	91	0.22	0.21	0.21	0.45	0.35	0.42

183	37	0.3	1.3	51	45	94	92	0.24	0.23	0.22	0.47	0.31	0.41
184	39	0.5	1.3	50	45	94	92	0.23	0.22	0.21	0.51	0.2.9	0.41
185	40	0.3	1.3	51	50	95	92	0.24	0.23	0.18	0.43	0.31	0.43
186	43	0.4	1.3	49	45	94	92	0.25	0.22	0.19	0.49	0.34	0.39
187	47	0.7	1.4	51	45	95	92	0.24	0.23	0.18	0.45	0.35	0.43
188	46	0.3	1.4	51	50	95	91	0.2	0.21	0.22	0.44	0.32	0.42
189	39	0.5	1.5	50	50	95	91	0.24	0.23	0.22	0.39	0.34	0.41
190	37	0.5	1.4	52	45	94	92	0.23	0.22	0.22	0.52	0.36	0.42
191	24	0.7	1.4	51	45	95	91	0.24	0.23	0.18	0.51	0.35	0.43
192	23	0.9	1.5	52	50	95	92	0.23	0.23	0.17	0.48	0.33	0.43
193	28	0.5	1.4	51	50	95	92	0.24	0.23	0.18	0.47	0.31	0.43
194	56	0.6	1.4	50	45	94	91	0.24	0.21	0.22	0.44	0.3.2	0.41
195	54	0.5	1.5	50	45	94	90	0.23	0.20	0.21	0.43	0.31	0.42
196	46	0.6	1.5	51	50	95	90	0.24	0.23	0.22	0.48	0.33	0.41
197	48	0.8	1.6	50	45	94	91	0.24	0.21	0.22	0.51	0.33	0.38
198	49	0.4	1.3	51	50	95	91	0.22	0.23	0.21	0.45	0.35	0.41
199	54	0.4	1.3	51	50	95	91	0.20	0.21	0.22	0.52	0.36	0.42
200	46	0.1	1.3	51	45	94	91	0.22	0.21	0.21	0.43	0.32	0.42
201	17	0.2	1.4	52	55	93	92	0.24	0.23	0.22	0.42	0.35	0.41
202	20	0.3	1.6	51	50	95	92	0.24	0.21	0.22	0.39	0.34	0.41
203	23	0.7	1.2	50	50	95	90	0.25	0.22	0.19	0.43	0.3.2	0.39
204	24	0.9	0.6	50	60	95	90	0.25	0.22	0.19	0.51	0.2.9	0.39
205	18	0.6	1.4	51	60	94	91	0.24	0.23	0.18	0.48	0.33	0.43
206	14	0.8	1.5	50	55	93	92	0.20	0.21	0.22	0.49	0.34	0.42
207	20	0.5	1.4	51	50	95	91	0.20	0.21	0.22	0.52	0.36	0.42
208	18	0.3	1.5	49	45	93	92	0,23	0.22	0.22	0.44	0.32	0.42
209	18	0.1	1.4	51	45	92	92	0.24	0.23	0.18	0.43	0.31	0.43

210	18	0.25	1.5	51	55	92	92	0.25	0.22	0.17	0.52	0.36	0.44
211	13	0.75	1.4	50	55	93	92	0.23	0.23	0.17	0.51	0.35	0.43
212	20	0.3	1.3	52	45	94	91	0.24	0.21	0.22	0.39	0.34	0.41
213	23	0.5	1.4	51	50	95	91	0.24	0.21	0.22	0.49	0.34	0.38
214	25	0.4	1.4	52	45	94	92	0.24	0.21	0.22	0.43	0.3.2	0.38
215	27	0.5	1.3	51	55	95	91	0.24	0.23	0.22	0.47	0.31	0.41
216	29	0.6	1.3	50	45	96	92	0.23	0.22	0.21	0.51	0.2.9	0.41
217	32	0.6	1.3	50	45	95	91	0.22	0.21	0.21	0.48	0.33	0.42
218	34	0.4	1.3	51	55	94	91	0.25	0.22	0.19	0.49	0.34	0.39
219	36	0.3	1.3	50	50	95	92	0.24	0.21	0.22	0.39	0.34	0.41
220	39	1	1.3	51	45	94	91	0.20	0.21	0.22	0.44	0.32	0.42
221	33	0.7	1.3	49	50	95	91	0.23	0.20	0.21	0.42	0.35	0.42
222	34	0.4	1.3	51	45	95	91	0.23	0.22	0.22	0.52	0.36	0.42
223	31	0.5	1.3	51	50	95	91	0.24	0.23	0.22	0.45	0.35	0.41
224	38	0.6	1.3	50	50	95	92	0.24	0.23	0.18	0.47	0.31	0.43
225	40	0.7	1.3	52	45	94	90	0.23	0.23	0.17	0.42	0.35	0.43
226	42	0.3	1.3	51	45	94	90	0.24	0.21	0.22	0.43	0.3.2	0.41
227	44	0.4	1.3	52	50	95	91	0.22	0.23	0.21	0.43	0.31	0.41
228	45	0.5	1.3	51	50	95	91	0.23	0.23	0.17	0.48	0.33	0.43
229	47	0.2	1.3	50	45	94	92	0.24	0.23	0.22	0.48	0.33	0.41
230	46	0.3	1.3	50	45	94	92	0.23	0.22	0.21	0.49	0.34	0.41
231	34	0.1	1.3	51	50	95	91	0.23	0.2	0.21	0.51	0.35	0.42
232	23	0.2	1.3	50	45	94	92	0.25	0.22	0.19	0.44	0.32	0.39
233	28	0.3	1.3	51	45	94	92	0.24	0.23	0.18	0.43	0.31	0.43
234	34	0.3	1.3	49	50	95	91	0.23	0.20	0.21	0.42	0.35	0.42
235	36	0.8	1.3	51	50	95	92	0.24	0.23	0.18	0.47	0.31	0.43
236	55	0.6	1.25	51	45	95	92	0,23	0.22	0.22	0.39	0.34	0.42

237	51	0.5	1.25	50	45	95	91	0.24	0.23	0.18	0.42	0.35	0.43
238	50	0.4	1.25	52	50	95	91	0.22	0.23	0.21	0.51	0.35	0.41
239	48	0.5	1.25	51	50	95	91	0.25	0.22	0.17	0.49	0.34	0.44
240	47	0.6	1.25	52	45	94	91	0.24	0.21	0.22	0.51	0.2.9	0.41
241	46	0.3	1.2	51	45	94	90	0.23	0.20	0.21	0.48	0.33	0.42
242	39	0.2	1.2	50	50	95	91	0.24	0.23	0.22	0.47	0.31	0.41
243	37	0.3	1.3	50	45	95	91	0.24	0.23	0.22	0.45	0.35	0.41
244	24	0.3	1.3	51	50	95	91	0.23	0.22	0.21	0.44	0.32	0.41
245	23	0.2	1.3	50	50	95	92	0.22	0.23	0.21	0.48	0.33	0.41
246	28	0.3	1.3	51	45	95	91	0.25	0.22	0.19	0.52	0.36	0.39
247	56	0.4	1.3	49	55	94	90	0.24	0.23	0.18	0.51	0.35	0.43
248	54	0.3	1.3	51	50	95	91	0,23	0.22	0.22	0.52	0.36	0.42
249	46	0.4	1.3	51	50	95	92	0.23	0.2	0.21	0.45	0.35	0.42
250	48	0.5	1.3	50	60	94	92	0,23	0.22	0.22	0.43	0.3.2	0.42
251	49	0.3	1.3	52	60	95	92	0.24	0.23	0.18	0.47	0.31	0.43
252	43	0.1	1.3	51	55	95	92	0.25	0.22	0.17	0.51	0.2.9	0.44
253	45	0.6	1.3	52	50	95	92	0.24	0.21	0.22	0.39	0.34	0.38
254	47	0.5	1.3	51	45	94	92	0.24	0.21	0.22	0.49	0.34	0.41
255	34	0.5	1.3	50	45	94	92	0.23	0.20	0.21	0.45	0.35	0.42
256	33	0.9	1.3	50	55	95	91	0.24	0.21	0.22	0.44	0.32	0.38
257	32	0.4	1.3	51	55	95	91	0.24	0.23	0.22	0.43	0.31	0.41
258	35	0.3	1.3	50	45	94	92	0.23	0.22	0.21	0.52	0.36	0.41
259	37	0.4	1.3	51	50	95	91	0.23	0.22	0.21	0.44	0.32	0.41
260	39	0.3	1.25	51	45	94	92	0.25	0.22	0.19	0.39	0.34	0.39
261	40	0.6	1.25	51	55	94	91	0.24	0.23	0.18	0.42	0.35	0.43
262	43	0.8	1.25	52	45	94	91	0.20	0.21	0.22	0.43	0.3.2	0.42
263	47	0.6	1.25	51	45	93	90	0.22	0.23	0.21	0.47	0.31	0.41

264	46	0.1	1.25	50	55	94	91	0,23	0.22	0.22	0.51	0.2.9	0.42
265	39	0.3	1.2	50	50	95	91	0.24	0.23	0.18	0.42	0.35	0.43
266	37	0.3	1.2	51	50	95	92	0.24	0.23	0.22	0.47	0.31	0.41
267	24	0.4	1.3	50	50	95	92	0.22	0.23	0.21	0.48	0.33	0.41
268	23	0.6	1.3	51	45	93	91	0.24	0.21	0.22	0.44	0.32	0.41
269	28	0.7	1.3	49	55	94	90	0.23	0.20	0.21	0.43	0.31	0.42
270	56	0.6	1.3	51	50	95	92	0.22	0.21	0.21	0.43	0.31	0.42
271	54	0.4	1.3	51	50	95	92	0.24	0.23	0.22	0.47	0.31	0.41
272	46	0.5	1.3	50	60	92	92	0.23	0.22	0.21	0.39	0.34	0.41
273	48	0.4	1.3	52	60	93	92	0.22	0.21	0.21	0.42	0.35	0.42
274	49	0.3	1.3	51	55	94	92	0.25	0.22	0.19	0.43	0.3.2	0.39
275	54	0.8	1.3	52	50	95	91	0.22	0.21	0.21	0.48	0.33	0.42
276	46	0.5	1.3	51	45	94	92	0.20	0.21	0.22	0.51	0.2.9	0.42
277	32	0.4	1.3	50	45	95	92	0.22	0.23	0.21	0.48	0.33	0.41
278	35	0.2	1.3	50	55	96	91	0,23	0.22	0.22	0.49	0.34	0.42
279	37	0.6	1.3	51	55	95	91	0.24	0.23	0.18	0.45	0.35	0.43
280	39	0.8	1.3	50	45	94	92	0.25	0.22	0.17	0.44	0.32	0.44
281	40	0.9	1.3	51	45	94	91	0.23	0.23	0.17	0.43	0.31	0.43
282	43	0.2	1.3	49	55	94	92	0.24	0.21	0.22	0.52	0.36	0.41
283	47	0.3	1.3	51	50	95	91	0.24	0.23	0.18	0.45	0.35	0.43
284	46	0.5	1.25	51	50	95	92	0.24	0.23	0.22	0.43	0.31	0.41
285	39	0.3	1.3	50	50	95	91	0.24	0.21	0.22	0.39	0.34	0.38
286	37	0.4	1.3	52	45	94	91	0.23	0.22	0.21	0.43	0.3.2	0.41
287	24	0.7	1.3	51	55	94	91	0.22	0.21	0.21	0.47	0.31	0.42
288	23	0.3	1.4	52	50	95	91	0.22	0.23	0.21	0.43	0.31	0.41
289	28	0.5	1.4	51	50	95	91	0.23	0.20	0.21	0.51	0.35	0.42
290	56	0.5	1.2	50	60	94	91	0.2	0.21	0.22	0.49	0.34	0.42

291	54	0.7	1.3	50	60	94	90	0.22	0.23	0.21	0.45	0.35	0.41
292	46	0.9	1.3	51	50	95	91	0.24	0.23	0.22	0.43	0.31	0.41
293	48	0.5	1.3	50	45	94	91	0.24	0.23	0.18	0.43	0.31	0.43
294	49	0.6	1.3	51	55	94	92	0.25	0.22	0.17	0.52	0.36	0.44
295	54	0.5	1.3	49	50	95	92	0.22	0.23	0.21	0.51	0.35	0.41
296	46	0.6	1.3	51	50	95	91	0.23	0.2	0.21	0.42	0.35	0.42
297	46	0.8	1.3	51	60	95	92	0.23	0.2	0.21	0.42	0.35	0.42
298	48	0.4	1.3	50	60	95	92	0.24	0.21	0.22	0.43	0.3.2	0.38
299	49	0.4	1.3	52	50	95	92	0.25	0.22	0.17	0.39	0.34	0.44
300	54	0.1	1.25	51	45	94	91	0.23	0.22	0.21	0.51	0.2.9	0.41