Glioblastoma and hypofractionated radiotherapy: A suitable option for vulnerable patients

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Abstract

Glioblastoma is the most common primary brain tumor. This disease is caracterised by poor diagnosis. The survival depends on multiples criteria as age and general conditions. The treatment is based on surgery or radiation therapy . For eldery patients or patient with low performance status « PS » <2, hypofractionated regimen was proposed. Two hypofractionated radiotherapy regimens were compared. The objective of the study is to analysize the efficiency of this therapeutic regimen. This study shows that hypofractionated treatment produces results in terms of global survival and progression-free survival, which are not statically significant compared with the normofractionated regimen. The hypofractionated regimen is a therapeutic alternative for patients not suitable for normofractionated treatment.

Keywords : Glioblastoma, Hypo fractionated regimen, overall survival, progression-free survival.

Introduction

Glioblastoma is the most common primary brain tumor. The median age of incidence is 65 years. Its prognosis is poor, with an average survival estimated at 9 to 15 months, which

depends on the patient's general condition, age, and certain molecular biology data. However, overall survival remains limited.

The objective of this study is to analyze the effectiveness of the hypofractionated regimen in subjects aged 65 years or older , or in cases of impaired performance status, that is, greater than or equal to 2, in order to extract guidelines to be applied in clinical routine.

Materials and methods

This study was carried out in the radiotherapy department of the national Institute of Cancer in Rabat,for the period between January 1st, 2023 and December 31th, 2023, over a period of one year, having included patients followed for glioblastoma treated by radiotherapy according to a hypofractionated regimen. Two protocols were proposed, either 40.05 Gy in 15 fractions or 25 Gy in 5 fractions. The external radiation therapy was delivred without chemotherapy. And were excluded patients treated for other brain tumors.

Results :

The primary endpoint of the study was overall survival, secondary endpoints were progression-free survival. In 2023, two hypofractionated radiotherapy regimens were compared in elderly people or those with low PS. Inclusion criteria were age greater than 65 years or performance status greater than or equal to 2. Patients were assigned to two groups during the study, one group receiving radiotherapy at a dose of 40.05 Gy in 15 fractions of 2.67 Gy per fraction, five fractions per week, and one group receiving radiotherapy with a total dose of 25 Gy in 5 fractions of 5 Gy, five fractions per week.

The number of patients included in the study was 13 patients, who were put on a hypofractionated regimen against 42 on a normofractionated regimen and with concomitant chemotherapy +/- adjuvant. 58% of patients were over 65 years. As for general condition, 63 % of patients had a low performance status less than 2, highlighted in table 1.

A total of 13 patients were included in the study. Ten patients received 40.05 Gy in 15 fractions, compared to 3 with the 25 Gy in 5 fractions protocol.

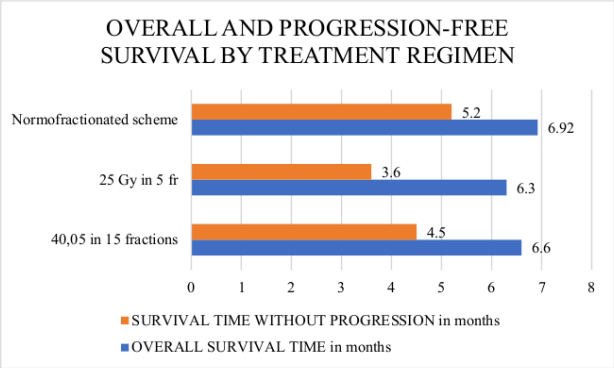
The study finds that the median overall survival time was 6.6 months (95% CI: 6.58; 6.62) for patients who received 40.05 Gy in 15 fractions versus 6.3 months(95% CI: 6.27; 6.32) for

patients who received 25 Gy in 5 fractions without statistically significant difference (p = 0.93). Progression-free survival times were 4.5 and 3.6 months, respectively, with no statistically significant difference (p = 0.68), and no significant difference between the different sub-groups according to performance status. On the other hand, for patients who received the normo-fractionated regimen with associated chemotherapy, the median overall survival time was 6.92 months and for progression-free survival 5.2 months with a statistically significant difference (p= 0.011), highlighted in table 2.

Table1 : Characteristics of study patients

Age	
More than 65 years old	58%
Less than 65 years old	42%
Gender	
Male	68%
Female	32%
Status Performance	
<2	63%
>2	37%
Regimen	
Hypo fractionated 40.05 Gy in 15 fractions	10
Hypo fractionated 25 Gy in 5 fractions	3
Concomitant Chemotherapy	None

Table 2: Overall survive and progression-free survival by regimen of radiation therapy normo and hypo fractionated



Discussion

In elderly patients, tolerance of high doses of radiotherapy and chemotherapy may be decreased compared to younger patients [1]. Hypofractionated radiotherapy has benefits due to the speed of its effect [2,3]. Due to the reduction in the number of sessions, travel constraints are reduced, which can be a factor in quality of life for patients. However, moderately hypofractionated radiotherapy may increase late radiotherapy toxicity, related to the increase in dose per fraction [4,5]. Indeed, a study carried out in 2004 by Roa and al., compared hypofractionated radiotherapy with normofractionated radiotherapy [6]. The primary objective was overall survival. Secondary objectives were the proportion of patients alive at 6 months, quality of life, and the need for corticosteroid therapy. Inclusion criteria were patients over 60 years old, with a Karnofsky index of more than 50% ; the index karnosky index highlighted in (table 3) and comparison with ECOG performance status highlighted in (table 4).

Table 3 : Karnosky Performance status [7]

KARNOFSKY PERFORMANCE STATUS SCALE
KPS scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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Comparing the ECOG Performance Status and the Karnofsky Performance Status Scales

The ECOG Performance Status Scale and the Karnofsky Performance Status Scale are two widely used methods to assess the functional status of a patient. Both scales are in the public domain to classify a patient according to their functional impairment, compare the effectiveness of therapies, and assess the prognosis of a patient. The Karnofsky index, between 100 and 0, was introduced in a textbook in 1949. Key elements of the ECOG scale first appeared in the medical literature in 1960.

There are several ways to map the two scales. The table below displays one commonly used comparison.

Table 4 : The table below displays one commonly used comparison. [8]

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

Patients received either normofractionated radiotherapy of 60 Gy in 30 fractions of 2 Gy, or hypofractionated radiotherapy at a dose of 40.05 Gy in 15 fractions of 2.67 Gy ; five fractions per week for both groups. The results found that among the 100 patients included in the study, overall survival was 5.1 months after standard radiotherapy, compared to 5.6 months after hypofractionated radiotherapy, with no significant difference between the two groups (p = 0.57).

Regarding secondary endpoints, there was no significant difference in 6-month survival or quality of life. However, the hypofractionated radiotherapy group had a lower requirement for corticosteroids (p = 0.02). In 2017, a study compared two hypofractionated radiotherapy regimens in people aged over 65 years [9]. The analysis was performed post-hoc by intention to treat data from a phase III trial of the International Atomic Energy Agency (IAEA), a multicenter, international, randomized, prospective, non-inferiority trial [10]. Note that post hoc analysis refers to an unplanned analysis initially carried out after the data has been exploited without having been planned in advance. Inclusion criteria were age over 65 years and a Karnofsky index of over 50%. Patients were assigned to two groups during the IAEA study : one group received radiotherapy of 40.05 Gy in 15 fractions of 2.67 Gy, five fractions per week, and the other group received a dose of 25 Gy in five fractions of 5 Gy, five fractions per week, for one week of treatment. The primary endpoint of the study was overall survival ; secondary endpoints were progression-free survival, quality of life, and toxicity. Finally, the study by Perry et al., in 2017, compared in a phase III trial hypofractionated radiotherapy and hypofractionated radiotherapy associated with temozolomide in a concomitant then adjuvant situation in people aged over 65 years in a preserved general condition [11]. Patients were randomized between exclusive radiotherapy of 40.05 Gy divided into 15 fractions, five fractions per week, and chemoradiotherapy which consisted of radiotherapy according to the same modalities as the first group, associated with concomitant chemotherapy with temozolomide at a dose of 75 mg/m2/day then 12 cycles of temozolomide in the adjuvant setting at a dose of 150–200 mg/m2. The primary endpoint was overall survival, secondary endpoints were progression-free survival, safety, and quality of life. Both overall survival and progression-free survival were longer for patients after chemoradiotherapy than after exclusive radiotherapy, 9.3 months versus 7.6 months ($p < 0.001$), and 5.3 months versus 3.9 months ($p < 0.001$). The results were therefore statistically significant, favoring the group receiving radiochemotherapy with a hypofractionated protocol compared to the group receiving exclusive hypofractionated radiotherapy. In our study, patients received

hypofractionated radiotherapy treatment without concomitant or adjuvant chemotherapy. The median overall survival time was 6.6 months for patients who received 40.05 Gy in 15 fractions and 6.3 months for patients who received 25 Gy in 5 fractions,without statistically significant difference in probability of survival at 6 months (p = 0.93). Progression-free survival times were 4.5 and 3.6 months, respectively, with no statistically significant difference (p = 0.68). As for the normofractionated regimen associated with chemotherapy, the median overall survival time was 6.92 months and for progression-free survival 5.2 months with a statistically significant difference (p= 0.011).

Our study thus presents similar results to those of the literature regarding the choice of the hypofractionated regimen, and the interest of the association of chemotherapy.

Conclusion

Hypofractionated radiotherapy may be offered to patients over 65 years or with low general condition as a therapeutic strategy in patients who can not receive long-term treatment or combination chemotherapy. In our study, both hypofractionated treatment regimens reported non-statically significant results between them, but with a significant difference compared to the normofractionated regimen which was associated with concomitant and adjuvant chemotherapy. This leaves the practicing physician the choice of the most appropriate hypofractionated protocol for the patient for a gain in survival and quality of life. However, this study opens the discussion on the crucial place of chemotherapy and the possibility of its inclusion even in vulnerable patients.

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