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Review article

Guidelines, “minimal requirements” and standard of care in glioblastoma around the Mediterranean Area: A report from the AROME (Association of Radiotherapy and Oncology of the Mediterranean arEA) Neuro-Oncology working party

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ABSTRACT

Glioblastoma is the most common and the most lethal primary brain tumor in adults. Although studies are ongoing, the epidemiology of glioblastoma in North Africa (*i.e.* Morocco, Algeria and Tunisia) remains imperfectly settled and needs to be specified for a better optimization of the neuro-oncology healthcare across the Mediterranean area and in North Africa countries.

Abbreviations: OS, overall survival; PFS, progression-free survival; WHO, World Health Organization; MA, Mediterranean area; AROME, association of radiotherapy and oncology of the Mediterranean area; MTDs, multidisciplinary teams meetings; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; MRS, magnetic resonance spectroscopy; TMZ, temozolomide; KPS, Karnofsky prognostic index; MGMT, Methylation of the O6-methylguanine-DNA methyltransferase; RTOG, Radiation Therapy Oncology Group; EBRT, external beam radiotherapy; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; GPN, gross natural product; EMR, Eastern Mediterranean Region; UK NICE, United Kingdom National Institute of Clinical Excellence; IOG, improving outcomes guidance.

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Over the last years significant therapeutic advances have been accomplished improving survival and quality of life of glioblastoma patients. Indeed, concurrent temozolamide-radiotherapy (temozolamide) and adjuvant temozolamide has been established as the standard of care associated with a survival benefit and a better outcome.

Therefore, considering this validated strategy and regarding the means and some other North Africa countries specificities, we decided, under the auspices of AROME (association of radiotherapy and oncology of the Mediterranean area; www.aromecancer.org), a non-profit organization, to organize a dedicated meeting to discuss the standards and elaborate a consensus on the “minimal requirements” adapted to the local resources. Thus, panels of physicians involved in daily multidisciplinary brain tumors management in the two borders of the Mediterranean area have been invited to the AROME neuro-oncology working party.

We report here the consensus, established for minimal human and material resources for glioblastoma diagnosis and treatment faced to the standard of care, which should be reached. If the minimal requirements are not reached, the patients should be referred to the closest specialized medical center where at least minimal requirements, or, ideally, the standard of care should be guaranteed to the patients.

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1. Introduction

Glioblastoma is the most common and the most aggressive primary malignant brain tumor in adults. In Europe and US, approximately 4000 new cases are diagnosed each year with an incidence of about 3 to 7/100000 habitants. Median age at diagnosis is 64 years and male to female sex ratio is 1,6 ([Dolecek et al., 2012](#); [Rachet et al., 2008](#)). In France 2400 new cases are diagnosed each year. The incidence is about 4 to 7/100000 habitants ([Badi et al., 2010](#)).

Epidemiology of glioblastomas in North Africa countries (*i.e.* Morocco, Algeria and Tunisia) remains imperfectly settled. Indeed, in the literature, studies depicting epidemiology of brain tumors in North Africa are lacking.

Based on clinical course of the disease, two major forms of glioblastoma are individualized: (i) primary or *de novo* and (ii) secondary glioblastoma. The last, results from tumor progression of an already diagnosed lower grade glioma (*i.e.* WHO [World Health Organization] grade II or III) while primary or *de novo* glioblastoma occurs spontaneously without any previous history of lower grade tumor. *De novo* or primary glioblastoma represent approximately 90% of all glioblastomas ([Ohgaki and Kleihues, 2013](#)) and develop in elderly patients.

Although the prognosis of primary glioblastoma remains dismal, over the last decade, significant therapeutic advances have been reached in its management leading to an increase of survival and better quality of life. These advances have been accomplished in terms of tumor staging (*i.e.* clinical, radiological, pathological and molecular), symptomatic treatments (*i.e.* anti-epileptic drugs, steroid therapy), supportive care and in anti-tumor treatments (surgery, radiotherapy, and cytotoxic chemotherapy). Therefore, these progresses should be implemented and benefit to patients in limited resources countries and emergent countries such as North Africa.

We report here the conclusions of the AROME (Association of Radiotherapy and Oncology of the Mediterranean Area; www.aromecancer.org) neuro-oncology working party that involved experts from north and south borders of the Mediterranean area (MA). These conclusions are structured as “minimal requirements and standards” for appropriate medical management of glioblastoma patients based on evidences-based medicine data and expert agreements. This AROME concept of guidelines has been already published for several cancers in 2010 ([AROME, 2011](#)).

2. Material and methods

2.1. AROME concept

AROME is a non-profit medical organization aiming to increase collaboration of oncologists and other health care professionals implied in cancer care around the MA. The scope of the Association is to recognize the special circumstances and issues in the MA, to discuss and acknowledge openly existing issues in order to improve the existing problems, with a particular interest for overcoming disparities in cancer care by various actions. Thus, AROME's special focus is to promote practical education and training for all professionals involved in cancer care in the MA countries.

2.2. Aims and scope of AROME guidelines

In summary, in the first AROME meeting held in Naples in April 2007, oncologists around the MA met and presented epidemiologic data from their respective countries. This was the first step for the recognition of the specific epidemiologic characteristics in the area, followed by another step of presenting and recognizing the availability of means to provide cancer care in the various countries. Ultimately it became evident that optimum means were not available in several countries, which led to the recognition of the fact that cancer care should be reevaluated and guidelines for treating specific cancer sites should be revisited, since they are inapplicable for several countries in MA. In 2010, we published the first “AROME guidelines for cancer care around the Mediterranean Area” a formalized consensus. These guidelines were structured as *minimum requirements* that should be proposed consisting of the minimal actions any oncologist should be able to perform anywhere in order to provide the acceptable minimum cancer care. On the other hand they aimed to rationalize cancer care and make better management of the available means so as to treat more patients in a most cost-effective manner. Furthermore, they aimed to become a useful tool for providing evidence that optimum care is achievable and to inspire pieces of action in this direction to increase the cancer care to a higher level ([AROME, 2011](#)).

2.3. Neuro-oncology working party

In the previous work ([AROME, 2011](#)), minimal requirements and standards in neuro-oncology have not been planned. Thus, we decided to dedicate a specific meeting inviting the first AROME

neuro-oncology panel that involved representative leaders for all specialties from France and North Africa countries. The standards for glioblastoma diagnosis and treatment were elaborated from a literature review and evidence based medicine data available at the time of the meeting in 2013.

Before the meeting and elaboration of the consensus on the minimal requirements according to the local means and standards, the panel addressed some relevant questions that have been first validated by e-mails exchanges. The selected questions for the debate during the meeting were:

- (i) What would be the minimal and standard work-up for a patient with a brain lesion suggestive of glioblastoma after a CT-scan performed in the context of neurological symptoms?
- (ii) What are the indications and contraindications of a stereotactic biopsy and a neurosurgical resection faced to a patient with a space-occupying lesion suggestive of glioblastoma on brain imaging?
- (iii) Are anti-tumor treatments feasible for a patient, with major contraindications to surgical procedures, suffering from a brain lesion highly suggestive of glioblastoma?
- (iv) What are the minimal items needed in a pathological report glioblastoma diagnosis?
- (v) What are the medical treatments of glioblastoma patients and their timing?
- (vi) What are the modalities of brain irradiation for glioblastoma patients?
- (vii) What are the main points to consider for anti-epileptic drugs and steroids delivery?

The objective of the AROME neuro-oncology working party was to respond to these questions in a consensus that would take into account the means available for diagnosis and treatment of glioblastoma.

3. Results

3.1. Diagnosis

Diagnosis of glioblastoma is exclusively based on pathological examination. However clinical symptoms of patients and imaging features of the lesion may help to anticipate the diagnosis.

3.1.1. Clinical features

Depending on the tumor location, clinical symptoms in glioblastoma consist mostly of intracranial pressure syndrome (*i.e.* headaches, diplopia, nausea/vomiting, vertigo), seizures, focal neurological deficits, and/or cognitive disturbances. Ocular fundus exam might reveal papilledema supporting the diagnosis of increased intracranial pressure and putative intracranial space occupying lesion.

In addition to medical history, neurological examination, general examination and treatments, several additional points need to be registered in the medical record of the patients since they participate to treatment decision-making and dosage of chemotherapy: (i) clinical autonomy of the patient according to performance status scales, (ii) age, (iii) height, (iv) weight, (v) history of seizure and (vi) results of biological tests. The most commonly used scales to assess performance status of cancer patients are the Karnofsky performance status (KPS) score and the Eastern Cooperative Oncology Group (ECOG) score/WHO score/Zubrod score (Oken et al., 1982). A peculiar attention should be paid to assess accurately the performance status when the KPS is close to 70% since the standard of care combining temozolomide (TMZ) and radiother-

apy has been established in patients with KPS $\geq 70\%$ (Stupp et al., 2009).

The panel has considered all these clinical items as “minimal requirements” before decision-making for biopsy or treatment in all patients (Table 1). In addition, this should be done in the frame of a multidisciplinary teams (MDTs) meeting, which is also a prerequisite before treatment.

3.1.2. Imaging tools

The standard imaging examination for glioblastoma diagnosis and treatment planning is magnetic resonance imaging (MRI) with at least T1SE without contrast infusion, T1SE with contrast infusion and T2SE or T2-FLAIR. MRI specifies the accurate location of the disease, potential complications (hemorrhage, leptomeningeal spread, and/or hydrocephalus), help to evaluate resection possibility and allows tumor volume delineation (with fusion imaging) for radiotherapy. Advanced imaging sequences including diffusion-weighted images (DWI), perfusion-weighted images (PWI), and magnetic resonance spectroscopy (MRS) are helpful to specify the potential differential diagnosis of glioblastoma. Indeed, on DWI high signal reflect increased cell density in favor of tumor process, PWI usually reveals an increased perfusion and MRS shows an increased Choline/NAA ratio with lactate and necrosis (Ricard et al., 2012).

Although spatial resolution of CT scan is limited, CT scan with contrast infusion is the “minimal requirement” for brain tumor diagnosis. In addition to evaluate necrotic space, edema and mass effect on brain structures, CT-scan contribute for surgery and radiotherapy planning. It is noteworthy, that the clinical trial establishing the standard of care of glioblastoma included patients assessed with a CT scan (Stupp et al., 2009).

In North Africa, due to prevalence of tuberculosis, brain tuberculoma needs particular attention as differential diagnosis of brain tumors. Therefore, in addition to clinical investigations, a chest X-ray examination and chest CT scan are indicated to rule out the diagnosis of tuberculoma but also brain metastases especially from lung cancer.

3.1.3. Tumor specimen

Safe and extensive surgical resection is recommended for neurological symptoms regression, final pathology and outcome improvement (Chaichana et al., 2014a). When surgical resection is not feasible, a biopsy is mandatory for pathological diagnosis.

When only biopsy (either in stereotactic or opened conditions) is indicated, this should be performed to get tissue for definitive pathological diagnosis before any treatment. In exceptional cases, biopsy might be contraindicated due to patient (*e.g.* high risk of per-surgery hemorrhage, confusion) or tumor characteristics (*e.g.* deep location, location in eloquent brain areas).

In exceptional cases, and after MTDs board discussion, an anti-tumor treatment might be initiated without pathological proof. However, a comprehensive check-up including systemic investigations and multiparametric brain MRI (T1SE without contrast, T1SE with contrast, T2SE or FLAIR, PWI, DWI and MRS) is mandatory to rule out, at best, putative differential diagnoses. This strategy, without pathological demonstration of the diagnosis, must remain exceptional. If the anti-tumor treatment is initiated without pathological proof, the patient and his family have to be informed about the potential diagnostic and therapeutic risk of errors. The panel suggested that in case of the lack of the standard imaging tool, namely multiparametric brain MRI, the “minimal requirement” should be CT with contrast infusion.

3.1.4. Pathology and molecular biology

The diagnosis of glioblastoma is mainly based on morphological features according to the WHO classification of primary brain

Table 1

Minimal requirements and standards for diagnosis in adult glioblastoma.

Parameters	Minimal requirements	Standards	Comments
Multidisciplinary board meetings for decision	Involving at least 3 specialists for each meeting	Involving all specialists in the field of brain tumors	Ideally including: surgeons, pathologist, MO, RO, NR, neurologist, onco-geriatrics Periods: every week
Clinical features	Complete medical record with: - Weight, tall, history of seizure - KPS score and clinical autonomy - Clinical symptoms	Exams and tests: - Ocular fundus exam - Biology tests	Minimal requirements are similar to standards
Imaging tools	CT scan + contrast infusion	- CT scan + contrast infusion - Multiparametric MRI (T1SE with and without contrast, T2SE or T2-Flair) - MRI advanced sequences (DWI /PWI)	MRS is optional for standards
Tumor specimen and pathologic diagnosis	Source = surgery or biopsy	Source = surgery or biopsy	No pathology proof before treatment: should be exceptional and after MTD board meeting and information of the patient and family
Pathology and tumor biology	- WHO classification - Checklist of the pathology parameters - Immunostaining with anti-IDH1	In addition to minimal requirements provide: - Tumor specimen frozen for research in frozen nitrogen or in -80 °C freezer - IDH1 mutational - MGMT promoter methylation status - 1pet 19 q deletion	- Pathology is mandatory before any treatment - Pathology review is recommended for doubts and particular cases
Treatment strategy	- Decision according to MTDs board meeting, KPS score and clinical conditions - Surgery: safe and extensive resection - Availability of TMZ and EBRT - Availability of TMZ for adjuvant 6 cycles (150–200 mg/m ²)	In addition to minimal requirements: - Surgery followed by brain imaging within the 48 h after resection - Inclusion in clinical research protocols	In case of unavailability of TMZ or EBRT, the patients should be transferred to a referent center
Other medical treatments	Anti-epileptic drugs, steroids, deep venous thrombosis prophylaxis. New drugs and combination could be used as standards according to their availability in the country		Short steroids duration + side effects prevention and PCP

Abbreviations: MO: medical oncologist; RO: radiation oncologist; NR: neuro-radiologist; MRI: magnetic resonance imaging; DWI: diffusion-weighted images; PWI: perfusion-weighted images; MRS: magnetic resonance spectroscopy; MTD: multidisciplinary board meeting; WHO: World Health Organization; IDH1: isocitrate dehydrogenase 1; MGMT: O-6-methylguanine-DNA methyltransferase; TMZ: temozolomide; EBRT: external beam radiotherapy; PCP: pneumocystis pneumonia.

tumors (Louis et al., 2007). The procedure for tumor tissue conservation is standardized. The tissue should be fixed in 10% buffered formalin or in zinc-formalin at least during one hour and ideally less than 24 h and paraffin embedded in order to preserve pathological features of the tumor. Although, it is not mandatory, a piece of the tumor could be frozen in nitrogen or in -80 °C freezer for future research protocols including innovative targeted drugs that might be guided by molecular features only detectable in fresh frozen tumor samples.

Frozen sections, imprints or smear preparations are not mandatory and need to be dedicated to specific cases. However, the purpose of these techniques could guide the neurosurgeon to ensure that representative samples have been obtained. The intra-operative diagnosis should be performed in the context of clinical and radiographic data. After hematoxylin and eosin staining and microscopy analysis, pathological diagnosis of glioblastoma is confirmed with high cell density, nuclear atypia, mitosis, microvascular proliferation and/or necrosis (Fig. 1). Occasionally, an oligodendroglial component could be associated to the glioblastoma and the final diagnosis is glioblastoma with oligodendroglial component (Fig. 2) (He et al., 2001).

The “minimal requirements” of glioblastoma pathologic criteria could be used as a checklist (Table 1; pathology section). According to the local tools, the panel recommended the use of the standardized pathological report that has been recently published by the French Division of International Academy of Pathology (Rigau et al., 2011). Finally, the experts have strongly recommended to fill systematically a standardized form for pathology and molecu-

lar features including all available parameters in all adult diffuse gliomas.

Although not mandatory for an appropriate management of glioblastoma patients, isocitrate dehydrogenase 1 (*IDH1*) mutational and methylguanyl methyltransferase (*MGMT*), promoter methylation status are interesting in the setting of glial tumors. At least, an immunostaining with anti-IDH1 antibody, which identifies the most frequent *IDH1* mutation (R-132H), should be done (Capper et al., 2009; Figarella-Branger et al., 2012). Silencing of the *MGMT* gene promoter by methylation is associated with better tumor response to temozolomide (TMZ) plus radiotherapy and predictive of response to the standard of care since about 10 years (Hegi et al., 2005). The panel did not recommend *IDH1* mutation and *MGMT* gene promoter methylation status as “minimal requirements”. However, immunostaining with anti-IDH1 antibody should be considered as “minimal requirement” (Table 1).

3.2. Primary tumor treatment

The standard of care of glioblastoma patients in good clinical conditions is: (i) maximal and safe surgical resection, (ii) radiotherapy with concurrent chemotherapy (temoradration) and (iii) adjuvant TMZ for six cycles. The delay between these treatments and sequence, which is paramount of importance, will be discussed in the next chapters. Table 1 presents “minimal requirements” and standard multidisciplinary management of glioblastoma.

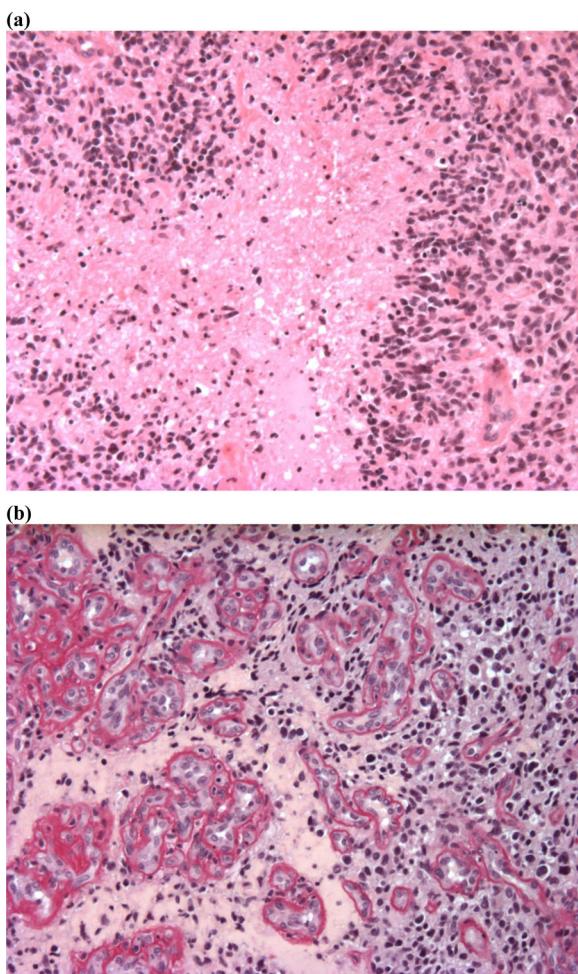


Fig. 1. (a) Glioblastoma poorly differentiated cells with pseudopalisading necrosis (HE); (b) Microvascular proliferation and glomeruloide pattern (Sirius red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2.1. Surgery

Neurosurgery has a pivotal step in diagnosis and treatment management of glioblastoma. Neurosurgical procedures (*i.e.* resection or biopsy) should be performed with a minimal delay of 2 weeks after clinical and radiological diagnosis. This delay has been advocated as a "minimal requirement" by the panel.

The optimal strategy is a maximal safe resection for all patients when it is feasible. It has been demonstrated that extensive resection improve outcome and quality of life of patients (Louis et al., 2007; Chaichana et al., 2014b). Quality and extent of surgical resection should be assessed using brain imaging, without and with contrast, within 48 h after the procedure. The panel recommended CT scan with contrast infusion as a "minimal requirement" for post-operative imaging procedure. As for primary diagnosis, the panel considered multiparametric MRI and CT scan as the standard post-operative imaging.

3.2.2. Delay between surgery and radiotherapy

The impact of the surgery-radiotherapy delay on outcome as compared to the other prognostic parameters related to the patients' selection (age, KPS, . . .), tumor aggressiveness (size, site, symptoms..) and biology (MGMT, IDH1, hypoxia..) is unknown.

In the RTOG study on three thousands patients, Blumenthal et al. reported a deleterious impact on survival of the short delay (≤ 2 weeks) and better outcome in patients who had radiotherapy ≥ 4 weeks after surgery (Lawrence et al., 2011). While many other sin-

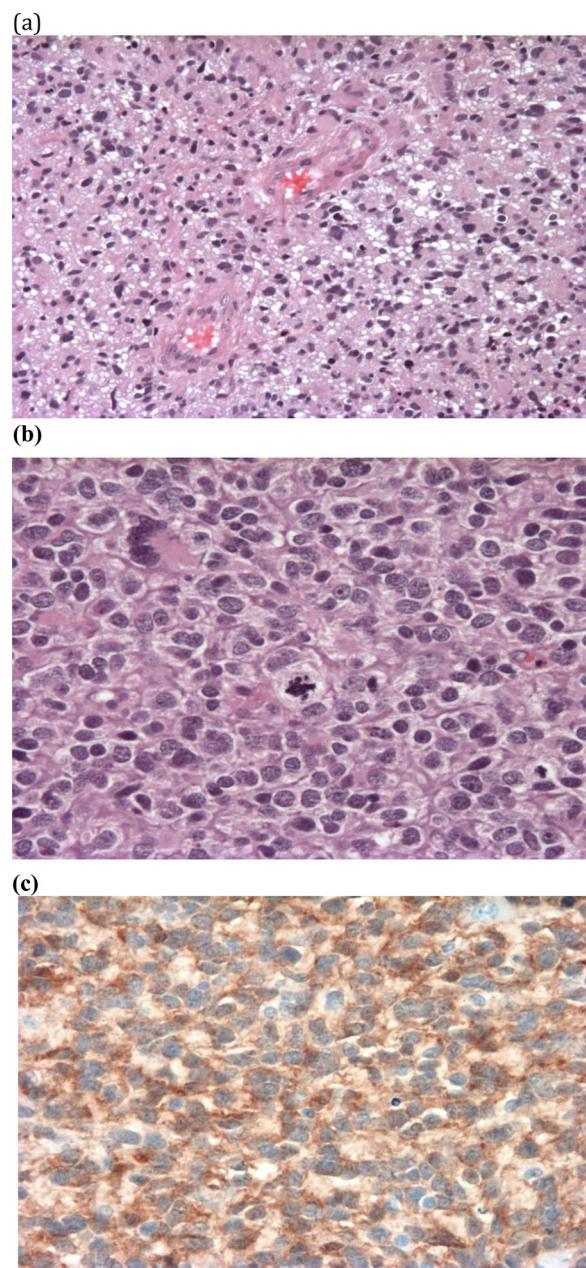


Fig. 2. Glioblastoma with oligodendroglial component.
(a) High cellular density, mitosis and nuclear atypias (HE).
(b) Oligodendroglial component (HE).
(c) Expression of IDH1 by tumor cells.

gle institutions experiences reported already this tendency, the impact of the delay on survival is still controversial (Valduvieco et al., 2013; Noel et al., 2012; Lawrence et al., 2012). However in some these old series, temoradiation was not the standard. Conversely, recent data on post-operative radiotherapy for TMZ treated glioblastoma patients with MGMT information, revealed >6 weeks delay between surgery and radiotherapy as an independent poor prognostic factor for survival in multivariate analysis (Irwin et al., 2007).

Thus, the panel recommended as a "minimal requirement" to set the delay between 4 and 6 weeks. In case of the lack of radiotherapy means or difficulties to obtain locally an early appointment to start temoradiation during the 4 to 6 weeks after surgery, patients and families should be informed and patients should be referred to specialized centers elsewhere in the country.

Table 2

Minimal requirements and standards for radiotherapy planning and delivery.

Parameters	Minimal requirements	Standard	Comments
Delay between surgery and EBRT (weeks)	4–6	≥4	Deleterious effect of delay <2 weeks
Device availability and EBRT technique	- Cobalt 60 - 3D CRT	- Linear accelerator - 3D CRT based on imaging fusion between CT scan-Multiparametric MRI	IMRT is considered for particular cases and in case of inclusion in clinical research protocols
Dose prescription			
Total dose and fractionation for patients <70 years	60 Gy in 30 fractions over 6 weeks (one fraction per day) Total dose delivered in 1 PTV according to the EORTC recommendations or 2 PTVs		- Combined to TMZ at a daily dose of 75 mg/m ² - If 2 PTVs are used: 46–50 Gy (large volume) followed by a boost of 10–14 Gy (PTV60)
Total dose and fractionation for elderly ≥70 years (Wick et al., 2012; Malmström et al., 2015)	If EBRT alone: 40 Gy in 15 fractions or 34 Gy in 10 fractions If temoradiation: preference for standard fractionation (1.8 or 2 Gy/fraction)		- MGMT status for TMZ or EBRT = option - EBRT alone = option after MTD board meeting validation
Radiotherapy planning			
Imaging tools	CT scan + contrast infusion	- CT scan with contrast infusion Imaging fusion with MRI T1SE with and without contrast or T2-Flair - CTV = GTV + 2 to 3 cm - PTV = CTV + 0.5 cm - If post-operative MRI: limited margins for CTV definition in case of no residual tumor (GTV + 0.5 to 1 cm)	New compounds to define hypoxia zones are under investigations
Target volumes definition	CTV = GTV + edema + 2 to 3 cm PTV = CTV + 0.5cm		- CTV > 250 cm ³ : CTV = GTV + 1 cm for 60 Gy - PTV should not extended outside the bone (temporal glioblastoma) - If contouring on T2-Flair: edema is not involved in CTV
CTV definition (Fig. 3)	MD Anderson: contrast + 2 cm; EORTC: contrast + 2 to 3 cm; RTOG: CTV1 (edema + 2 cm) and CTV2 (contrast + 2.5 cm)		Volumes not defined on post-operative imaging
Organ at risk	2/3 of the brain < 50 Gy 2/3 of the brain stem < 53 Gy	2/3 of the brain < 50 Gy 2/3 of the brain stem < 53 Gy	V100 < 45 Gy V100 < 50 Gy

Abbreviations: Gy: gray; MRI: magnetic resonance imaging; MTD: multidisciplinary board meeting; TMZ: temozolomide; EBRT: external beam radiotherapy; IMRT: intensity modulated radiotherapy; 3D CRT: 3-dimensional conformal radiotherapy; GTV: gross tumor volume; CTV: clinical target volume; PTV: planning target volume.

3.2.3. Radiotherapy

3.2.3.1. Machines and volume definition. Linear accelerator is the best device option for external beam radiotherapy (EBRT) delivery. This is the standard of care. If in some limited resources countries only cobalt machines are available, the panel considered these devices as an alternative for EBRT delivery with however the necessity of 3D planning. The panel recommends the last as a “minimal requirement”.

The standard target volume definition and margins should be defined on brain images with contrast infusion (*i.e.* CT or T1SE weighted MRI, T2-flair). The image fusion between MRI and CT scan with contrast infusion is the standard planning procedure. However, in case of the lack of MRI, CT scan with contrast infusion should be considered as minimal requirements for 3D conformal EBRT planning. When fusion-imaging tools are lacking, the delineation of target volumes on the CT scan should take into account MRI images of the tumor and edema.

The clinical target volume (CTV) includes the surgical cavity in case of gross total resection or the contrast-enhanced residual disease (gross tumor volume, GTV) plus 2 cm depending on the residual disease volume (*i.e.* below or above 250 cm³). Finally, planning treatment volume (PTV) requires adding 0.5 cm to the CTV (Fig. 3). The panel considers this as “minimal requirement” and standard. In Table 2 are presented the several margins expansion published and recommendation of the panel for CTV and PTV definition according to the tools namely MRI availability and imaging fusion possibility. The list of the organ at risk is also presented in Tables 3A and 3B.

3.2.3.2. Dose and fractionation. For dose and fractionation, there is no distinction according to means. Concurrent TMZ and EBRT

should deliver 60 Gy in 30 fractions of 2 grays over 6 weeks (Stupp et al., 2009). Hypofractionation or modified EBRT schedules (50.4 Gy given in 1.8 Gy fractions or 40 Gy in 15 fractions) (Roa et al., 2004; Keime-Guibert et al., 2007) could be discussed according to age and association (patients with tumors lacking MGMT promoter methylation) or not of TMZ concurrently to radiotherapy. The panelists have based their consensus on the data from the two important randomized Phase III trials published recently from the German and the Nordic groups (Wick et al., 2012; Malmström et al., 2015). Although these studies were carried out differently, common themes emerge that are important to our understanding of optimal management of this patient population.

In the German trial (Wick et al., 2012) MGMT promoter methylation status was missing in almost 45% of patients, known to be methylated in 16% and 24% patients who received either TMZ or EBRT, respectively. Median OS was significantly higher in EBRT arm as compared to TMZ (9.6 versus 8.6, *p* = 0.03) with higher rates of toxicity in the last. Furthermore, among patients receiving upfront EBRT, MGMT methylation status was not associated with increased OS. However, among patients receiving TMZ, unmethylated status patients had a significantly shorter event-free survival (EFS) (HR 1.95; *P* = 0.01) and a trend to shorter OS (HR 1.34; *P* = 0.129) compared with EBRT. In contrast, patients with methylated status receiving TMZ had significantly longer EFS (HR 0.59; *p* = 0.01) and trend to longer OS (HR 0.69; *p* = 0.139) compared to EBRT. This suggests an important predictive role for MGMT promoter methylation status in determining optimal treatment among elderly glioblastoma patients with favorable KPS for whom monotherapy with EBRT or TMZ is being considered.

In the Nordic trial (Malmström et al., 2015) patients were randomized between three arms: (i) TMZ for six cycles, dosed

Table 3A

Brain tolerance to Radiotherapy according to Emami et al. (1991).

Organ	TD 5/5			TD 50/5		Endpoint	
	1/3	2/3	3/3	1/3	2/3		
Brain	60	50	45	75	65	60	Necrosis, infarction
Brain stem	60	53	50	—	—	65	Necrosis, infarction
Optic nerve	—	—	50	—	—	65	Blindness
Chiasma	—	—	50	—	—	65	Blindness
Ear	30	30	30	40	40	40	Acute serous otitis
Ear	55	55	55	65	65	65	Chronic serous otitis

Table 3B

Brain tolerance to radiotherapy according to RTOG guidelines Chang et al. (2007).

Structures	Volume (cc)	Total dose (Gy)	Dmax (Gy)	Trials reference
Brainstem	1%	60	54	RTOG 0225
Temporal lobe	1%	65	60	RTOG 0225
eyeball	Mean	35	50	RTOG 0615/0225
Lens	—	—	25	RTOG 0615
Optic nerves	1%	60	54	RTOG 0225
Chiasm	1%	60	54	RTOG 0225
Cochlea (each)	5%	55	—	RTOG 0615
Inner and middle ear	Mean	50	—	RTOG 0225

according to the Stupp et al. trial (Chaichana et al., 2014a); (ii) hypofractionated EBRT to 34 Gy in 10 daily fractions; or (iii) standard RT to 60 Gy in 30 daily fractions. Despite the fact that only 34% of patients received all six cycles of TMZ, median survival was superior in the TMZ group, 8.3 months versus 7.5 months in the hypofractionated RT group, and 6.0 months in the standard RT group. This was statistically significant between the TMZ and standard EBRT groups ($p=0.01$) but not between TMZ and hypofractionated EBRT ($p=0.24$). For patients aged over 70 years, TMZ (HR 0.35; $p<0.0001$) and hypofractionated RT (HR 0.59; $P=0.02$) were associated with significantly longer survival than standard EBRT.

These two European trials have helped to clarify the relative benefits of EBRT versus TMZ among elderly glioblastoma patients. In particular, it appears important to routinely test all tumors for MGMT promoter methylation in order to make fully informed adjuvant treatment decisions. Thus, patients who are being considered for monotherapy as opposed to combined chemoradiotherapy appear to have most benefit from TMZ if their tumor is MGMT methylated versus EBRT (hypofractionated, in particular) if MGMT is unmethylated. When the MGMT status is lacking, the panel recommended the 40 Gy in 15 fractions schedule as the best choice for elderly if only EBRT without TMZ is indicated. If temoradiation is planned in elderly, the panel recommended the dose 50 Gy using standard fractionation (1.8–2 Gy/fraction).

Dose escalations up to 90 Gy have not proven to improve the overall survival or/and progression free survival either using EBRT or high dose brachytherapy (Fitzek et al., 1999; Chen et al., 2007).

3.2.4. Chemotherapy

The standard chemotherapy used for first-line treatment of glioblastoma patients is TMZ. It should be delivered at 75 mg/m² daily concurrently with radiotherapy. Adjuvant TMZ should be administered at the dosage of 150–200 mg/m². The dosage modulation of adjuvant TMZ is guided by clinical and biological tolerances. In absence of tumor progression, the minimal number of TMZ cycles adjuvant is 6. The maximal number is under debate. Although, many centers reach 12 cycles of adjuvant TMZ no evidence based medicine data supports this strategy. The panel considered TMZ for 6 cycles as “minimal requirement”. In case of unavailability of the drug, the patients should be referred to the closest specialized referent centers.

4. Discussion

Inequalities in the MA include the different socioeconomic status between countries from south of Europe and North Africa or Middle East. Among rich countries, there is little correlation between gross national product (GNP) per person and life expectancy. Efforts by major organizations have already been made for ameliorating the situation in limited resources countries. For example, only 50% of Eastern Mediterranean Region (EMR) countries have cancer control plans and major gaps in national capacity to prevent, detect, and manage cancer in the EMR exist, while national guidelines for the clinical management of common cancers are available in one third of these countries (Khabir, 2003).

The purposes of clinical practice guidelines are to improve the quality of patient care (namely survival and quality of life) and assist clinical decisions by rationalizing the use of available resources and prioritizing research goals. Heterogeneity in guidelines development is controversially seen: while some think it is a draw back to the uniformity of cancer patient care, AROME group believes that such heterogeneity is necessary if countries with limited resources or diversity of cultures are to be taken into account. Guidelines intend to have implications in making treatment decisions with an impact on the patient-physician relationship. However, the intrinsic cultural and religious beliefs and the level of education of the patients can vary significantly around the MA. Therefore, existing “western” guidelines can not be directly “adopted” by most countries around the MA.

In 2010 we published the first « minimal requirements and standards » for several cancers that are frequently seen around the MA (AROME, 2011). Our purpose was to bring to light the vast spectrum of possible practices adopted in the MA, to trigger conversation, to serve as a useful tool for any professional dealing with cancer in the area and to promote a multidisciplinary, cost effective up-to-date management of cancer in the region. We aimed to form a basis for the development of practices and policies leading from the *minimum requirements* to grow to the *standard of care*. An update of these guidelines is planned this year regarding to the amelioration of available means, which would coincide, with *standard of care* in many countries around the MA.

In the previous work we did not include CNS tumors such glioblastoma. Neuro-oncology multidisciplinary courses are lacking in the majority of the southern countries of the MA. Since 2010, AROME have dedicated a yearly course involving leaders from

both borders of the MA in order to give the opportunity to young oncologists to attend a multidisciplinary neuro-oncology practical course. In 2013, we decided to create a neuro-oncology working party involving experts and teachers who were invited during the course. While the course concerned several CNS cancers, we have focused "minimal requirements and standards" on only glioblastoma, the most aggressive primary malignant brain tumor in adults. Indeed, evidence-based guidelines created in a multidisciplinary fashion using predetermined criteria for grading scientific data and translating this to similarly ranked recommendations is a valuable approach for glioblastomas (Olson et al., 2009) but only when all the means for diagnosis and care are available. For the purpose, and in the situation where inequalities exists among countries, or even inside regions of a given country, we followed the same concept that we have initiated for the most frequent cancers in the MA and published elsewhere in 2010 (AROME, 2011).

The main goal of the working party was to define the minimal requirements in terms of material and humans resources for appropriate diagnosis and treatment of glioblastoma patients without impacting quality of care. One of the important messages and expert agreement was that the patients should be systematically referred to the closest specialized medical center for any or all parts of the medical plan when any or all parts of the minimal humans or material resources are lacking. Overall, the working party stated that only minor modulations of the standards are feasible for an appropriate medical management of glioblastoma patients without impacting negatively the quality of healthcare.

The panel has advocated to structure in the referent centers with a MTDs board meeting as prerequisite for glioblastoma management. The collaborative medical network (*i.e.* multidisciplinary tumor-board) should include neuroradiologists, neurosurgeons, pathologists, neuro-oncologists (or neurologists and oncologists) and radiation oncologists trained in the field of brain tumors. In terms of material, the "minimal requirements" were also stated for diagnosis and treatments (Tables 1 and 2). In fact, the maximal benefit from the recent advances of surgical techniques and oncological management could be obtained with coordinated and specialized interdisciplinary care delivering best-available treatment for each individual patient in a timely manner. The UK National Institute of Clinical Excellence (NICE), in its Improving Outcomes Guidance (IOG) for people with brain and other CNS tumors, has identified key aspects of neuro-oncology services that need development (NICE, 2006). Their principal recommendations include establishing direct referral pathways, MTDs of neurosurgeons, oncologists, pathologists and radiologists to review diagnoses and determine appropriate treatment for every individual, supportive pre- and post-operative counseling of patients and enhanced opportunities for participation in clinical trials (NICE, 2006). Moreover, they showed recently that service reconfiguration and implementation of NICE guidance resulted in significantly more patients being discussed by the MDTs increased from 66 to 87%, reduced emergency admission in favor of elective surgery, reduced median hospital stay from 8 to 4.5 days, increased use of post-operative MRI from 17 to 91% facilitating early discharge and treatment planning, and reduced cost of inpatient stay from £2096 in 2006 to £1316 in 2009 (Guilfoyle et al., 2011).

To our knowledge, the AROME neuro-oncology guidelines are the first that took into account the available means and fixed, in one hand, a minimal level and the other hand the standards to reach for optimal diagnosis and treatment of glioblastoma.

For diagnosis, pathology parameters and tumor biology is a crucial point that mainly depend on acquired expertise in the field by a referent pathologist. The search for molecular markers can not be performed by appropriate and validated immunohistochemical and molecular techniques in many low and middle income countries as advocated in occidental region. In the French guide-

lines (Rigau et al., 2011) for diffuse gliomas, experts have stated that the search for *IDH1* R132H and *P53* expression are required for all gliomas. In addition, the search for *EGFR* amplification and *MGMT* promoter methylation was recommended (Figarella-Branger et al., 2012). The AROME working party did not consider *IDH* mutation and *MGMT* as minimal requirement while at least immunostaining with anti-*IDH1* antibody has been recommended. The lasts can indeed discriminate 4–5% of glioblastomas with favorable prognostic. *MGMT* promoter methylation status is considered by the panel as a standard to reach in all the MTDs involved in brain tumors management. The predictive impact of *MGMT* status on outcome in elderly patients (Wick et al., 2012; Malmström et al., 2015) represents a strong rational for this recommendation from the panel. This will be discussed in the treatment section below.

On the other hand, in order to help the discussion in the frame of the MTDs meetings, the experts have strongly recommended filling systematically a standardized form for pathology and molecular features including all available parameters in all adult diffuse gliomas.

Anatomic MRI is the standard tool for brain tumors characterization at diagnosis step after surgery and also for radiotherapy planning. This standard should be reached by all centers of the limited resources countries. Although spatial resolution of CT scan is limited, the AROME working party has suggested CT scan with contrast infusion as the "minimal requirement" for brain tumor diagnosis and radiotherapy planning. The target volumes definition guidelines vary depending on histological grade of gliomas and scientific societies recommendations. For glioblastomas, the Radiation Therapy Oncology Group favors a two-step technique, with an initial volume (CTV1) including any T2 hyperintensity area (edema) plus a 20 mm margin treated with up to 46 Gy in 23 fractions, followed by a reduction in CTV2 to the contrast enhancement region in T1 with an additional 25 mm margin. The European Organisation of Research and Treatment of Cancer recommends a single-phase technique with a unique GTV, which comprises the T1 contrast enhancement region plus a margin of 20–30 mm. The details of delineation recommendations for 3D conformal radiotherapy delivering 60 Gy in 30 fractions are presented in Table 2. Future innovations should concern advanced imaging techniques with functional information on cellular density (diffusion MRI), angiogenesis (perfusion MRI), metabolic activity and cellular proliferation [positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) (Dhermain, 2014)].

As for radiotherapy device availability, the panel considered TMZ as "minimal requirement". In case of unavailability of machines or TMZ, the patients should be referred to a referent center. Indeed, robust standard of care has been established for the first-line treatment of glioblastoma patients. The Stupp et al. updated data in 2009 showed that concurrent temozolamide and adjuvant TMZ is associated with overall survival rate of 20%, 10% and 5% at 2 years, 5 years and 7 years respectively in patients aged ≤ 70 years with KPS $\geq 70\%$ (Stupp et al., 2009).

Temozolamide could be considered as the standard for elderly patients with high KPS. However, patients' selection for monotherapy (TMZ or EBRT) versus temozolamide in this population is a crucial point of discussion. Recent survival data suggested an important predictive role for *MGMT* promoter methylation status in determining optimal treatment among elderly glioblastoma patients with favorable KPS for whom monotherapy with RT or TMZ is being considered. The NOA-08 (Wick et al., 2012) and Nordic (Malmström et al., 2015) trials have helped to clarify the relative benefits of RT versus TMZ among elderly glioblastoma patients. In particular, they suggested to routinely test all tumors for *MGMT* promoter methylation when patients are being considered for monotherapy as opposed to combined chemoradiotherapy. In the

context of limited resources countries where MGMT status is lacking, the panel recommended hypofractionated schedule as the best choice for elderly if only EBRT without TMZ and standard fractionation if TMZ is administered concurrently in high KPS patients. This will have to be updated regarding the results of the ongoing EORTC 26062–22061 study that will help shed light on whether adding TMZ to hypofractionated EBRT may be beneficial and whether this varies according to MGMT status.

Despite aggressive, multimodal upfront therapies, many glioblastomas will relapse. One of the future challenges is to understand better the mechanisms of radioresistance and discover relevant targets to overcome glioblastoma radioresistance for a durable disease control. Angiogenesis and hypoxia are known to contribute to tumor growth and aggressiveness (Danet et al., 2003; Duda et al., 2007). Thus, VEGF receptor family, one of the key players in angiogenesis, has been selected for clinical trials. In 2009 the FDA approved the use of bevacizumab for recurrent glioblastoma (Cohen et al., 2009; Iwamoto et al., 2009), which allowed new combinations of double drug regimen of TMZ and bevacizumab plus radiation. While phase II studies showed an interesting median OS of 15.9 months (Hainsworth et al., 2012), the two recent randomized trials showed significantly improved PFS but failed to demonstrate any increased OS when bevacizumab is added to standard temozolamide (Chinot et al., 2014; Gilbert et al., 2014). However, both trials did not explore VEGF and VEGFR2 polymorphisms that are considered as central components in the development and progression of glioblastoma.

5. Conclusion

In glioblastoma significant therapeutic advances have been accomplished over the last decade. In addition, many clinical trials are currently testing innovative therapeutic strategies that hopefully will be converted, soon, into clinical benefits for glioblastoma patients. Therefore, major efforts should be performed to stick to the validated standard of care and to implement upcoming progresses into medical management of glioblastoma patients. The AROME neuro-oncology working party reported here the first “minimal requirements” which should be considered as prerequisite for the management of glioblastomas. This limit of guidelines below, which they should not fall, must contribute to: (i) educate practitioners on the importance of structuring the management of patients with no risk of loss of chance and (ii) influence decisions of health policy in some countries where cancer is still not considered as priority in the healthcare programs.

Obviously after the implementation of minimal requirements according to the means, the goal is to reach everywhere around the MA the standards. Furthermore, clinical research development should be also considered as a perspective to benefit patients from innovation and new molecules that could improve glioblastoma patients' survival, which is still one of the lowest in oncology.

Conflict of interest

None of the panel members has any conflict of interest relative to this work.

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