Hypofractionated Radiotherapy Versus Conventional Radiotherapy in Management of Patients with High Grade Gliomas Older Patients and Poor Performance State

Thesis

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List of Abbreviations

Abb.	Full term
5-ALA	*5-aminolevulinic acid*
AA	*Anaplastic astrocytomas*
ADC	*Apparent diffusion coefficient*
AEDs	*Antiepileptic drugs*
ASCO	*American Society of Clinical Oncology Clinical*
ATRX	*A thalassemia / mental retardation syndrome X-linked*
BED	*Biological effective dose*
BTCG	*Brain Tumor Cooperative Group*
BTV	*Biological tumor volume*
CBTRUS	*Central Brain Tumor Registry of the United States*
CBV	*Cerebral blood volume*
CDK	*cyclin-dependent kinase*
CR	*Complete response*
CRT	*Chemoradiotherapy*
CT	*Computer tomography*
CTV	*Clinical target volumes*
DSC	*Dynamic susceptibility weighted contrast-enhanced*
DWI	*Diffusion Weighted Imaging*
EGFR	*Epidermal growth factor receptor*
EORTC	*European Organization for Research and Treatment of Cancer*
FDG	*18-fluorodeoxyglucose*
FGF	*Fibroblast growth factor*
FSRT	*Fractionated stereotactic radiotherapy*
GBM	*Glioblastoma multiforme*
G-CIMP	*Glioma-CpG island methylator phenotype*
GRT	*Gross total resection*

List of Abbreviations cont…

Abb.	Full term
GTV	*Gross tumor volume*
HFRT	*Hypofractionated radiotherapy*
HGGs	*High-grade gliomas*
HRQOL	*Health-related quality of life*
hTERT	*High frequency of telomerase reverse transcriptase*
IARC	*International Agency for Research on Cancer*
IDH	*Isocitrate dehydrogenase*
IDH1/2	*Isocitrate dehydrogenase enzyme ½*
IFRT 125	*I implants following standard*
iMRI	*Intraoperative MRI*
IMRT	*Intensity modulated RT*
KPS	*Karnofsky Performance Status*
LOH	*Loss of heterozygosity*
LQ	*Linear-quadratic*
MDM2	*Mouse double-minute 2*
MGMT	*O6-methylguanine-DNA methyltransferase (),*
MRI	*Magnetic resonance imaging*
MRS	*MR Spectroscopy*
MS	*Median survival*
MVA	*Microvascular density or area*
NABTT	*New Approaches to Brain Tumor Therapy*
OARs	*Organs at risk*
OS	*Overall survival*
PBI	*Partial brain irradiation*
PD	*Progressive disease*
PDGF	*Platelet-derived growth factor*
PET	*Positron emission tomography*
PFS	*Progression free survival*

List of Abbreviations cont…

Abb.	Full term
PR	*Partial response*
PRV	*Planning risk volume*
PTEN	*Phosphatase and tensin homologue*
PTV	*Planning target volume*
rCBV	*Relative cerebral blood volume*
RCx/TMZ	*Receive concomitant chemoradiotherapy and adjuvant temozolimide*
RPA	*Recursive partitioning analysis*
RT	*Radiation therapy*
RTOG	*RT Oncology Group*
SD	*Stable disease*
SEER	*Surveillance, epidemiology and end results*
STR	*Subtotal resection*
TAC	*Time activity curve*
TERT	*Telomerase reverse transcriptase*
TMZ	*Temozolimide*
TP53	*Tumor protein*
UK MRC	*United Kingdom Molecular Research Council*
VEGF	*Vascular endothelial growth factor*
VMAT	*Volumetric modulated arc therapy*
WBRT	*Whole-brain radiotherapy*

Abstract

In our study steroid dependency (failure to taper steroid after radiotherapy) was a predictor for poor survival in both conventional and hypofractionated arm and with statistically significant difference on those patients nondependent on steroids.

In our study (clinical symptoms at presentation) in each arm failed to correlate to survival except the seizure which was significant associated with lower survival in conventional arm only. Finally, our study failed to identify tumor size as prognostic factor for GBM.

Our recommendations is to adopt short hypofractionated radiotherapy in management of elderly and poor performance patients with high grade glioma as the hypofractionated conformal radiotherapy was found to be as effective as the conventional radiotherapy with no severe adverse effects. Especially in patients over 70 years old in whom survival was statistically significant better than with conventional arm.

Considering the benefit of the short-course regimen in terms of time sparing for patients, and for radiation oncology centers, which are often overloaded by long patient waiting lists, the hypofractionated radiotherapy should be evaluated among younger and good performance patients.

Studies with greater number of patients are advised to realistic evaluation of glioblastoma prognostic factors. And we recommend further study about hypofractionated radiotherapy with temozolomide.

Keywords: Glioblastoma multiforme - Hypofractionated radiotherapy- Karnofsky Performance Status- Overall survival

INTRODUCTION

Malignant gliomas, including glioblastoma multiforme (GBM) are the most common primary brain tumors in adults and the age adjusted incidence of these high-grade gliomas has increased over recent years. The incidence annually is 2 to 3 per 100,000 people in the United States and Europe. GBM accounts for 12% to 15% of all intracranial tumors and 50% to 60% of astrocytic tumors ***(Kohler et al., 2011).***

Epidemiological data on CNS tumors as they occur in Egypt have been rather incomplete although there are some regional reports. In an epidemiological study done in the Egyptian National Cancer Institute, CNS neoplasms constitute about 3% of primary malignant tumors ***(EL-Bolkainy, 1998).***

A study was done to estimate the frequency of CNS tumors in east delta region, Egypt. In which the data were collected during the 8-year period from January 1999 to December 2007 from Pathology Department, Mansoura University, and other referred pathology labs. The study showed that: Intracranial tumors represented 86.7% of cases in comparison to only 13.3% for spinal tumors. Gliomas were the CNS tumors of the highest frequency (35.2%) ***(Zalata et al., 2011).***

The risk stratification scheme utilizing Radiation Therapy Oncology Group Recursive Partitioning Analysis of Malignant Glioma (RPA) has been used to categorize patients

with anaplastic astrocytoma or glioblastoma into different prognostic groups. The age was the most important predictor of survival, with patients <50 years faring better than older patients. Karnofsky performance status (KPS >70 more favorable than <70) was the next most significant prognostic factor in patients with malignant glioma.risk factors also include extent of resection, and neurologic function at the time of presentation ***(Siker et al., 2011).***

The combination of surgery, radiation therapy, and chemotherapy represents the standard approach to the treatment of malignant gliomas. Generally, surgery is performed through an open craniotomy. The goals of surgery are to provide a histologic diagnosis, to alleviate intracranial hypertension and focal neurologic deficits resulting from a mass effect, and to permit rapid corticosteroid dose tapering. The influence of surgical resection in malignant gliomas has been controversial. The aim of palliation of symptoms was always clear, but the survival advantage was debated ***(Pang et al., 2007).***

The benefits of postoperative radiation therapy for glioblastoma was first proven in the Brain Tumor Study Group randomized trial in the 1970s. Median survival was increased to 37.5 weeks from 17 weeks when postoperative radiotherapy was given compared with best supportive care alone. Subsequent dose response studies have established 60 Gy delivered in 1.8- to 2.0-Gy fractions as the best treatment regimen. In 2005, after the publication of the results of a

European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada phase III randomized trial comparing postoperative radiotherapy and postoperative radiotherapy with concurrent and adjuvant temozolomide, the latter was established as the standard of care because it showed statistically significant survival benefit ($p<0.001$) ***(Stupp et al., 2005).***

The use of conventional RT schemes (60–66 Gy in 30–33 fractions) often requires 6–7 weeks. This long period of treatment affects patient psycho-sociologically and reduces the quality of life while increasing cost. Shortening the treatment and controlling the symptoms of these patients are important considerations. Numerous studies have found that shorter course of RT might be an appropriate option for the patients with high grade gliomas, especially those who have poor prognosis ***(Meral et al., 2007).***

the United Kingdom Molecular Research Council (UK MRC), and European Organization for Research and Treatment of Cancer (EORTC) prognostic groups have consistently shown that elderly patients and those with poor performance do poorly. Shortened treatment time may be advantageous for many elderly patients as it potentially maximizes out-of-hospital time in this disease with limited prognosis ***(Scott et al., 2012).***

In a retrospective study from the University of Texas M. D. Anderson Cancer Center, 59 patients with glioblastoma who were