Comparative Study of Conformal Radiotherapy & Conventional Radiation Therapy With Conformal Boost in Management of Intracranial Meningioma.

Thesis Protocol Submitted for the Partial Fulfillment of

M.D Degree in Radiation Therapy

By

Rabab Ahmed Mohammed Abdul Moneim

M.B.B.ch, M.Sc. Cairo University
Assistant Lecturer of Radiation Oncology

Supervised by

Prof. Dr. Ehsan Gamal El- Din ElGoneimy

Professor of Clinical Oncology
Faculty of Medicine- Cairo University

Prof. Dr. Magda Mustafa Kamal Hussien

Professor of Clinical Oncology
Faculty of Medicine- Cairo University

Prof. Dr. Mohammed Abdulla Hassan

Assistant Professor of Clinical Oncology
Faculty of Medicine- Cairo University

Department of Clinical Oncology & Nuclear Medicine,
Kasr El-Aini Faculty of Medicine,
Cairo University

2009

CONTENTS

List Of Figures

List Of Tables

ACKNOWLEDGMENT

I am greatly honored to express my gratitude to ***Prof. Dr. Prof. Dr. Ehsan Gamal El- Din ElGoneimy*** *Professor of Clinical Oncology Faculty of Medicine- Cairo University, for her supervision, precious guidance, great encouragement, and maternal support.*

My profound gratitude to ***Prof. Dr. Magda Mustafa Hussien,*** *Professor of Clinical Oncology, Faculty of Medicine- Cairo University, for her supervision, enlightening help, honest encouragement, with soft promptitude, and sympathy.*

I would like to convey my gratitude to ***Prof. Dr. Mohammed Abdulla Hassan,*** *Assistant Professor of Clinical Oncology, Faculty of Medicine- Cairo University, for his supervision, continuous support, and kind collaboration.*

Deepest thanks and credit must go to all my doctors and colleagues for their sincere help, and effort to complete this work.

Thanks to Dear GOD

To the memory of my

Dearest Mother & Father

To my brothers and sisters

THANKS To ALL of them

Abstract

Among the 44 patients presented in the study, the 15 patients achieved complete remission, had a small tumor volume less than 5cm^3 and the dose delivered was more than 54 Gy. While patients who entered in disease progression in both groups were of young age ranging from 20 to 37 years (except one case in group II aged 59 years but grade III pathology).

Key word

Conventional

Conformal

Conformal

Intracranial

Introduction

Meningiomas account for about 20% of brain tumors. They are generally well circumscribed & slow growing but there are wide variations in their natural evolution, from small, indolent & asymptomatic tumor, to lesions encasing major vessels, cranial nerves, optic pathways or compressing vital structures of the brain, thus causing major morbidity & mortality. Between 90-95% of meningiomas are benign, 5% are called atypical & 2-3%are clearly malignant ***(Rene, 2004).*** To date no single technique including surgery has proved to be fully satisfactory. The low clinical incidence (in the range of few cases per 100,000 per year) & long life expectancy are additional factors of importance. The relatively small number of patients receiving radiation therapy makes the set up of proper randomized studies to assess the relative benefit of different therapies difficult. The biological behaviors of these lesions with almost absent metastatic potential & the excellent prognosis; 80-90% survival at ten years as well as very slow growth rate allow efforts to be focused on local control & in particular on the minimization of treatment toxicity, (***Wolbers et al , 2007).***

The clinical relevance of conformal radiation therapy has been unequivocally established since it has been shown that late radiation induced toxicity to normal tissues can be reduced, while dose is simultaneously escalated to the target tissues. The development of Conformal Radiation Therapy has had the most significant impact on improving the physical basis of radiation therapy during the past 15 years. Conformal Radiation Therapy has become a mantra for late 20^{th} & early 21s centuries, as it offers the potential for substantial improvement in tumor control probability, at a fixed normal tissue complication probability through its ability to focus high dose treatment volume around a target volume, it can be used to create highly uniform dose volumes (as in breast

radiotherapy), or deliberately inhomogeneous dose distribution (as in prostate radiotherapy due to overlapping regions of interest with organs at risk). It is also suited for radiotherapy of head & neck, lung, brain & pelvic tumors in which the target is either concave & / or close to dose limiting structures. ***(Alhei, et al, 1999).***

Aim of Work:

The aim of the current work is to establish the recently introduced novel technology of Conformal Radiation Therapy into routinely daily work in Kasr El-Aini Center of Oncology & Nuclear Medicine (NEMROCK), Kasr El-Aini School of Medicine, Cairo University. Moreover, to compare the physical as well as clinical outcome (including toxicity and progression free survival) of patients with cranial meningiomas. These patients were randomized to receive either conventional radiation therapy followed by conformal boost or, conformal radiation therapy only.

EPIDEMIOLOGY

- Incidence:-

Meningiomas are usually benign growths that originate from the leptomeninges. They account for about 20% of brain tumors &13% to 17% of intracranial tumors in the U.S. Multiple meningiomas are 1% to 6% of the total count. Between 90-95% of meningiomas are benign, 5% are called atypical & 2-3% are malignant ***(Johns, 2007).*** Of all intracranial meningiomas, 85% are located supratentorially, one third to one half of which is located along the base of the anterior and middle fossae. Table **(A)** lists the most common sites of occurrence and their relative incidence. Tow key factors consistently associated with trends in incidence of the tumor:

Age: According to Central Brain Tumor Registry of the United States (CBTRUS) the mean age of onset of 1ry brain tumor is 53 years. However, the average age of onset is 62 years in meningioma. It is rare in pediatric population**.** The incidence of intracranial meningiomas rises with increasing age and has been reported to be 3.5 times higher in patients older than 70 years of age than in younger patients, regardless of sex (Kuratsu and Ushio, 1997). The tumor growth rate, however, seems to be lower in the elderly. Meningiomas are multiple in 5% to 40% of patients, especially when they are associated with neurofibromatosis type 2 (NF2). ***(Peter et al., 2005)***

The increasing incidence with age could be due to the length of exposure to causal factors required for malignant transformation, the necessity of many genetic alterations before clinical disease, or poorer immune surveillance. ***(Rohinger et al, 2005)***

Sex: The incidence is higher in women 80% than men. Biologic or social or hormonal factors may account for these observed sex differences. ***(Rohinger et al, 2005).***

Table (A) Common Sites and Relative Incidence of Intracranial Meningiomas in Adults

Site	*Relative Incidence (%)*
Parasagittal or falcine	**25**
Convexity	**19**
Sphenoid ridge	**17**
Tuberculum sella	**9**
Posterior fossa	**8**
Olfactory groove	**8**
Middle fossa or Meckel's cave	**4**
Tentorial region	**3**
Peritorcular region	**3**
Lateral ventricle	**1–2**
Foramen magnum	**1–2**
Orbital or optic nerve sheath	**1–2**

Based on data from Cushing, Eisenhardt . Meningiomas 1989:

PATHOGENESIS & BIOLOGY

Meningiomas arise from the arachnoid "cap" cells that line the inner dura (fibrous covering the brain) and may arise anywhere. Most meningiomas are ovoid in shape & adhere to the dura. Those arise from the falx (mid line septum of the brain) or the tentorium may be dumbbell in shape. High grades can invade the bone or muscles, but such invasion is not a sign of malignancy, they can grow through the foramina at the base of the skull and grow outside the skull .As they grow, they compress normal brain causing increase intra cranial tension. (***Rohinger et al,2005)***

In the past decade, the field of oncology has shown dramatic growth in the understanding of basic biologic processes. Tumor cells have sustained genetic mutations that allow them to overcome growth inhibition allowing them to proliferate in the absence of external causes. Other genetic changes allow them to induce angiogenesis and develop their own blood supply. High grade meningiomas are associated with deletion on chromosomes 6p, 9q and 17p and mutations in P53.***(Bondy et al, 2005).***

1- Cell proliferation:-

Normal cells rely on growth factors secreted in their local environment to stimulate their growth. However, many CNS tumors have developed the ability to express their own growth factors along with the

respective receptors, resulting in an autocrine loop that allows for self-stimulation. Platelet derived growth factor (PDGF) related genes including both the ligands and the receptors are expressed in meningiomas. ***(Drummond et al,2006)***

Insulin-link growth factors and expression of transforming growth factor-a (TGF-a), a ligand that binds to this receptor, is increased in meninigiomas. For many tumors, mutations in two different pathways are important for deregulating the cell cycle. The first of these is the p16/cdk4 or cdk6/cyclin D/R pathway. The second is the p21/p53/mdm2/p19ARF pathway. Mutations in both of pathways are common in many brain tumors and are thought to play a casual role in the genesis of these meningiomas. Homozygous detections at the CDKN2 is expressed in anaplastic meningiomas. ***(Dumanski et al,1998)***

2. Angiogenesis:-

In order for a tumor to grow beyond a certain size, it must develop a blood supply. A number of growth factors are known to be important in angiogenesis. The most prominent of these is vascular endothelial growth factor (VEGF), which is over expressed in many brain tumors including meningiomas. ***(Ferrara et al, 2000)***

The hematopoietic growth factors granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have been identified in meningioma samples, and their expression has correlated with angiogenesis, tumor proliferation and meningioma grade ***(Ferrara et al, 2000)***.

3. Genetics and Molecular Biology :-

Thirty to eighty percent of sporadic meningiomas and nearly all neurofibromatosis-related meningiomas have mutations in the ***NF2*** gene (located in chromosome band 22q12) that result in mutations in the protein MERLIN. Chromosomal mapping techniques have identified chromosome sub band 22q12.3-qter, which is near the ***NF2*** gene but is believed to represent a separate and distinct locus in meningioma formation. Loss of expression of another tumor suppressor gene, *DAL-1* which is located in 18p11.3, has been found in 30% to 70% of meningiomas and is thought to play a role in early tumor genesis .***(Bondy et al, 2005)***

Other tumor suppressor genes implicated in the development or progression of meningiomas are *SMARCB2* (22q11.2), p53 (17p), and CDKN2B (9p21). The fact that malignant and atypical meningiomas tend to have more chromosomal aberrations than benign tumors do, suggests progressive loss of tumor suppressors and potential activation of oncogenes. Some of the genes implicated in meningioma oncogenesis are *c-sis, C-myc, Ha-ras, K-ras, c-fos, c-erbB,* and *S6k.****(Shu et al, 1999).***

A variety of other chromosomal aberrations have been implicated in the formation and progression of meningiomas, including losses on 1p, 2p, 6q, 10, and 14q and gains on 1q, 9q, 12q, 15q, 7q, and 20. Alterations on chromosomes 1, 10, and 14 and reactivation of the telomerase seem to be particularly important in the progression of more biologically aggressive meningiomas. Radiation induced meningiomas have been shown to express genetic aberrations that are different than those of sporadic meningiomas. In particular, there are fewer losses of genetic