NEC 32.2 (Vogelbaum) Glioblastoma, Part I: Surgical Management and Adjuncts

Surgery For Glioblastoma in Elderly Patients.

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Key Points

- The incidence of GBM increases with age, with highest rate in the population between 75 and 84 years old. Given the increased life expectancy, elderly patients represent up to 25% of patients with GBM.
- Age alone is not a predictor of survival in GBM. General condition and performance status strongly influence and guide therapy.
- In this age-group, the biological age is more relevant than the chronological one.
- Surgery aimed at the maximal safe resection, when feasible, followed by adjuvant therapy according to MGMT methylation might be the first therapeutic option.

- Future clinical trials focusing on GBMs in the elderly subjects could provide more specific data for patient's selection.

Synopsis

Management of GBM in the elderly population represents a field of growing interest due a longer life expectancy. In this age-group, more than in the young adult, biological age is much more important than chronological one. The date of birth should not exclude *a priori* access of treatments. Maximal safe resection is proved to be the first option when performance status and general health is good. Adjuvant therapy and decision about management of recurrence should be choose in a multidisciplinary group according to performance of the patients and MGMT methylation.

Introduction and Background

Glioblastoma (GBM) is the most common primary malignant tumor of the Central Nervous System (CNS), accounting for 48.3% of primary malignant brain tumors and 57.3% of all gliomas. The incidence of GBMs increases with age. The highest rate is recorded in the population between 75 and 84 years old; the disease is two times more frequent in this age range than in the population aged between 55 and 64 years[1].

Despite advances in surgery and adjuvant treatments, the prognosis remains poor, with a median overall survival of fewer than 18 months in the adult population. An analysis conducted on more than 88000 patients with GBM treated between 2004 and 2013 reports a mild increase in the number of patients surviving three years after the initial diagnosis[2].

The definition of "*elderly*" is controversial. The elderly age starts at 65 years old, according to the World Health Organization (WHO); as for GBM patients, the National Comprehensive Cancer Network sets the age to consider a patient into the "elderly category" at 70 years[3,4] . The *real-life* evidence shows that subjects up to 70 years may still have an active social and intellectual life. Especially in HICs (high-incoming countries), a longer life expectancy is recorded than in the past and or in comparison with LMICs (low and middle-incoming countries). In this age range, the *physiological* age is becoming more relevant than the date of birth to shape the indication and intention to treat.

Age is a negative prognostic factor, and every year of increase in age is associated with a statistically significant decrease in survival in GBM patients[4–6].

Having this being premised, it is thus mandatory to review the best (current) management of GBMs in the elderly population, since life expectancy (i.e., adding *years to life*) is growing throughout the world (in Italy life expectancy in 2017 was 83,2 years according to WHO) and elderly patients represent up to 25% of patients with GBM. In addition, numbers are expected to double in the next two decades[7,8].

The management of GBMs is currently multidisciplinary. A balance among available options, such as surgery, chemotherapy, radiation therapy, and experimental approaches, is essential to grant the best feasible outcome and preserve the Quality of Life (i.e., adding *life to years, QoL*)[9]. The scope of this review is to report and discuss the state-of-the-art of surgical and adjuvant treatment in elderly patients affected by GBMs.

Current Evidence

Histomolecular features

Phenotypical differences across age ranges are only partially explained by differences in known molecular features, such as IDH mutational status, O^6-methylguanine-DNA methyl-transferase (MGMT) methylation, and TP53 mutation. IDH mutation, the most important positive prognostic factor in gliomas, is differently expressed in GBM between adult and elderly: IDH1/2 mutations are rarely present in adult GBM and virtually missing in the elderly[10–12]. Although the physiological methylation of cells of the CNS decreases with age, the results of the NOA-08 trial revealed that age does not affect the MGMT promoter methylation frequency. The expression of vascular endothelial growth factor (VEGF) increases in patients older than 55 years old with recurrent GBM[13]. Moreover, TP53 mutation and CDKN1A/p16 alteration are negative markers in patients older than 70 years, conversely than younger subjects[11,14].

Prognostic Factors

The first study about prognostic factors employing the recursive partitioning analysis (RPA) was conducted on data collected in the 70s and 80s, therefore in the pre-Temozolomide (TMZ) era[15]. With a plethora of variables, the authors identified six different classes of risk based on pre- (age, race, gender, KPS, neurological examination, comorbidity, tumor location and size) and post-operative (Histology, EOR, adjuvant therapies) variables, correlating risk classes with oncological outcome. Further updates were released in the following

years, with fewer prognostic classes (cit.). In the latest edition, the extent of resection and the MGTM promoter methylation were reported as the most relevant prognostic factors for survival in the elderly subjects[14,16–20].

Along with the previous factors, in elderly a special emphasis should be given to performance status and to general condition as variables strongly influencing and guiding therapies. In this context, the process of selection of those patients who could benefit from treatments, especially surgery, remains a crucial issue. Physiological assessment taking in to account organ function and associated comorbidities, may better predict patient health status than chronological age itself [21]. Elderly patients are not identical and age per se is not a synonymous of frail, that, instead, concerns much more with the physical status of the individual patient. Frailty is generally defined as an unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity[22]. In the elderly patient assessment, surgeons and neuro-oncologists along with the individual patient and family interview, are helped in the decision-making process by the use of scales or questionnaires of evaluation aimed at a more personalized approach[11,23–26]. In addition to the well-known KPS, various scale of fraility have been proposed, , such as the IDAL questionnaire, that assess the ability and motivation to use the phone, to go shopping, or food preparation, to do household work, to take medication, or to use transportation or to handle finances; other are the Oncodage G8 questionnaire, the MMSE or the Chalson Comorbidity Index (CCI) [11,27,28].

Surgery

Maximum safe resection is an important prognostic factor in all GBM patients[29,30]. Surgery aims at impacting on the Progression-Free Survival (PFS) and on the Overall Survival (OS) as well as to fulfill other relevant goals such as histological and molecular diagnosis, the relief of the mass effect, the improvement of the neurological status and the reduction of the use of steroids.

Extent of resection is also a prognostic factor for survival in elderly patients.. A recent prospective study conducted on 1452 elderly patients, showed that the craniotomy for tumor resection was a feasible and safe procedure[31]. A pioneering randomized trial analyzed the differential outcome of a group of elderly patients undergoing either surgical resection or biopsy: data showed an improvement in survival of 3 months for the group undergoing resection[32]. Although the difference in survival was small, the randomization design

made this study a milestone in the field. A later retrospective case-control study demonstrated a gain of 40% in survival in the resection group (OS 5.7 months vs 4.0 months) compared to the biopsy group[33]. Further retrospective studies confirmed these initial findings in primary GBMs[18,34–39]. A wide metanalysis included a large group of more than 12000 patients older than 60 years, from 34 studies[35]. Patients who underwent to Gross Total Resection (GTR) experienced a gain in OS of 7.05 months on the average, a better functional recovery, a longer PFS, and comparable mortality and morbidity compared to those submitted to biopsy only. A further mono-institutional retrospective study evaluated the outcome and its associated prognostic factors in 178 elderly subjects, treated from 2004 to 2015. The results confirmed that the elderly population submitted to resection have a statistically significant increase in survival when the complete resection of the contrast-enhancement tumor was achieved, with a 2-years-OS three times longer than that recorded in patients submitted to biopsy alone[40].

Further studies introduced the concept of EOR thresholds stratification, and assessed the association between the achieved threshold and the outcome: Oszwald showed that a significant increase in survival was observed when the residual volume (RTV) was less than 5%, Pessina et al less than 2 cm^3, as absolute value[40,41]. Multiples tools are described to increase EOR: intraoperative fluorescence surgery has been recently approved by FDA in USA and it is widely available in neuro-oncological centers. Efficacy on OS of 5-ALA in GBM surgery was first proved with a randomized prospective phase III trial[42]. Despite its widespread use, there are no study in literature focused only on elderly patients[43,44].

When resection is pushed toward maximal level, the issue of preserving patient integrity is becoming crucial. The use of mapping and monitoring techniques is helpful. There is no dedicated report on the feasibility and safety of awake surgery in the elderly patients; Generally, age is not considered an absolute contraindication for an awake anesthesia, although a a strict and careful patient's selection is strongly advised.

Regarding patients' selection, a low pre-operative Karnofsky Performance Status (KPS), a tumor bigger than 4cm and the existence of pre-operative deficits (motor, language) have been found to factors negatively influence surgical outcome[40,45]; in particular, the functional status evaluation (KPS), regarding elderly, is the most important prognostic factor and thus represent an essential selection

criteria[17,18,40,46]. Tab.1 describe the principal studies that investigated oncological outcome of elderly patients after the introduction of Temozolamide (TMZ) in clinical routine; work that compared outcome of biopsy and resection were included.

In patients where stereotaxic biopsy is not feasible due to high risk of complications, advanced MR (perfusion and/or spectroscopy study) or metabolic imaging (11-C-Methionine PET, FET-PET) are recommended[47].

In the pre-operative stage, it is also important to exclude potential differential diagnosis. To perform a Total Body CT scan with the iodine-contrast agent is advisable to rule out a possible metastatic origin of the brain lesion, or to carefully look at DWI images to exclude infection.

Lastly, surgery (resection or biopsy) has also the goal of providing adequate tissue for complete histo-molecular characterization, considering that the assessment of the MGMT methylation status is incorporated in the clinical routine[16,17,48] due to its relevant prognostic predictivity, in first-line treatments and potential newer therapeutic regimes[49].

Adjuvant Treatments

Several studies support the role of adjuvant treatments in elderly. If evidence about surgery has been available since the early 90s, data about the safety and efficacy of post-surgical RT in the elderly were published in 2007. The French database (ANOCEF) showed that Radiotherapy (50Gy in 1.8Gy fractions) is superior to the best supportive care in elderly patients with a KPS>/= 70, since it led to an OS of 29.1 vs 16.9 weeks and a PFS of 14.9 vs 5.4 weeks[50]. Initially, the use of hypo-fractionated protocol was reserved to patients with unfavorable prognostic factors defined by age or performance status[51] to minimize the radiation time exposure. The Canadian Phase II trial and NORDIC phase III randomized trial demonstrated that a hypo-fractionated regimen is preferable in most cases, both for oncological and functional reasons. The hypo-fractionated schedule is nowadays the *standard* therapy in patients with unmethylated MGMT promoter. The NORDIC trial showed in patients older than 70y a survival of 7.0 months when the hypo-fractionated protocol was applied and in of 5.2 months when the standard (60 gy in 2Gy fractions over 6 weeks) RT was used[16].

The NOA-08 trial confirmed these findings, comparing two arms of treatment: RT (60Gy in 30 Fractions) Vs. continuative TMZ (one week on/one week off). RT improved survival in patients with an unmethylated MGMT (PFS 4.6 months in RT group Vs 3.3 months in TMZ group), while TMZ yielded to better PFS in patients with a methylated MGMT promoter (PFS 8.4 months in TMZ group Vs 4.6 in RT group). Both the NORDIC and NOA-08 trials confirmed the prognostic relevance of MGMT methylation status and the consequent use of TMZ, in patients undergone to biopsy or partial resection. However, data on the combination of RT and on the best therapeutic strategy for elderly patients with an unmethylated MGMT promoter are still lacking[17].

Since the association with short-course radiotherapy proved to be safe and useful in elderly patients, temozolomide became the subject of a further trial (CCTG CE.6/EORTC 26062) that enrolled 281 patients with resectable tumors, in two arms: short-course Radiotherapy (15 fractions of 2.67 Gy each) with temozolomide and up to 12 cycles of maintenance vs exclusive radiotherapy[52,53]. The results favored the chemoradiation arm with an impact on PFS (5.3mo Vs 3.9mo) and on OS (9.3mo Vs 7.6mo). The trial confirmed the importance of MGMT promoter methylation as a favorable prognostic factor; methylated patients had almost a 2-times greater OS than the comparison study arm. The results showed also an advantage in the use of TMZ in the patients with an unmethylated MGMT promoter: OS was 10.0 months Vs 7.9 months.

Globally, radiotherapy is associated with a improvement in OS, (with controversial evidence of cognitive and QoL decline); for this reason short-course of RT delivered by targeted radiation technique is usually recommended. Conversly, TMZ therapy is largely effective and well-tolerated in the elderly, with a rate of severe side effects less than 15%. TMZ is recommended in patients with methylation of the MGMT promoter following RT. Exclusive TMZ is also an option for patients with a very unfavourable prognosis[54]. While Chemoradiation is used in selected patients with MGMT promoter methylation, the stand-alone hypo-RT treatment or TMZ Chemotherapy is delivered according to MGMT promoter Methylation status. Based on most recent evidences, first line treatments are reported in Figure 1.

Management of Recurrences

Despite the best optimal multidisciplinary treatments, GBMs inevitably recur and progres. The are no consensus or evidence on choice of the best strategy to apply on recurrence. However, two recent studies[55,56] proved that any (i.e. Chemotherapy, RT, surgery) treatment is superior (in term of PFS and OS) to support/palliative therapy alone. The most important limitation of those studies was that they did not considered the quality of life of enrolled patients as a goal.

At the best of our knowledge, only two retrospective studies addressed the issue of surgery for recurrent GBM in the elderly. Considering the limitations of the study, such as the selection bias of the population selected for surgery and the small size of the cohort, an improvement in survival of, at least, seven months[57] was reported in the group who underwent a second surgery for recurrent GBM. A previous work[58], conversely, did not show any advantage in survival (4 months) in the group of patients that underwent to a second-surgery; no data about alternative treatments were also reported.

Re-Irradiation (Re-RT) is a well-established option for treatment of recurrent GBM in young adluts also after a second surgery. A recent paper investigated the feasibility and safety of Re-RT in a cohort of elderly patients with good success in term of OS (6.9 months after Re-RT) with only minor side effect[59]. The decision about Re-RT should not be based on age per se.

As a good clinical practice point, by a meticulous patient's selection, evaluating. KPS, previous treatment, tumor volume, location of recurrence, the time between last treatment and recurrence, a surgical removal of the recurrent tumors could be considered with the consensus of a Neuro-Oncological board, while keeping the Quality of Life into account.

Epilepsy and Corticosteroids

As in the younger population, there is no consensus on the use of AED prophylactic therapy in patients with no history of seizures or on the fast tapering of AEDs when the tumor is stable[60,61]. The onset of seizures can severely compromise the clinical status of an elder patient. The choice of the drug to administer should be done carefully, especially regarding comorbidity or aggressive behavior side effects, along with the compliance on daily drug intake. The starting dose should be lower than in the younger patients, and monotherapy with a "new" AED is usually the first choice[48,62]. About the use of corticosteroids, a consensus agreement advocates keeping the use at

a minimum. Steroids are usually given to control pre-operative edema, and a rapid tapering is generally recommended in the post-operative period. A plethora of patients receiving a complete resection can accomplish radiotherapy without or with a limited dosage of steroids.

Thromboembolic Event

GBM is one of the more prothrombotic tumors across all age groups[48]. However, the risk is not age-related as for other diseases. The reported risk is approximately 18% per year despite pharmacologic thromboprophylaxis. The event is related to decreased mobility, presence of a moderate or severe motor deficit, steroids intake, radiotherapy, and to the disease itself by the release of vasoactive molecules.

For prophylaxis, LMWH is the first choice for its safety profile. A ICV filter might be an option for patients who are suitable for pharmacologic anticoagulation[63–66].

Timing for prophylaxis after surgery should be individualized, especially in this class of patients. A prompt start (24/48 hours after surgery) of administration of LMWH should be considered. A synergy with hematologists is encouraged to evaluate patients with a high-risk profile in the pre-operative stage, such as those with pre-existing multiple cardio-vascular disease, with previous thrombotic or thromboembolic events and those who take anti-coagulants or anti-platelets drugs to establish the timing of suspension and the better protocol to re-start therapy.

Supportive and Palliative Care

The *end* after an oncological disease (i.e. an *end of the disease*) is a delicate issue. A single surgical manuscript cannot cope with such a delicate complexity. However, it is relevant to observe that the *end-of-the-disease* issue faces *end-of-life* issues in the elderly population. In this context, physicians are often asked to answer at some troublesome questions during the initial consultation for an elderly subject with such a lethal form of cancer right from the clinical-radiological presentation of the disease. Addressing these ethical

aspects with patients and their caregivers is also frequent during the clinical course of the disease. These issues touch each individual in his/her own intimate beliefs and behaviors. Such issues also have a differential understanding and bylaws in different countries and, therefore, result in differential attitudes in approaching and dealing with them. A reasonable despite simplistic advice is to individualize the medical management with the family or caregivers.

Future Directions

Compared to the younger adult population, the elderly subjects receive less salvage therapies. Bevacizumab, a monoclonal antibody targeting VEGF, is approved for recurrent GBM outside Europe, where may be administered as an off-label regimen. The antibody is not proven to be superior to lomustine[67] but plays an important role in symptom-relief and steroid-sparing effects[68]. The AVAglio trial investigated the likely efficacy in the elderly, given the significant VEGF overexpression in these age-group tumors. The trial reported a significant increase in the PFS in all patient included, being however the elderly only the 8% of all sample enrolled. Efficacy and safety in the elderly should be addressed in future trials[69].

Tumor treating fields (TTFs), instead, represents a novel promising treatment. A randomized phase III trial proved a significantly longer survival in patients receiving TTFs in association with TMZ with a median OS longer of 20 months[70]. Further studies should be performed in the elderly population, assessing compliance in handling the device, cost-effectiveness, and effect after hypo-fractionated radiotherapy.

Conclusion

Management of GBM in the elderly population represents a field of growing interest due to the epidemiological relevance, increase in *time to life* and *life to years* in the general population. Despite the prognosis remains poor, aggressive safe surgical treatment, with brain

mapping and monitoring techniques can be pursued after careful pre-operative assessment. In this age-group, the biological age is more relevant than the chronological one. A multidisciplinary teamwork is to be encouraged and pursued.
Future clinical trials focusing on GBMs in the elderly patients could provide with more specific data for patient's selection and biomarkers for patients and family counseling about the risk-benefit ratio of the therapeutic management.

Clinics Care Points

- GBMs in elderly patients represents a field of growing interest due a longer life expectancy
- Age is not per se a contraindication to aggressive treatment as surgery; general clinical condition guides treatment.
- When feasible a Maximum Safe Resection is to address in order to guarantee access to the best treatment options and a longer Overall Survival
- Adjuvant treatments will be based on MGMT methylation statuts, expecially if complete resection could not be achieved
- At Recurrence multiple option can be considered as for young adults.
- More space in future clinical trial should be reserve to elderly patients.

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complications. J Neurooncol 2018;138(1):123–32. Doi: 10.1007/s11060-018-2777-9.

First Author (year of publication)	N of patients	Elderly Definition	KPS	Type of Surgery	Post-operative deficits	Morbidity or mortality	Adjuvant Treatment	Progression Free Survival	Overall Survival
Kleinschmidt (2005)[71]	18	≥ 75	n.a.	6 Biopsy 12 Resection	n.a.	n.a.	6 RT, 1 CT 2 RT+CT	n.a	3.08 Biopsy 5.42 Resection
Combs (2008)[72]	43	≥ 65	26 ≥ 70	14 Biopsy 17 STR 12 GTR	n.a.	n.a.	43 RT+CT	n.a.	6.0 Biopsy 16.0 STR 18.0 GTR
Sijben (2008)[73]	39	≥ 65	≥ 60	11 Biopsy 28 Resection	n.a	n.a.	20 RT 19 RT+CT	4.5 Biopsy 5.2 Resection	5.0 Biopsy 8.5 Resection
Gerstein (2010)[74]	51	≥ 65	44 ≥ 70	23 Biopsy 15 STR 13 GTR	n.a.	n.a.	51 RT+CT	4.73 Biopsy 4.17 STR 9.5 GTR	7.89 Biopsy 15.5 STR 27.4 GTR
Kimple (2010)[75]	30	≥ 70	Mean ≥ 63.3	14 Biopsy 7 STR 9 GTR	n.a.	n.a.	9 RT 9 RT+CT	n.a.	7.0 Biopsy 4.6 STR 8.3 GTR
Lai (2010)[76]	1355	≥ 65	n.a.	296 Biopsy 485 STR 574 GTR	n.a.	n.a.	1005 RT 350 RT+CT	n.a.	5.6 Biopsy 8 STR 9.3 GTR
Laigle-Donadey (2010)[77]	39	≥ 70	Mean ≥ 73.6	21 Biopsy 14 STR 3 GTR	n.a.	n.a.	39 CT	n.a.	8.4 Biopsy 9.07 STR 9.07 16.0 GTR
Chaicana (2011)[33]	80	≥ 65	Mean ≥ 80	40 Biopsy 25 STR 15 GTR	4 Biopsy 7 Resection	1 Biopsy 0 Resection	64 RT 8 CT	n.a.	4.0 Biopsy 5.4 STR 5.8 GTR
Ewelt (2011)[34]	103	≥ 65	66 ≥ 70	43 Biopsy 37 STR	n.a.	n.a.	37 RT 35 RT+CT	2.1 Biopsy 3.4 STR	2.2 Biopsy 7.0 STR

				23 GTR				*6.4 GTR*	*13.9 GTR*
Kushnir (2011)[78]	74	*≥ 65*	68 *≥ 65*	*26 Biopsy* *42 Resection*	n.a.	n.a.	8 RT 27 RT+CHT 34 CT	n.a.	*5.56 Biopsy* *11.83 Resection*
Hashem (2012)[79]	20	*≥ 65*	13 *≥ 70*	*10 Biopsy* *8 STR* *2 GTR*	n.a.	n.a.	20 RT+CHT	n.a.	*8.26 Biopsy* *15.41 STR* *21.25 GTR*
Oszvald (2012[41]*)*	146	*≥ 65*	Median = 70	*66 Biopsy* *61 STR* *19 GTR*	n.a.	n.a.	63 RT 58 RT+CT	*3.9 Biopsy* *4.5 STR* *7.1 GTR*	*4.0 Biopsy* *11.4 STR* *17.7 GTR*
Scott (2012)[18]	702	*≥ 70*	387 *≥ 70*	*324 Biopsy* *231 STR* *141 GTR*	n.a.	n.a.	419 RT 234 CT	n.a.	*3.1 Biopsy* *8.0 Resection*
Tanaka (2013)[80]	105	*≥ 65*	Mean = *74.9*	*52 Biopsy* *53 Resection*	*16 Biopsy* *10 Resection*	*4 Biopsy* *0 Resection*	23 RT 41 RT+CT 1 CT	n.a.	*6.5 Biopsy 6.5* *11.0 Resection*
Fariselli (2013)[81]	33	*≥ 70*	*≥ 70*	*4 Biopsy* *13 STR* *16 GTR*	n.a.	n.a.	26 RT 7 RT+CT	n.a.	*7 Biopsy* *8 STR* *11 GTR*
Lee (2013)[82]	20	*≥ 70*	n.a.	*4 Biopsy* *13 STR* *16 GTR*	n.a.	n.a.	16 RT+CT	n.a.	*11.8 Biopsy* *5.0 STR* *28.9 GTR*
Uzuka (2014)	79	*≥ 75*	Median = 60	*32 Biopsy* *21 STR* *26 GTR*	n.a.	n.a.	33 RT 19 RT+CT 27 CT	n.a.	*9.1 Biopsy* *13 GTR*
Almenawer (2014)[35]	211	*≥ 65*	Mean = 74.2	*73 Biopsy* *71 STR* *67 GTR*	*20 Biopsy* *9 STR* *4 GTR*	*4 Biopsy* *2 STR* *1 GTR*	101 RT 72 CT	*2 Biopsy* *3.9 STR* *5.6 GTR*	*5.4 Biopsy* *8.6 STR* *10.6 GTR*
Hoffermann (2014)[83]	124	*≥ 65*	Mean = 70	*17 Biopsy* *62 STR* *35 GTR*	*n.a.*	*0 Biopsy* *5 STR* *0 GTR*	7 RT 60 RT+CT 6 CT	n.a.	*4 Biopsy* *9 STR* *15 GTR*
Abdullah (2015)[36]	58	*≥ 80*	*≥ 60*	*40 STR* *12 GTR*	12	*2*	10 RT 10 RT+CT	n.a.	*4.2 Resection*
Lombardi (2015)[84]	237	*≥ 65*	*≥ 60*	*40 STR* *12 GTR*	n.a.	n.a.	237 RT+CT	n.a.	*16.1 STR* *17.7 GTR*
Welzel (2015)[85]	146	*≥ 65*	*79 ≥ 70*	*113 Resection*	n.a.	n.a.	n.a.	*4.8 Resection*	*4.4 Biopsy*

				33 Biopsy				*3.5 Biopsy*	*8.1 Resection*
Babu (2016)[37]	120	*≥ 65*	Median = 80	*63 STR* *174 GTR*	n.a.	n.a.	110 RT+CHT	n.a.	*9.6 STR* *14.1 GTR*
Di Cristofori (2017)[27]	117	*≥ 65*	Median = 70	*38 STR* *79 GTR*	*6 Resection*	*Resection 13*	84 RT+CT 16 CT	n.a.	*7 STR* *11 GTR*
Karsy (2018)[86]	82	*≥ 75*	Median = 80	*18 Biopsy* *33 STR* *19 GTR*	*2 Biopsy* *5 STR* *2 GTR*	*6 Biopsy* *10 STR* *6 GTR*	32 RT 22 CT	n.a.	*3.7 Biopsy* *5 STR* *12.1 GTR*
Hager (2018)[58]	59	*≥ 65*	Median = 90	*17 Biopsy* *17 STR* *25 GTR*	n.a.	n.a.	11 RT 41 RT+CT 25 CT	*9.7 Resection* *5.6 Biopsy*	*20.7 Resection* *7.4 Biopsy*
Pessina (2018)[40]	178	*≥ 65*	142 *≥ 70*	*45 Biopsy* *62 STR* *63 GTR* *8 CR*	*4 Biopsy* *4 STR* *3 GTR* *0 CR*	*1 Biopsy* *0 STR* *2 GTR* *0 CR*	46 RT 132 RT+CT	n.a.	*8.1 Biopsy* *11.9 STR* *15.1 GTR* *24.5 CR*

Tab.1 The table summarizes the studies comparing oncological outcome of elderly patients that underwent either resection or biopsy after the introduction of Temozolomide. Studies without a report of the Overall Survival (OS) were excluded. Number are reported as absolute value. We report the sample size included, age threshold, KPS (median, mean or majority patients'value), type of surgery, post-operative deficits, post-operative morbidity and mortality, type of adjuvant treatment, months of Progression Free Survival (PFS) and OS. Not avaiable (n.a.) is indicated when the study did not explicitly report the information requested. References are quoted in the main text.

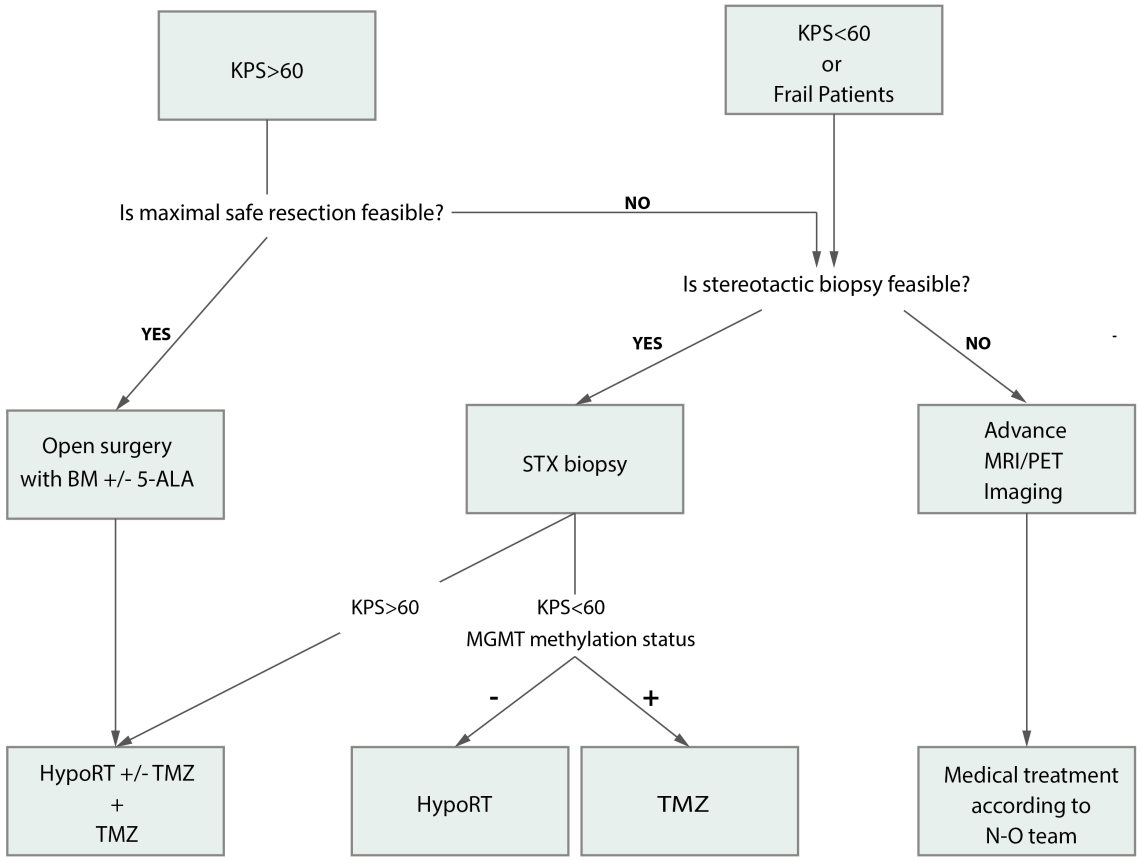

Fig.1 Figure report a flow-chart to an evidence-based algorithm of treatment for elderly patients with GBM.