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Review article

How surgery, radiotherapy and chemotherapy each contribute to the outcome of treatment for adult patients with Glioblastoma?

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ABSTRACT
Introduction: glioblastoma is a common condition associated with high morbidity and mortality; most of newly diagnosed patients will die within two years. The current standard therapy is maximal surgical resection followed by radiotherapy plus concomitant and adjuvant temozolamide. **Objective:** it is the aim of this review to evaluate how determinant surgical resection, radiotherapy and chemotherapy are to the outcome of patients with glioblastoma. **Methods:** a literature search is done to identify trials evaluating the outcome of adults with glioblastoma after being treated with surgery, radiotherapy or chemotherapy. The Oxford Centre for Evidence-based Medicine Levels of Evidence model is used to grade the quality of the available evidence. **Results:** 18 articles, reporting results of 15 studies were included. Five trials evaluated the effect of surgery in survival. Surgical provides as much as 4.9 months benefit in overall survival in cases in which complete resection is possible. A systematic review and four clinical trials reported that radiotherapy increases the mean overall survival in a range from three to five months. The European organization for research and treatment of Cancer and The National Cancer Institute of Canada Clinical Trials Group (EORT-NCIC) described in 2005 an increase of the survival by two - three months on patients receiving concomitant and adjuvant TMZ compared to patients receiving radiotherapy alone. Addittion of a novel chemotherapeutic agent seems to improve the outcome of patients compared to the current standard of care. **Conclusion:** surgery, radiotherapy and chemotherapy, each have a modest effect in the outcome of adults with glioblastoma. (MÉD.UIS. 2012;25(3):209-19).

Key words: Glioblastoma. General Surgery. Radiotherapy. Chemotherapy. Treatment Outcome.

Cirugía, radioterapia y quimioterapia, ¿cómo cada uno contribuye al resultado del tratamiento en adultos con glioblastoma?

RESUMEN
Introducción: el glioblastoma es un tumor frecuente asociado a alta morbilidad y mortalidad, la mayoría de pacientes mueren antes de 2 años desde el diagnostico. La terapia estándar actual es resección quirúrgica máxima asociada a radioterapia mas temozolomida concomitante y coadyuvante. **Objetivo:** evaluar que tan determinantes son la resección quirúrgica, radioterapia y quimioterapia para el resultado del tratamiento en pacientes con glioblastoma. **Métodología de búsqueda:** una revisión de la literatura es hecha para identificar estudios que evalúen el resultado del tratamiento de adultos con glioblastoma tras ser tratados con cirugía, radioterapia o quimioterapia. El modelo de niveles de evidencia del Centro de Medicina basada en la evidencia de Oxford es usado para calificar la calidad de la evidencia encontrada. **Resultados:** 18 artículos, reportando resultados de 15 estudios son incluidos. Cinco estudios evalúan el efecto de cirugía en la sobrevida. La resección quirúrgica provee un beneficio tan alto como 4,9 meses en la sobrevida global en los casos en que la resección máxima es posible. Una revisión sistemática y cuatro ensayos clínicos han reportado que la radioterapia incrementa el promedio de sobrevida global en un rango de tres a cinco meses. La organización Europea para la investigación y manejo del Cáncer y el grupo de ensayos clínicos del instituto Nacional de Cáncer de Canadá (EORT-NCIC) describió en el 2005 un incremento en la sobrevida global en dos a tres meses en pacientes que reciben tratamiento concomitante y coadyuvante con temozolomida en comparación con pacientes que solo reciben radioterapia. La adición de uno de los nuevos agentes quimioterapéuticos parece mejorar el resultado del manejo comparado con el actual tratamiento estándar. **Conclusión:** el tratamiento quirúrgico, la radioterapia y la quimioterapia; cada uno tiene un efecto modesto en el resultado del tratamiento de pacientes con glioblastoma. (MÉD.UIS. 2012;25(3):209-19).

Palabras clave: Glioblastoma. Cirugía General. Radioterapia. Quimioterapia. Resultado del Tratamiento.

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Introduction

Glioblastoma (GB) is a diffusely growing malignant brain neoplasm classified by the World Health Organization (WHO) as a Grade IV astrocytoma. It has a yearly incidence of 3 to 5 newly diagnosed cases per 100.000 population and distinctive histological and clinical features that make it a particularly aggressive and devastating tumour[1,2]. The mean progression-free and overall survival (OS) times for patients treated with the current standard-of-care therapy (debulking surgery plus radiation plus concomitant and adjuvant temozolamide) within clinical trials are around 7 and 15 months, respectively[3]. Selected patient populations with favourable prognostic factors have been reported to have a mean OS of 19 to 22 months[3,8]. However, to date, not an effective curable treatment is available and more than 70% of patients will die in two years following diagnosis[5]. It is the aim of this review to evaluate how determinant surgical resection, Radiotherapy (RT) and Chemotherapy (CT) are in the outcome of patients with GB and how much each of those treatment modalities can add to the survival/outcome of the patients.

Histopathologically, GB is a hyper cellular diffusely infiltrating tumor with nuclear atypia and mitotic activity; which is also associated with necrosis and/or micro vascular proliferation. The majority of GB raises de novo as primary GB; however, anaplastic gliomas can evolve to secondary GB and represent 10% of them. GB is the most aggressive and most studied tumor in the brain1 and most of the current knowledge comes from studies carried out in patients younger than 65 years.

Current standard treatment for patients younger than 65 years newly diagnosed with GB is maximal surgical resection when feasible, plus 60 Gy of focal fractioned irradiation on daily fractions of 2 Gy for six weeks. This associated to concomitant CT with Temozolamide (TMZ), seven days per week from the first to the last day of CT (six weeks) followed by six cycles of five days of adjuvant TMZ every 28 days. Biodegradable polymers, put into the tumour bed at surgery, can target residual tumour cells by gradually releasing carmustine over several weeks (gliadel) and is a therapeutic option approved for newly diagnosed High Grade Gliomas (HGG)[8].

Almost a half of the patients with GB are older than 65 years, they are less responsive to treatment and have worst prognosis; the most common treatment for this group of age is hypo fractionated RT (40 Gy in 15 fractions). Depending on age and Karnofsky Performance Status (KPS), Debulking Surgery (DS) or concomitant and adjuvant CT can be considered[10,11].

Despite optimal treatment, all malignant gliomas eventually recur; in those cases reoperation may be considered, and RT or CT have a modest controversial value[12-4]. Bevacizumab, an anti- Vascular Endothelial Growth Factor (VEGF) was approved in 2009 as a single agent for recurrent GB in the US[15,16]. Different antiangiogenic and inmunomodulator drugs, inhibitors of integrin receptors and glutamate receptor blockers are being studied; they target specific pathways on tumoral pathogenesis and appear to be promising[17-9].

Methods

A general search was performed in PubMed (United States National Library of Medicine) to find the most recent trials evaluating the outcomes of adults with GB after being treated with surgery, RT or CT. The following combination of words was used: "glioblastoma" or "grade iv gliomas" or "glioblastoma multiforme" or "high grade gliomas" and "surgery" or "resection" or "radiotherapy" or "chemotherapy" or "antineoplastic agents" and "outcome" or "treatment outcome". The search was then limited to adults (19 + years) and published since January 2010.

The search retrieved 243 papers, their titles and abstracts were reviewed and 31 papers considered relevant were selected. Their full texts were reviewed and their references used to identify key past trials that support the current treatment and outcome of GB. Studies that included patients with low grade and/or grade III gliomas were excluded as well as studies that did not evaluate the effect of the treatments separately. The Oxford Centre for Evidence-based Medicine Levels of Evidence model, updated in 2009 (see Table 1) is used to grade the quality of the available evidence.

Table 1. Oxford Centre for Evidence-based Medicine Levels of Evidence.

Level	Therapy/Prevention, Aetiology/Harm	Notes
1a	SR (with homogeneity*) of RCTs	*By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies.
1b	Individual RCT (with narrow Confidence Interval"i)	"i Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because: EITHER a single result with a wide Confidence Interval OR a Systematic Review with troublesome heterogeneity. Such evidence is inconclusive, and therefore can only generate Grade D recommendations
1c	All or none§	§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
2a	SR (with homogeneity*) of cohort studies	
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	
2c	"Outcomes" Research; Ecological studies	
3a	SR (with homogeneity) of case-control studies	
3b	Individual Case-Control Study	
4	Case-series (and poor quality cohort and case-control studies §§)	§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	

Produced by: 63. Phillips et al, 1998. Updated by: 64. Howick, 2009.

RESULTS

Preliminary search identified 31 papers reporting the outcomes of adults with GB after being treated with surgery, RT or CT. After detailed review 13 of these studies were found ineligible since they did not reported the effect of the treatment modalities separately or included patients with Grade II or III gliomas. 18 articles, reporting results of 15 trials were therefore eligible for inclusion; three papers reported subsequent analyses of trials whose primary results had been already published[30,42,56].

The Table 2 summarizes the characteristics and main findings of five trials (six publications) evaluating the effect of surgery in the outcome of adult patients with GB. Not any of these trials reached the level of evidence 1. A systematic review (level of evidence 1a) and four clinical trials were found describing the impact of RT in the outcome of GB patients (see Table 3). As shown in Table 4, a systematic review and meta-analysis (level of evidence 1a) failed to show any beneficial effect for the different CT regimens used before concomitant and adjuvant TMZ was described. The European organization for research and treatment of Cancer and The National Cancer Institute of Canada Clinical Trials Group (EORTNCIC) described in 2005 an increase in survival of patients receiving concomitant and adjuvant TMZ compared to patients receiving RT alone[55]. This findings have been reconfirmed with further analysis and follow up of the same cohorts[30-56]. Addition of a novel chemotherapeutic agent seems to improve the outcome of patients compared to the current standard of care[3] (see Table 4).

Table 2. Characteristics of trials valuating the effect of surgery in the outcome of adult patients with GB.

Ref. Author, year	Treatment regimen	Patients characteristics			Main results	LOE
		n	Age(r)	KPS(r)		
40. Vuorinen et al, 2003.	RT + Biopsy RT + DS	13 10	70 (66–80) 72 (67–79) older than 65y	70 78	OS was 2.7 times longer (95% CI 1.004–7.568, p = 0.049) after DS. There was no significant difference in PFS between these two treatments (p = 0.057)	2b
41. Stummer et al, 2006.	DS DS with 5-ALA	161 161	59 (30–73) 60 (23–73)		PFS was 19.9% (9·1–30·7) higher in patients operated with 5-ALA than in the group operated under white light microsurgery (p=0·0003)	2b
42. Stummer et al, 2008.	DS DS with 5-ALA Adjustment for bias ref 41	122 121	Multivariate analysis to control prognostic factors.		Patients without residual tumor survived longer (16.7 vs. 11.8 mo, p < 0.0001). Residual tumor, age, and KPS were significantly prognostic. Re-interventions occurred earlier in patients with residual tumor (6.7 vs. 9.5 mo, p = 0.0582)	2b
45. Lacroix et al, 2001.	Single cohort DS + RT+ CT Evaluation of EOR	416	53 (14)		Significant OS advantage on resection of 98% or more (13 mo, 95% CI: 11.4–14.6 mo), compared with 8.8 mo for resections of less than 98% (95% CI 7.4–10.2 m; p < 0.0001). Retrospective cohort (1993-1999)	3b
47. Ewelt et al, 2011.	Surgery (Biopsy or DS) Surgery + RT Surgery + RT+ CT Evaluation of EOR	31 37 35	74.4 70.6 68.5 Older than 65y	60 70 80	Complete resection group had a PFS of 10 mo (95% CI: 5.6–14.4) vs. 4.2 mo (95%CI: 3.8–4.6) for patients with partial resection (p<0.05). COX-regression shows that the degree of resection was a significant factor for OS (p = 0.017). Retrospective (2002-2007)	3b
31. Sanai et al, 2011.	Single cohort DS + RT+ CT Evaluation of EOR	500	60 (21-90)	80 (20-100)	EOR were predictive of survival (p < 0.0001). Significant survival advantage with as little as 78% EOR. Stepwise improvement in survival was evident even in the 95%–100% EOR range. Retrospective cohort (1997-2009)	3b

5- ALA: 5-aminolevulinic acid, CI: Confidence Interval, CT: Chemotherapy, DS: Debulking Surgery, EOR: Extent of resection, KPS: Karnofsky Performance Status, LOE: Level of Evidence, mo: months, n: number of patients, (r): range, OS: Overall Survival, PFS: Progression free survival, RT=Radiotherapy, y: years.

Table 3. Characteristics of trials evaluating the effect of Radiotherapy in the outcome of adult patients with GB.

Ref. Author, year	Treatment regimen	Patients characteristics			Main results	LOE
		n	Age	KPS		
52. Laperriere et al, 2002.	Systematic review of various aspects of RT.	9 RCT in total including 6 homogeneous trials of RT vs. no RT.			Six RCT detected a significant survival benefit favouring post-operative RT compared with no RT (RR, 0.81; 95% CI, 0.74 - 0.88, p, 0:00001). Two RCT demonstrated no significant difference in survival rates for WBRT versus more local fields. A RCT detected a small improvement in survival with 60 Gy in 30 fractions over 45 Gy in 20 fractions.	1a
10. Keime-Guibert et al, 2007.	Supportive care alone Supportive care + RT Patients 70 years or older	42 39	73 y 75 y		The median OS for patients who received supportive care + RT was 29.1 weeks, as compared with 16.9 weeks for the 42 patients who received supportive care alone. The HR for death in the RT group was 0.47 (95% CI, 0.29 to 0.76; p = 0.002).	1b
51. Sandberg-Wollheim et al, 1991.	PVC PVC + RT	71 68	60 y 57 y	80 % 85%	Patients less than 50 y treated with PVC + RT had significantly longer survival (MTP: 81 wk, MST: 124 wk) than patients treated with PVC alone (MTP: 21 wk, MST: 66 wk) after correcting for prognostic factors in a multi-variate analysis (p = 0.037). Age, KPS, and absence of extensive necrosis in the tumor were significant prognostic factors.	1b
49. Shapiro and Young, 1976.	DS + Carms/ Vinc DS + Carms/ Vinc + RT	16 17	60 y 58 y	71% ± 14% 57% ± 17%	MST of RT group was 30 wk, while that of no RT group was 44.5 wk. The OS curves were not significantly different. RT do not increase morbidity	2b
50. Walker et al, 1980.	RT Carmustine + RT Semustine Semustine + RT	111 118			Multi-arm collaborative study. 61. Walker et al, 1978. and 62. Kristiansen et al, 1981. are publications based on the same study. Significant survival benefit favouring CT+RT compared with CT alone. No significant difference in survival between RT alone and CT+RT (data not shown).	2b

Carms/Vinc: Carmustine + Vincristine, CI: Confidence Interval, CT: Chemotherapy, DS: Debulking Surgery, HR= hazard ratio, KPS: Karnofsky Performance Status, LOE: Level of evidence, MST: Mean Survival Time, MTP: Mean time to progression, n: number of patients, OS: Overall Survival, PVC: procarbazine, vincristine, and lomustine (CCNU), RCT: Randomized Controlled Trials, RR: Risk ratio, RT=Radiotherapy, WBRT: Whole brain radiotherapy, wk: weeks, y: years.

Table 4. Characteristics of trials evaluating the effect of chemotherapy in the outcome of adult patients with GB.

Ref. Author, year	Treatment regimen	Patients characteristics		Main results	LOE
		n	age		
54. Stewart 2002.	SR and meta-analysis of RT alone vs. RT + CT* (no TMZ)	Data from 3004 patients from 12 RCT (1 no published)		Modest prolongation of OS associated with CT, HR: 0·85 (95% CI 0·78–0·91, p<0·0001) or a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1y survival of 6% (95% CI 3–9) from 40% to 46%.	1a
55. Stupp et al 2005. EORT-NCIC	RT RT + TMZ	286 287	57 (23-71) 56 (19-70)	At a median follow-up of 28 mo, the median survival was 14.6 mo with RT+TMZ and 12.1 mo with RT alone. The unadjusted HRfor death in the RT+TMZ group was 0.63 (95% CI, 0.52 to 0.75; p<0.001). Two-year survival rate was 26.5% with RT+TMZ and 10.4 % with RT alone.	1b
30. Stupp et al, 2009. EORT-NCIC	RT RT + TMZ 5 years analysis of EORTC-NCIC trial[55]	286 287	57 (23-71) 56 (19-70)	OS was significantly higher at 2, 3 4 and 5 years in patients treated with RT +TMZ compared to RT alone (HR 0·6, 95% CI 0·5–0·7; p<0·0001). A benefit of combined therapy was recorded in all clinical prognostic subgroups, including patients aged 60–70 y. Methylation of the *MGMT* promoter was the strongest predictor for outcome and benefit from TMZ.	1b
56. Mirimanoff 2006. EORT-NCIC	RT RT + TMZ RPA of EORTC-NCIC[55]	286 287	57 (23-71) 56 (19-70)	In RPA the groups with better prognosis (class III and IV), the survival advantage remained significant (p <0.0001). In RPA the groups of patients with worst prognosis (class V), the survival advantage of RT+TMZ was of borderline significance (p=0.054).	1b
3. Grossman et al, 2010[3]. EORTC-NABTT	DS+RT+TMZ (HC) DS+RT+TMZ DS+RT+TMZ + NA	287 49 244	56 (19-70) 58 (29-69) 55 (21-70)	Median, 12-mo, and 24-mo survival rates for the EORTC patients (n = 287) and the comparable NABTT patients receiving RT + TMZ + NA (n = 244) are 14.6 vs. 19.6 mo, 61% vs.81%, and 27% vs. 37%, respectively. This represents a 37% reduction in odds of death (p < 0.0001) through 2 years of follow-up.	2b

***Includes different doses and combinations of Carmustine, Lomustine, Dicarbazine, Mitolactol, Bleomycin, Nimustine, but no TMZ.**

CI: Confidence Interval, CT: Chemotherapy, DS: Debulking Surgery, EORT-NCIC: European organization for research and treatment of Cancer and The National Cancer Institute of Canada Clinical Trials Group, HC: Historical Cohort, HR= hazard ratio, LOE: Level of evidence, mo: month, n: number of patients, NA= New Agent (talampanel or poly-ICLC or Celengetide), NABTT: New Approaches to Brain Tumour Therapy consortium, OS: Overall Survival, RCT: Randomized Controlled Trials, RPA: recursive partitioning analysis, RT=Radiotherapy, SR: Systematic review, TMZ=Temozolamide, y: years.

OS and Progression Free Survival (PFS) were the most commonly used outcome measures. OS is considered the gold standard end point for patients with HGG; it is thought to prove an objective and unequivocal clinical benefit particularly useful in GB given its short life expectancy. However, OS can be affected by the treatment start time, factors unrelated to the studied therapy, and salvage therapies used

at recurrence[20,21]. PFS is the time from treatment initiation to progression or death from any cause and reflects the treatment effect without influences from recurrence therapies[22]. Radiographic methods used to determine progression in the case of PFS and the assessment of overall radiographic response become problematic or even unreliable after the introduction of new therapies and the description of pseudo progression. The use of corticosteroids and radiation can modify the permeability of tumoral blood vessels and therefore the correlation between tumour enhancement and tumour evolution[23,24]. Particularly important is pseudo progression; an increase in contrast enhancement and peritumoral edema sometimes associated to neurologic worsening described after RT plus TMZ[25,26]; or pseudo response, an apparent improvement in contrast enhancement due to diminished vascular permeability described after treatment with bevacizumab. Even when those changes do not reflect the real effect of the treatment, they modify the radiographic features that could be used to evaluate response or progression[27]. Nowadays, not any imaging based method can reliably assess progression or response in HGG; the recently defined Revised Assessment in Neuro-Oncology (RANO) criteria are expected to resolve these issues[20].

Discussion

Much has been trialled to improve the outcome of patients with GB; however, no current therapy is capable of modifying the process of the disease. Prolongation in survival and improvement in quality of life can be reached using the best available treatment. The first papers published about GB reported a survival of seven weeks in patients without any treatment; similar to the recent findings of two months on elderly patients who did not receive any treatment[28,29]. In the last three decades, implementation of DS, RT and CT has prolonged the survival of patients with GB to 12-18 months[3,30]. The aforementioned benefit on survival is not seen in all patients receiving optimal treatment, but some patients have been clearly identified to be no responsive. Several factors have been associated to either poor response or good prognosis[29-37]. Those factors are currently thought to be more important to outcome that the treatment by itself. For instance, age and KPS are such strong outcome predictors that patients older than 70 years and low KPS are usually treated with supportive care or RT alone[29]. The appearance of the tumour in the scans, its enhancement, size and location are important for surgery planning and determine the possible extent of resection without new neurological deficit[31]. The histological analysis of the tumour and WHO classification, do not entirely correlate the outcome due to the heterogeneity of malignant gliomas. However, new molecular analyses of the tumour seem to provide powerful prognostic factors. For instance, the methylation of DNA repair enzyme O-6 Methyl Guanine-DNA Methyl Transferase (MGMT) in GB is predictive of improved prognosis and better response to TMZ[32,33]. Mutation in codon 132 of the isocitrate dehydrogenase 1 (IDH 1) gene can help to diagnose secondary GB and confer a prognostic advantage on patients with anaplastic astrocytoma[34,35]. Also, 1p/19q co-deletion is an indicator of anaplastic oligodendroglioma vulnerability to a wide range of therapies including PVC[36,37]. These molecular features allow a better classification of tumours and aid in the differentiate patients who should receive aggressive initial treatment from those who do well regardless of the given treatment, thus allowing decision making based on side effects[38]. Nonetheless, given the short list of effective therapies, there is a long way to get the entire utility of those markers; such as, that patients with non-methylated MGMT promoter tumours who are known to be poor responders to TMZ are still treated with it because there is no better option available[39].

SURGERY

Surgical approach to patients with GB is critical since it reduces the symptoms of increased intracranial pressure and mass effect, and provides tissue for histologic classification and molecular evaluation, which allows classification, prognosis and therapeutic approach. Further than allowing histological diagnosis and reducing mass effect, surgical resection effect on survival is minimal and difficult to evaluate due to ethical issues on randomization of non-surgical management or subtotal resection. One prospective study randomized biopsy or DS on 30 patients older than 65 years with radiologic evidence of malignant gliomas and found a modest survival benefit (2.9 months) on patients with tumour resection; however, this was a small and unblinded trial on patients with poor prognosis[40]. Stummer et al described that GB patients who underwent complete resection of contrast enhancing tumour under fluoroscopic guide with 5-aminolevulinic acid had a significantly higher PFS at six months (41%) than patients with less extensive resection done under

conventional white light microsurgery (21.1%)[41]. A follow up of the same study controlled different bias and variables and concluded a 4.9 months benefit of complete resection[42]. Several trials have reached the same conclusion and there is an established consensus that total resection improves OS[43,44]. As total resection is not always possible, it has been evaluated what is the minimal resection needed to have a benefit. Lacroix and colleagues studied the effect of Extent Of Resection (EOR) in patients with GB and concluded a longer survival in patients who had a resection of more than 98% of the tumour especially if age, KPS score and primary imaging features were favourable[45]; it became a paradigm in neurosurgery and clinical decisions were for long time based in that retrospective, non-randomized trial. Recently, 500 adults consecutively diagnosed with GB were evaluated to see the role of EOR on survival; a significant benefit was seen with as low as 78% and the benefit increased proportionally with the EOR31. This has been also proven in the elderly population with GB[46,47].

The benefit of surgery is related to better response to adjuvant therapies and does not come solely from the surgery; patients with complete resection and TMZ have significantly higher OS than incomplete resection plus TMZ[42]. Surgery is of paramount importance for treatment of GB since it allows histological diagnosis and decompression, has a modest benefit in OS that increases proportionally with the EOR and seems to improve the response to CT. New surgical technologies such as neuronavigation, intraoperative MRI, functional MRI, intra operative mapping, and fluorescence guided surgery are being used to improve safety and EOR[43,48].

RADIOTHERAPY

RT was firstly described as increasing the mean OS in a range from three to five months[49-51]. Laperriere et al conducted a systematic review and found a significant survival benefit favouring post-operative RT with a risk ratio of 0.81 (CI 95 % 0.74-0.88). No significant difference between whole brain and local radiation was found, and a modest benefit on survival on 60 Gy divided in 30 fractions over 45 Gy in 20 fractions was described[52]. No benefit from RT in patients older than 70 was found. Not much research has been done on the evaluation of RT in GB over the last ten years, and the evidence found comes from some works in elderly patients who are still thought no to benefit from RT or CT. A multi-institutional trial randomized 85 subjects with GB from 10 institutions to RT plus supportive care or supportive care alone and found that patients in the RT group lived three months longer[10]. Those results were recently reconfirmed by a large population based study which proved that an abbreviated course of RT with a total dose of 40 Gy in 15 fractions is as effective as the standard scheme[29]. It is now widely accepted that RT prolongs the survival of young patients with GB in three to five months and around two months in patients older than 70 years[10,53].

CHEMOTHERAPY

In 2002 the Glioma Meta-analysis Trialist (GMT) group published the results of a meta-analysis of 12 randomized trials that failed to prove CT useful in patients with GB[54]. However, the history of CT for GB hanged in 2005 when the European Organization for Research and Treatment of Cancer (EORTC) and the National Canada Institute of Cancer (NCIC) published a trial on 573 patients from 85 centres randomized to RT alone or RT plus concomitant and adjuvant TMZ for newly diagnosed GB. The median OS was 2.5 months longer in the group with RT plus TMZ, and the two-years survival of 26.5% on subjects with RT plus TMZ was significantly higher than 10.4% in the group with RT alone[55]. Those findings were complemented with the five year follow up of the same patients showing a sustained benefit of RT plus TMZ over time in all of the prognostic groups[30]. Furthermore, as pre-treatment prognostic factors can be more relevant to the outcome than the therapy, the EORTC study was recently tested with a recursive partitioning analysis; the overall prognostic significance was retained between the different recursive groups; and as expected, particularly strong in patients with favourable prognostic factors[56]. Nowadays, new treatments for GB are compared with postsurgical RT plus TMZ and new chemotherapeutic agents are evaluated in addition to that gold standard. Anaplastic oligodendroglioma was the first described malignant brain tumor to be uniquely chemo sensitive as PCV was demonstrated to be effective in those patients[57]. Later, CT with PCV and TMZ were shown to be equally valuable to improve the outcome, although TMZ showed a better safety profile[6,44,58].

Recently, the New Approaches to Brain Tumors Therapy (NABTT) consortium evaluated the addition of new chemotherapeutic agents to RT plus TMZ in patients with GB. The addition of talampanel, poly-ICLC or cilengetide to the standard treatment

increased the OS from 14.6 months as described in the EORTC study in 2006 to 19.6 months in the new agent added group[3]. The trial was designed as a four single-cohorts study with historical controls accrued internationally from 2000 to 2002 and not strong enough to support the addition of a novel agent to the standard treatment. However, it is significant that it shows how CT has contributed to improve the outcome of these patients. For instance patients treated with postsurgical RT in 2000 had a mean OS of 12 months and only 8% of them survived for more than two years[40]; while the mean OS of patients treated in 2010 with postsurgical RT plus TMZ plus a new chemotherapeutic agent was 19.6 months and 37% of them lived for more than two years[3]. Although part of that benefit must be due to improvement in general care of oncologic conditions; most of it can be reliably attributed to CT.

Research on surgery, RT and CT for GB in the elderly and in patients with low KPS is rapidly evolving. However, some patients are still found to have only biopsy and support care or RT alone. This allows an individual evaluation of each treatment modality. Patients with different kinds of treatments can be conveniently stratified and the predictive factors can be controlled to evaluate the independent effect of an intervention. As can be seen in Table 5, two retrospective trials on contemporary patients assessed the individual value of surgery, RT and CT and confirmed that all of them actively contributed to an improved outcome in patients with GB (Level of evidence 3b)[59,60]. It is evident that the population in the study by Marina et al had a worse prognosis, but the proportion of improvement was similar in both studies, showing again that surgery, RT and CT, each have a modest but significant effect in the outcome of adults with GB.

Table 5. Survival of patients with poor prognosis (elderly patients and/or low performance status) in two studies with treatment stratification.

Treatment stratification		59. Kushnir and Tzuk-Shina. 2011		60. Marina et al. 2011	
		n.	Mean OS	n.	Mean OS
All the patients		74	8.9 mo	74	2.3 mo (0.2-48 mo)
Surgical stratification	Biopsy/no surgery	32	5.22 mo	38	1.6 mo
	Debulking surgery	42	11.83 mo	36	5.8 mo
Radiation treatment	Partial or no RT	24	4.09 mo	22	1.6 mo
	RT	50	11.31 mo	52	5.2 mo
Chemotherapy stratification	No Chemotherapy	39	5.89 mo	54	1.7 mo
	chemotherapy	35	12.4 mo	20	9.8 mo

mo: months, n: number of patients, OS: overall survival, RT: Radiotherapy.

Conclusion

In the last three decades, the implementation of DS, RT and CT has prolonged the survival of patients with GB to 12-18 months. Although the outcome seems to be more related to predictive factors such as age, KPS and molecular profile of the tumor, each modality of treatment has shown to improve the outcome by itself. Surgery is determinant since it reduces the symptoms of increased intracranial pressure and mass effect and provides tissue for histologic and molecular analysis. Surgery provides a modest benefit of three months OS in the case of GB and as much as 4.9 months when complete resection is possible. RT has been found to increase the mean OS in a range from three to five months and has shown itself useful in the elderly population. Concomitant and adjuvant TMZ increases the OS by two-three months and some studies suggest a further two month increase in OS when a new chemotherapeutic agent is added to postsurgical radio-chemotherapy. Surgery, RT and CT, each have a modest effect in the outcome of adults with GB; nonetheless, when used together as the best available treatment, they considerably improve the outcome. Future research must focus on evaluation of molecular outcome predictors and development of targeted agents that can impact the natural history of the disease.

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