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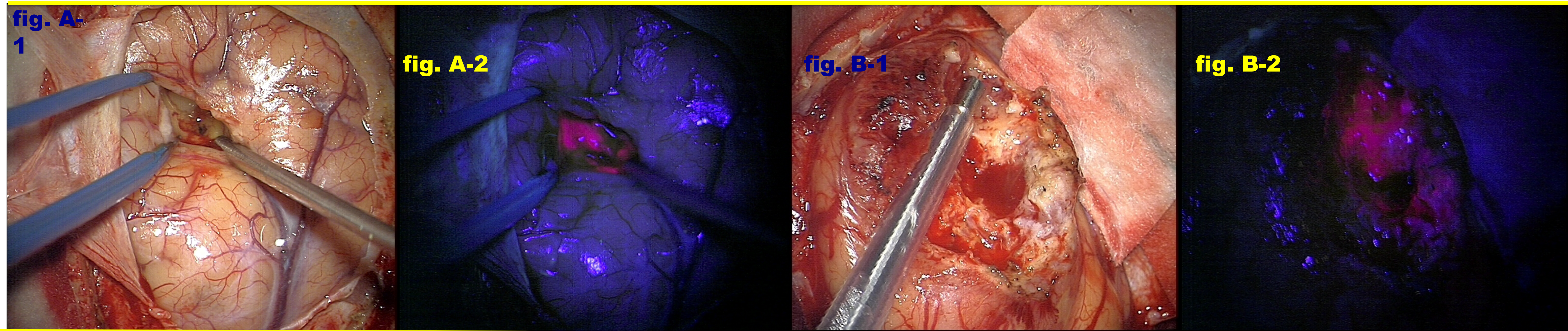
Neurosurgery

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Conflict of Interest: The authors declare that they have no conflict of interest

INTRODUCTION: The prognosis of patients with glioblastoma (GBM) aged 65 years or older is universally poor: their median survival ranges from 4 to 9 months. The main reason is that older patients are often treated more conservatively than younger; this less aggressive treatment is a result of reluctance to offer aggressive treatment for fear of postoperative complications. Several series report that the 5-ALA fluorescence-guided resection increases the extension of tumour removal, improving survival. The aim of this study is to evaluate the impact of 5-ALA on outcome in elderly GBM. The relevance of co-morbidities (CM) in this clinical setting was considered and evaluated in all patients utilizing a slightly modified Cumulative Illness Rating Scale (CIRS, according to Salvi et al, *J Am Geriatr Soc* 56:1926–1931, 2008). All the patients have been submitted to radiotherapy and chemotherapy; second and in some cases third line treatments were utilized in recurrent cases. In more than 90 % of patients tumour tissue showed intraoperative red fluorescence (fig. A); mainly in recurrent GBM, when MRI documented heterogeneous lesions with enhancing areas mixed with gliotic scars, fluorescence-guided surgery allowed a better definition of active tumour tissue (fig. B).



METHODS: The present experience is related to 44 patients with age ≥ 65 years, treated in our Institute, affected by GBM (38 newly diagnosed and 6 recurrent tumours). At diagnosis the age ranged from 65 to 83 years (median 71 yrs.). All patients underwent preoperative and early postoperative MRI, showing contrast enhancing lesions. All patients with KPS >70 and resectable lesions were selected for fluorescence-guided microsurgical removal. An oral dose of 20 mg/kg 5-ALA was administered to each patient. Surgical resection was performed by a Zeiss OPMI Pentero operating microscope; intraoperative 440 nm light was periodically applied during and at the end of resection to visualize the 5-ALA fluorescence, in order to detect tumour infiltration or remnants as red tissue (fig. A-2, B-2). Only 22 patients (all MGMT positive) received, as first line treatment, focal RT plus concomitant daily temozolomide, followed by adjuvant chemotherapy with TMZ; other 16 patients received RT fractionated focal irradiation, at a dose of 40 Gy delivered in 15 fractions; six patients received temozolomide only due to neurological disabilities. In this population second and in some cases third line treatments were utilized in recurrent cases (lomustine, fotemustine and procarbazine). **CM** were identified in all patients utilizing CIRS; a severity score was assigned (1, no problems; 2, current mild problem or past significant problem; 3, moderate disability or morbidity; or 4, severe problem) to each body system. The CIRS comorbidity index (CIRS-CI) was based on the number of body systems that present a severity score of at least 3. Mainly age as well as chronic cardio-pulmonary decline represented the most relevant CM. All patients had a median follow-up of 15 months (6-82).

	N	%
Total sample	44	
Sex		
Male	24	54
Female	20	46
Age (yrs)		
Median (range)	71	(65-83)
≤ 75 years	26	60
>75 years	18	40
KPS score		
Median (range)	85	(60-100)
Co-morbidity (CIRS-CI)	N	%
≤ 3	34	76
≥ 3	10	24

RESULTS: At the operating theatre in more than 90% of patients tumour tissue yielded red fluorescence with different intensity; mainly in recurrent GBM, fluorescence-guided surgery allowed a better definition of active tumour, with a clear border from perilesional “healthy” brain or necrotic tissue, that could be prominent after radiotherapy. Postoperative KPS improved in the net majority of patients. Early postoperative MRI confirmed gross total resection without contrast enhancement in 80 % of patients. In the present experience the procedure did not determine any relevant additional neurological deficit, nor CM. Considering overall survival (OS) of all patients (recurrent GBM included) we obtained a median extension of at least 9.0 months (6 – 28 months). Early postoperative MRI confirmed gross total resection without contrast enhancement in 80 % of patients. In newly diagnosed GBM patients median OS was 18 months, with a rate of survival at 2 years of 35%. Univariate analysis of the whole cohort showed that age greater than 75 years, intermediate or high CIRS-CI, and the presence of >3 comorbidities were associated with shorter survival. In multivariate analysis the predictive role on OS for ages greater than 75 years, intermediate and high CIRS-CI was confirmed.

DISCUSSION: The present 5-ALA experience concerns newly diagnosed and recurrent malignant glioma patients with enhancing lesions in preoperative MRI. In this group of patients the fluorescence guide has been useful to distinguish normal or necrotic tissue from active tumour tissue. It was helpful to localize the tumour in sub-cortical lesions and extend the resection of infiltrating tumour, mainly in recurrence after radiotherapy. Early postoperative MRI resulted without lesional contrast enhancement, mainly when surgical resection was realized in tumours distant from eloquent areas. Elderly patients affected by malignant glioma are suitable for this surgical procedure, improving the probability of achieving maximal tumour resection, when feasible. The 5-ALA-guided removal is easy to perform with acceptable safety. It improves tumour detection and allows extended resection of malignant glioma. 5-ALA guided surgical resection improves survival in elderly patients, without any further additive neurological deficit, resulting helpful mainly in the recurrent setting with a consistent effect on overall survival. Furthermore, this experience supports the importance of evaluating CM, that should drive therapeutic decisions in elderly GBM. The presence of CM represents an important issue in elderly patients because the correlation with frailty, and the role as predictor of disability and mortality. The evaluation of CM should drive the therapeutic decisions in elderly GBM.