MANAGEMENT OF RECCURENT BRAIN GLIOMA

Thesis

Submitted for partial fulfillment of MD Degree in
Radiation Oncology & Nuclear Medicine

By

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(2009)

Acknowledgement

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First and for most, thanks are due to ALLAH, to whom I relate any success in achieving any work in my life.

My words stand short of my supreme gratitude and thanks to ***Prof. Dr. LAILA FARIS,*** Professor of Radiation Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shames University, for her continuous supervision, valuable guidance, generous encouragement, great support and overall her kindness that gave me and this work the scope to light.

Special thanks are due to ***Prof. Dr. Mamdouh Salama*** Professor of Neurosurgery, Faculty of Medicine, Ain Shames University, for dedicating so much of his precious time and support in preparing this work.

I am also profoundly grateful to ***Dr. Amin El-Sayed,*** Assistant Professor of Radiation Physics, Faculty of Medicine, and to, ***Dr. Iman Elsharawy, Dr. Hatem Abd Alla,*** Assistant Professors of Radiation Oncology, and Nuclear Medicine, Ain Shames University for their continuous close supervision, support, constant help and fair stimulating remarks throughout this study. Words of thanks are so little for their great help in preparation of this work.

Finally, I wish to thank all members of my family for their continuous help, encouragement and support.

LIST OF APPREVIATIONS

AA: Anaplastic astrocytoma
AGT: Alkylguanine-DNA alkyltransferase.
AIC: Aminoimidazole-4-carboxamide.
AO: Anaplastic oligodendroglioma.
ASUSH: Ain Shams University Specialist Hospital.
ATTL: Autologous tumor-specific T lymphocyte.
AUC: Area under curve.
BBB: Blood brain barrier.
BCM20: Brain Cancer Module.
BCNU: Carmustine.
bFGF: basic fibroblast growth factor.
BID: Twice daily.
BMC: Blood mononuclear cell.
CCNU: Lomustine.
CDK4: cyclin dependant kinase 4.
CPT-11: Irinotecan.
CR: Complete response.
CRT: Conformal radiotherapy.
CTLs: Cytotoxic T-lymphocytes.
CTV: Clinical target volume.
DC: Dendritic cells.
DP: Disease progression.
DVH: Dose Volume Histograms.
EIAEDs: Enzyme-inducing antiepileptic drugs.
EORTC: European Organisation for Research and Treatment of Cancer.
EGFR: Epidermal Growth Factor Receptor.
FasL: Fas ligand.
FP: Fixation point.
FSRT: Fractionated stereotactic radiotherapy.
GBM: Glioblastoma multiforme.
GTV: Gross tumor volume.

HDAC: Histone Deacetylase.
HDR: High dose rate.
HIF-1α: Hypoxia Inducible Factor- 1α.
H-FSRT: Hypofractionated stereotactic radiotherapy.
HR-QOL: Health-related quality of life.
IGF2: insulin like growth factor 2.
IL-2: Interleukin-2.
IOERT: Intraoperative electron radiotherapy.
KPS: Karnofsky performance Status.
IMRT: Intensity-modulated radiotherapy.
LDR: Low dose rate.
LGG: Low grade glioma.
LOH: Loss of heterozygosity.
LQ: Linear quadratic
LR-RIT: Locoregional radioimmunotherapy.
MAb: Monoclonal antibody.
MGMT: Methylguanine-DNA methyltransferase.
MvEC: Microvascular endothelial cell.
MMP: Matrix metalloproteinase.
MMR**:** Mismatch repair.
MRS: Magnetic resonance spectroscopy.
MTIC: 5-(3-methyl-1-triazeno)imidazole-4-carboxamide.
MTD: Maximum tolerated dose.
mTOR: Mammalian target of rapamycin.
NCCN: National Cancer Comprehensive Network.
OA: Oligoastrocytoma.
O-2A: Oligodendrocyte type 2 astrocyte.
OARs: Organ at risks.
OD: Oligodendroglioma.
OER: Oxygen enhancement ratio.
OS: Overall Survival.
O^6-BG: O^6-benzylguanine.
O^6-MG: O^6- Methylguanine.

PARP: Poly-ADP-ribose polymerase.
PCP: Pneumocystis carinii pneumonia.
PCV: procarbazine, lomustine, and vincristine.
PD: prescribed dose.
PET: Positron Emission Tomography.
PFS: Progression free survival.
PDGFR: Platelet derived growth factor receptor.
PDGFR: PDGF receptor.
PlGF: placental growth factor.
PI3K: Phosphoinositol 3-kinase.
Poly-ICLC: Polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose.
PR: Partial response.
PTEN: Phosphatase and tensin homolog.
PTV: Planning target volume.
PXA: Pleomorphic xanthoastrocytoma.
QOL: Quality of life.
QLQ-C30: Quality of life questionnaire core-30.
Rb gene: Retinoblastoma gene.
RT: Radiotherapy.
SD: Stable disease.
SDF-1: Stromal cell-derived factor-1.
SGCA: Subependymal Giant Cell Astrocytoma.
SPECT: Single photon emission computed tomography.
SRS: Stereotactic radiosurgery.
TD: Tolerance dose.
TNF: Tumor necrosis factor.
TPS: Treatment planning system.
TSG: Tumor suppressor genes.
TZM: Temozolomide.
VEGF: Vascular endothelial growth factor.
VEGFR: VEGF receptor.
WHO: World health organization.

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INTRODUCTION

Primary intracranial tumors account for 1.4% of all cancers. Malignant gliomas constitute 50-60% of all primary intracranial tumors. **(Wrensch et al., 1999)**

Brain gliomas include astrocytomas [(low grade, anaplastic, and glioblastoma multiforme (GBM)], oligodendrogliomas, ependymomas, and mixed gliomas. **(Kenilworth., 1999)**

Abnormalities in receptor tyrosine kinase pathway and loss of tumor suppressor genes (TSN) are critical factors in the transformation of glial cells into malignant cells. **(Holland E., 2001)**

Following primary treatment, recurrence occurs in approximately 70% of gliomas. **(Hvizdos, Goa., 1999)**

Patients with recurrence usually present with new complaints including headache, nausea, vomiting, personality changes, seizures, and, or focal neurological syndromes. **(Bauman et al., 1996)**

To confirm the diagnosis of recurrence, MRI is very helpful. Re-biopsy is also indicated in some cases. **(Hadani et al., 2001)**

It is extremely important to distinguish tumor recurrence from radiation induced necrotic changes. This can be achieved by Thallium201 SPET, 18Ffluorodeoxyglucose PET, and MR spectroscopy.

(Hazle et al., 1997)

Treatment of recurrent glioma includes surgical resection, chemotherapy, radiation therapy, and, or novel molecular, and targeted therapies. **(Stephen, Raymond., 2003)**

The main goal of surgery is removal of the enhancing tissues to decrease pressure effect and to provide diagnosis in ambiguous cases. **(Stephen, Raymond., 2003)**

Temozolomide as an imidazotetrazine agent is effective in recurrent glioma. It is associated with a response rate of about 27.5% **(Yung et al., 1999).**

Myelotoxicity (primarily neutropenia and thrombocytopenia) is the major adverse effect of temozolomide observed in number of clinical trials **(Osoba et al., 2000).**

Brain reirradiation seems feasible, and effective.
The tolerance of the brain depends on dose per fraction, total dose administered, overall treatment time, time interval between primary treatment and reirradiation, volume of brain irradiated, adjunctive therapies, and other factors. **(Schultheiss et al., 1995) (Veninga et al., 2001)**

A wide variety of radiotherapy (RT) techniques have been used including conventional radiotherapy, 3D- conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), brachytherapy, stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FSRT), and

hypofractionated stereotactic radiotherapy (H-FSRT). **(Veninga et al., 2001)**

By 3D-CRT, the entire three- dimensional distribution of radiation to the tumor and normal tissue can be calculated. This tool allows treatment plans to be designed that limit higher doses to affect normal tissue. Additionally, this tool allows additional dose escalation to the tumor. **(Hudes, et al., 1999)**

Temozolomide can be administrated with reirradiation. Such combination is associated with objective responses of about 20%. **(Schonekaes et al., 2002).**

Molecular therapies represent another line of management of recurrent glioma. They include growth factor receptors inhibitors (e.g. imatinib, iressa), antiangiogenic agents (e.g. bevacizumab, thalidomide), and others **(Fine et al., 2003).**

AIM OF THE WORK

This study was done to assess the response rate, survival benefits and toxicity profile of temozolomide, and brain reirradiation by using conformal radiotherapy for the treatment of recurrent brain glioma.

The study included 30 patients with recurrent brain glioma treated in the Oncology Unit, Ain Shams University Specialist Hospital (ASUSH) between February 2005 and December 2008.

Chapter 1 EPIDEMIOLOGY

Malignant brain tumors account for about 1.4 % of all cancers and are responsible for 2.4% of cancer-related deaths. The annual incidence of primary malignant brain tumors is 6.4 per 100,000 populations. **(Jemal et al, 2005)**

Malignant glioma is the most common form of malignant brain tumors. They represent 50% to 60% of all primary brain tumors, and about 0.8% of all malignant tumors in adults. The incidence is 4 per 100.000 populations per year. **(Dillon., 2001)**

In Egypt: although there is no general cancer registry, in the last 3 years; 2006, 2007, 2008, the department of clinical oncology, Ain Shams University received 80 patients with brain glioma (1.4%), of them 56 patients (70%) recurred.

Definition of recurrence:

The term "tumor recurrence" is frequently used synonymously with "tumor progression".

The criteria used to define recurrent brain glioma remain ambiguous due to the following:

First, the infiltrative nature of glioma cells makes it difficult to eliminate microscopic disease despite macroscopic gross-total resection. Studies have shown that glioma recurrence often occurs in the form of local continuous growth within 2 to 3 cm from the border of the original lesion. **(Choucair et al., 1986)**