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ORIGINAL ARTICLE

Pathways of follow-up care in an Italian center: retrospective study on patients with gliomas II and III

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Abstract

Introduction Glioma is the most common primary brain cancer in adults. Long-term and progression-free survivals are dependent on the type and grade of glioma, as well as on the extent of resection and postoperative treatments. In Italy, it is unclear how long follow-up care should last and whether the primary care sector is either willing or able to take this on. The aim is to determine pathways of follow-up care and evaluate the professional attitude of doctors to prescribe to patient visits and exams after surgery.

Methods A retrospective study was performed on patients with glioma II and III who underwent surgery at tertiary care Neurological Institute Besta of Milan (FINCB) from 2012 to 2020. Data were collected through electronic medical records and inserted in an ad hoc developed database.

Results Three pathways have been identified: a common preliminary pathway (from the pre-operative visit to surgery) for all patients undergoing surgery for gliomas II and III and two follow-up pathways (with or without second surgery).

Conclusions FINCB has developed care pathways that are sometimes personalized according to the doctor's expertise and attitude to prescribe new examinations. Given the lack of guidelines on this issue, we can cautiously conclude that it is necessary to identify whether, in addition to standard care, personalized supportive care intervention and pathway plan can significantly improve patients' outcome.

Keywords Brain tumors · Checkup · Care pathways · Follow-up

Introduction

Glioma is the most frequent malignant primary brain tumor (BT). Overall age-adjusted incidence rates for all gliomas range from 4.67 to 5.73 per 100,000 persons. Incidence of glioblastoma (WHO grade IV), the most common and malignant glioma in adults, ranges from 0.59 to 3.69 per 100,000 persons [9]. Survival varies significantly by grade across glioma subtypes. The 2016 WHO BT classification introduced new criteria to incorporate traditional histopathology and molecular signatures into an integrated diagnosis. These recent developments have led to the new term "lower-grade glioma" (LLG) to designate both grades II and III gliomas.

LGGs are slow-growing, infiltrative primary BT typically affecting younger adults with a peak age of 34 years. The most common histological subtypes of LGG include astrocytoma and oligodendrogliomas, and the last has increased survival, as opposed to the astrocytic variant [10]. The most common symptoms are frequent seizures and cognitive deficits resulting in a negative impact on quality of life [21].

Gliomas are best treated with a multidisciplinary team approach, including specialists from neurosurgery, radiology, pathology, radiation oncology, and neuro-oncology. Usually, maximal safe surgical resection is the first treatment proposed to glioma patients, obtaining tissue for diagnosis, reducing masse effect, and improving both quality of life and survival [19].

Radiation therapy is one option for treatment of patients with LGG beyond chemotherapy, but surgery remains the primary treatment for LGG. When LGGs recur, they may either be the original tumor/grade or they may also undergo

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malignant transformation into high-grade tumors. Treatment options at the time of recurrence can include further surgery, radiation therapy and/or chemotherapy, or clinical trials [20].

The post-surgical management of LGG is based on the distinction of low-risk and high-risk patients. Low-risk patients are defined by age less than 40 years and total resection. These patients should be followed with MRI without treatment. However, adjuvant treatments are predominantly suggested even if a watchful waiting can be an option for younger patients [23]. The high-risk patients, astrocytoma IDH non-mutant, anaplastic astrocytoma, and anaplastic oligodendroglioma need more aggressive therapy consisting of a combination of radiotherapy and chemotherapy [17].

The role of postoperative rehabilitation in adult with BT patients has been investigated in few studies [4-11]. However, given the positive impact of rehabilitation interventions on functional outcome and patients' quality of life, there is an increasing consensus about the need to improve strategies for physical and cognitive disability management in BT patients [15].

After surgical and adjuvant treatments, the patients will have regular checkups. Follow-up care differs depending on the type of cancer and treatment, the side effects experienced, and any other health conditions.

The frequency of clinical and neuroimaging follow-up changes in the different subgroups of patients according to their recurrence risk. There is no simple answer to the question of how long follow-up care should last. Patients are usually monitored regularly for about 5 years. After that, if there is no tumor recurrence or new side effects there should be a discussion about whether the person with the tumor can be discharged or whether the schedule of regular but infrequent follow-up should be maintained [8]. In general, it is likely that general practitioners will take on more responsibility for routine follow-up for this population of patients, but it is unclear whether the primary care sector is either willing or able to take this in Italy.

Moreover, it is not clear how much the follow-up pathways affect regional health expenditure because catchment areas for neuroscience centers and oncology/radiotherapy centers often do not coincide [3]. There is need to efficiently use the health care system limiting costs of health care systems and patients [1].

To explore this issue more, we conducted a 9-year retrospective observational study of patients with glioma II and III who underwent surgery at Neurological Institute Besta of Milan (FINCB) from 2012 to 2020 to identify pathways of follow-up care and evaluate the attitude of the different doctors to prescribe follow-up visits and exams. This study is part of the research project "Controlli periodici (follow-up) dopo la diagnosi e le terapie in pazienti liberi da malattia e asintomatici: verso una personalizzazione delle strategie di follow-up," supported by a grant of Lombardy Region 2019–2021.

Material and methods

Data collection

The inclusion criteria of the study were as follows: (1) age ≥ 18 at the time of diagnosis; (2) resident in Lombardy (Northern-Western Region of Italy; (3) pathologic diagnosis of WHO grade II and III glioma; (4) patients subjected to surgery at FINCB between January 2012 and December 2017; (5) 3-year follow-up pathways, i.e., until March 2020. The Cancer Registry of FINCB has been the source of the data analyzed for this study.

Data of each patient were collected through electronic medical records and inserted in an ad hoc developed database. The database is composed by three sections: information on demographics data of patient (name, surname, gender, date of birth, status alive or dead, etc.); information about patient's clinical data (symptoms, diagnostic exams, neurosurgery, visits, treatments, etc.) and information on presence of recurrence BT (exams, visits, surgery, treatments, etc.). Recurrence was defined as presence of radiological recurrence or progression and was treated with a second surgery. Gross total resection was defined as complete tumor removal, sub-total as > 90% tumor removal, and partial as < 90% tumor removal.

Descriptive statistics were used to report the features of the sample and the different pathways of follow-up.

Results

The sample included 153 patients with a history of gliomas II and III (70 patients glioma II and 83 patients glioma III), 94 males and 59 females with mean age of 46 years (age range = 18–78 years).

In March 2020, 115 patients were alive (61 patients with glioma II and 52 patients with glioma III). Of them 16 patients have had a recurrence BT in the period that we analyzed (7 patients with glioma II and 9 patients with glioma III). For details on the vital status of the patients with gliomas II and III, see Tables 1 and 2.

We can identify from the collected data a common pre-surgery pathway (from pre-operative visit to surgery) for all patients undergoing surgery for gliomas I and II.

Unfortunately, we are not aware whether any patients had surveillance before pre-operative visit.

In addition, we identified different follow-up pathways: pathways for glioma II and III patients after the first surgery

Table 1 Vital status of the patients with glioma II

	N	%	Average duration of illness (from first surgery)	Range (min.–max)
Total alive in March 2020	61	87		
Patients after second surgery for radiological progression or recurrence	7	10		
Patients after first surgery	54	77.1		
Total deaths in March 2020	9	12.8		
Patients after second surgery for radiological progression or recurrence	3	4.2	1 year	11 months to 2 years
Patients after first surgery	6	8.5	1 year	11 months to 2 years

Table 2 Vital status of the patients with glioma III

	N	%	Average overall survival (from first surgery)	Range (min.–max)
Total alive in March 2020	54	65		
Patients after second surgery for radiological progression or recurrence	11	13.2		
Patients after first surgery	43	51.8		
Total deaths in March 2020	29	35		
Patients after second surgery for radiological progression or recurrence	5	6	2 years	1 year to 5 years
Patients after first surgery	24	28.9	1 year	1 month to 5 years

and pathways for glioma patients after the second surgery for radiological progression or recurrence.

Pre-surgery pathway for glioma patients (from pre-operative visit to surgery)

A total of 153 patients with gliomas II and III have carried out a pre-operative visit before surgery following a first evaluation with Besta or outside Besta professionals. Thirty-nine patients were coming from visits performed in the outpatient services of FINCB while 94 patients were sent by external doctors who had recommended the neurosurgery at FINCB after a first visit.

After the pre-operative visit, 153 patients with glioma II and III were operated at FINCB receiving total, sub-total, partial, or biopsy removal of glioma.

Follow-up pathways for glioma patients

After neurosurgery all the 153 patients started the follow-up pathway. For this study we analyzed their care pathways for the duration of 3 years. We divided the population and the respective follow-up strategies in 4 groups based on the WHO grade and the number of surgical treatments:

1. Glioma II patients after first surgery.
2. Glioma III patients after first surgery.
3. Glioma II patients after second surgery for radiological progression or recurrence.
4. Glioma III patients after second surgery for radiological progression or recurrence.

Glioma II patients after first surgery

For the 70 glioma II patients after first surgery, the follow-up pathway provides on average 3 visits per year with specialists of FINCB, i.e., every 4 months (range min. 3 months and max. 5 months) and 2 diagnostic exams per year at the FINCB, i.e., every 5 months (range min. 3 months and max. 7 months). This sample is composed by 29 females and 41 males with mean age of 44 years.

The follow-up pathway for visits and exams has been followed by 54 patients because 16 patients both without and with recurrence or progression died during the pathway. For details see, Table 3.

Glioma III patients after first surgery

This sample is composed by 30 females and 53 males with mean age of 48 years. The follow-up pathway provides on

Table 3 Follow-up pathway of patients operated of glioma II after first surgery at FINCB

Follow-up pathways—visits	N. pz	Average months	Range (min.–max)
From surgery to first visit	70	4	2 months to 14 months
Second visit	70	4	2 months to 36 months
Three visit	60	4	2 months to 19 months
Four visit	60	4	2 months to 23 months
Five visit	60	4	2 months to 20 months
Six visit	54	4	2 months to 9 months
Seven visit	54	3	3 months to 10 months
Eight visit	54	4	5 months to 12 months
Follow-up pathways—exams	N. pz	Average months	Range (min.-max)
From surgery to first visit	70	6	2 months to 26 months
Second visit	70	7	2 months to 34 months
Three visit	60	6	2 months to 36 months
Four visit	60	6	3 months to 36 months
Five visit	60	5	4 months to 12 months
Six visit	54	3	4 months to 6 months
Seven visit	54	4	3 months to 12 months
Eight visit	54	4	4 months to 10 months

average 4 visits per year with specialists of FINCB, i.e., every 3 months (range min. 1 months and max. 23 months) and 2 diagnostic exams per year at the FINCB, i.e., every 5 months (range min. 1 months and max. 22 months).

The follow-up pathway for visits has been followed by 36 patients of which 26 patients died during the pathway and 21 patients had a second surgery for radiological progression or recurrence and they were analyzed with patients undergoing second surgery. The follow-up pathway for exams has been followed by 52 patients of which 19 patients died during the pathway and 12 patients had a second surgery for radiological progression or recurrence and they were analyzed with patients undergoing second surgery. For details, see Table 4.

Table 4 Follow-up pathway of patients operated of glioma III after first surgery at FINCB

Follow-up pathways—visits	N. pz	Average months	Range (min–max)
From surgery to first visit	83	4	min. 3 months, max 9 months
Second visit	76	4	min. 1 months, max 28 months
Three visit	67	3	min. 1 months, max 29 months
Four visit	61	5	min 1 months, max 36 months
Five visit	55	3	min 1 months, max 16 months
Six visi	53	3	min 1 months, max 20 months
Seven visit	52	3	min 1 months, max 20 months
Eight visit	47	3	min 1 months, max 15 months
Nine visit	47	3	min 1 months, max 15 months
Ten visit	36	5	min 1 months, max 40 months
Follow-up pathways—exams	N. pz	Average months	Range (min.–max.)
From surgery to first visit	83	6	3 months to 20 months
Second visit	76	6	3 months to 20 months
Three visit	67	5	1 months to 37 months
Four visit	61	4	1 months to 14 months
Five visit	55	5	1 months to 17 months
Six visi	53	8	1 months to 37 months
Seven visit	52	5	1 months to 15 months

Follow-up pathways for glioma patients after second surgery

Glioma II patients after second surgery for radiological progression or recurrence

The follow-up process included 9 patients with glioma II undergoing a second surgery since 1 patient undergoing only chemotherapy and was not included in the analyses. We analyzed their pathways for the duration of 3 years.

For the patients with glioma II undergoing second surgery, the follow-up pathway provides on average 4 visits per year with specialists of FINCB, i.e., every 3 months (range min. 3 months and max. 4 months) and 3 exams per year at the FINCB, i.e., every 4 months (range min. 2 months and max. 7 months). For details on the follow-up pathways, see Table 5.

Glioma III patients after second surgery for clinical or radiological progression

The follow-up process for patients after second surgery for radiological progression or recurrence included the 16 glioma III.

Among these, 13 patients received a second surgery, 3 patients underwent only chemotherapy and radiotherapy and were not included in the analyses. For this study we analyzed their pathways for the duration of 3 years.

The follow-up pathway provides on average 6 visits per year with specialists of FINCB, i.e., every 2 months (range min. 1 months and max. 7 months) and 3 diagnostic exams per year at the FINCB, i.e., every 4 months (range min. 2 months and max. 9 months). For details, see Table 6.

Table 5 Follow-up pathway of glioma II patients after second surgery for radiological progression or recurrence at FINCB

Follow-up pathways—visits	N. pz	Average months	Range (min–max)
From second surgery to first visit	7	3	3 months to 6 months
Second visit	7	3	2 months to 7 months
Third visit	7	4	3 months to 8 months
Follow-up pathways—exams	N. pz	Average months	Range (min–max)
From second surgery to first exam	7	2	2 months to 8 months
Second exam	7	7	3 months to 18 months
Third exam	7	3	1 month to 5 months

Table 6 Pathway follow-up of patients after second surgery for radiological progression or recurrence at FINCB

Follow-up pathways—visits	N. pz	Average months	Range (min–max)
From second surgery to first visit	13	2	1 month to 15 months
Second visit	13	1	1 month to 4 months
Third visit	13	2	2 months to 4 months
Four visit	13	1	1 month to 3 months
Five visit	9	4	1 month to 7 months
Six visit	9	4	2 months to 8 months
Seven visit	9	1	1 month to 4 months
Eight visit	9	2	1 month to 15 months
Nine visit	9	2	1 month to 3 months
Ten visit	9	5	1 month to 9 months
Follow-up pathways—exams	N. pz	Average months	Range (min–max)
From second surgery to first exam	13	3	1 month to 10 months
Second exam	13	4	1 month to 8 months
Third exam	9	5	2 months to 9 months
Four exam	9	5	1 month to 14 months
Five exam	9	5	2 months to 9 months
Six exam	9	4	5 months to 7 months

Discussion

The aim of this study was to determine the follow-up care pathways for patients with gliomas II and III followed by the Neurooncology Department of FINCB. We identified a pre-surgery pathway for glioma patients after first surgery or after second surgery for radiological progression or recurrence (from pre-operative visit to surgery) and different follow-up pathways: pathways for glioma II and III patients after first surgery and pathways for glioma patients after second surgery.

For pathways for glioma II and III patients after first surgery, our study highlighted different frequencies in regular checkups between glioma II patients and glioma III patients.

This result is similar to the National Institute for Health and Care Excellence (NICE) guideline that found possible regular clinical review schedule for people with glioma.

According to NICE guidelines, in 2 years, the patients perform visits and exams from minimum every 3 months to max. every 6 months and then annually [8].

Conversely, Canadian Cancer Society describes follow-up visits for general brain cancer every 6 to 12 months for the first 5 years for low-grade tumors and then every 1 to 2 years. The chance that a brain cancer will come back is greater within 5 years, so you need close follow-up during this time [22].

For pathways for glioma patients after second surgery for radiological progression or recurrence, our study highlighted an intensive regular checkups.

The most effective follow-up protocol (including duration, frequency, and type of examinations) to detect recurrence after treatment for glioma is not well known.

Several guidelines suggest 3-month intervals for MRI and follow-up visits in most patients, but also longer intervals could be considered appropriate in cases of less aggressive tumors. The European Association for Neuro-Oncology (EANO) and the Italian Association of Neuro-oncology (AINO) guidelines provide recommendations for adult patients' clinical care with gliomas [14-18].

Despite this practice, there is controversy about how often patients should be evaluated, what tests should be performed, and whether these more or less intensive strategies have any significant impact on patient outcomes.

Some neuro-oncologists prefer flexible follow-up based on their clinical experience; they recommended that personalized follow-up might be useful to detect recurrence, based on changes in the person's symptoms and function. This may improve a person's quality of life by alleviating symptoms and developing adaptive strategies. However, the frequent routine imaging (and waiting for the result) may cause anxiety.

New or changing symptoms likely could mean that the tumor has been modified in extension or amount of edema, and therefore waiting until the next routine scan could limit treatment options.

However, a seizure in a patient with a well-known history of epilepsy does not require a scanning or clinical assessment examination. Again, the increase or diminution of steroids treatment does not require an MRI or CT as routine.

If routine imaging is recommended, the type (conventional vs advanced MRI techniques), frequency, and duration of scanning would be given according to different subtypes of gliomas emerging from the new BT classification [8].

A glioma patient IDH mutated and 1p-19q co-deleted usually could have a longer.

Progression-free survival (PFS) and overall survival (OS) in comparison of an IDHwt non co-deleted tumor patient. For this, also the schedule of follow-up could be accordingly adequate.

As no research literature exists which establishes the effectiveness of a specific healthcare intervention, uncertainty exists about the most appropriate intervention to define a standard and an effective follow-up pathway [8].

Four limitations of this retrospective observational study need to be acknowledged. First, as our study followed a protocol, we have identified patients who underwent surgery between 2012 and 2017 and we analyzed the follow-up pathways only for 3 years. This has significantly narrowed the sample and the course of the follow-up pathways. Second, we have considered only LGG and this did not allow us to analyze the follow-up pathways in depth. Third, our registry is not collecting any data on visits and exams performed by patients in other institutions in between or in parallel to our own follow-ups. Four, due to the relatively small amount of clinical sample referenced in this study, there is a lack of multi-center external data verification to support the clinical significance stratified follow-up model.

Conclusions

This retrospective observational study reports the pre-surgery and the follow-up care pathways for patients with glioma II and III at FINCB. Three pathways have been identified: a common preliminary pathway (from the pre-operative visit to surgery) for all patients undergoing surgery for gliomas II and III and two follow-up pathways (with or without second surgery). The care pathways developed at FINCB are sometimes personalized according to the doctor's expertise and aptitude to prescribe new examinations due to the paucity of univocal multidisciplinary organizational models for BT management.

Keeping in mind the retrospective observational study performed and the lack of guidelines on this issue, we can

cautiously conclude that it is necessary to identify whether, in addition to standard care, personalized supportive care intervention and pathway plan can significantly improve patients' outcome. This would imply that there is not a pathway fitting all and this has costs and consequences on health care system organizations that should be considered. However, if personalized care provides better quality of life and increased survival to BT patients, a more careful analysis of risks and benefits is worthwhile doing.

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Author contribution Fabiola Silvaggi and Matilde Leonardi developed the idea for the study. Fabiola Silvaggi analyzed the data. Fabiola Silvaggi drafted the manuscript. Matilde Leonardi, Antonio Silvani, and Elena Lamperti revised critically for important intellectual content and approved the manuscript.

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Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Ethical approval Ethical approval was not requested in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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