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Tiago Filipe Guia Barbosa

Role of reoperation in recurrent glioblastoma

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Role of reoperation in recurrent glioblastoma

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Role of reoperation in recurrent glioblastoma

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Dedicatória

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THE ROLE OF REOPERATION IN RECURRENT GLIOBLASTOMA

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ABSTRACT

Introduction: The treatment of choice for glioblastoma multiforme (GBM) requires primarily surgical resection as an important tool to achieve the best survival. For the recurrent glioblastoma, the role of surgery is not completely settled, and is randomly used with no established criteria.

The aim of this study is to evaluate the role of surgery in the recurrent glioblastoma and compared with the best medical therapy to determine who can benefit the most from reoperation, instead of chemotherapy alone.

Material and methods: We retrospectively analysed 40 patients with recurrent glioblastoma submitted to surgery between 2009 and 2014 and analysed putative prognostic factors associated with overall survival and the time to progression. We compared these results with all patients submitted to a single resective surgery treated during the same period. At the same time, we evaluated different variables within the group of reoperated patients to see which were related to a better outcome.

Results: Reoperated patients group included 29 men and 11 women, with a median age of 55 years and a median Karnofsky Performance Score (KPS) of 90. Non-reoperated patients included 44 men and 24 women, with a median age of 70 years and a median KPS of 90. Reoperated patients had a superior median overall survival (17

months) compared with the non-reoperated (14 months) (*P*=0.018). Factors associated with longer overall survival within the group of reoperated patients were time to second progression (TTP2) superior to 6 months (*P*=0.013) and focal progression, versus multifocal (*P*=0.031). Multifocal progression was an independent predictor of survival. The second surgery was not associated with increased morbidity.

Conclusions: Surgery confers a longer median overall survival when compared to patients with only best chemotherapy in patients with recurrent glioblastoma. The patients with lesions amenable to gross total removal at recurrence should undergo surgery, which results in a better outcome.

Keywords: Glioblastoma, Survival, Reoperation, Recurrence, Prognosis, Retrospective Studies

EL PAPEL DE LA REOPERACION EN EL GLIOBLASTOMA RECURRENTE

RESUMEN

Introducción: El tratamiento de elección para el glioblastoma multiforme (GBM) requiere primeramente una resección quirúrgica, la cual se constituye como una herramienta importante para lograr una mayor supervivencia. Para el glioblastoma recurrente, el papel de la cirugía no está completamente claro y se emplea sin criterios establecidos.

El objetivo de este estudio es evaluar el papel de la cirugía en el glioblastoma recurrente y compararlo con el mejor de los tratamientos médicos para determinar quién puede beneficiarse más de una reintervención, en lugar de someterse únicamente a quimioterapia.

Materiales y métodos: Se analizaron retrospectivamente por una parte, 40 pacientes con glioblastoma recurrente sometidos a cirugía entre 2009 y 2014, y, factores

pronósticos putativos asociados con la supervivencia global y el tiempo hasta la nueva progresión entre ambos grupos. Se compararon estos resultados con todos los pacientes sometidos a una sola cirugía de resección tratados durante el mismo periodo. Al mismo tiempo, se evaluaron diferentes variables dentro del grupo de pacientes reoperados para ver cuáles de ellas se relacionaban con un mejor resultado.

Resultados: El grupo de pacientes reoperados incluyó 29 hombres y 11 mujeres con una edad mediana de 55 años y una mediana según la Escala de Karnofsky (KPS) de 90. Los pacientes no reoperados incluyó 44 hombres y 24 mujeres, con una edad mediana de 70 años y una mediana KPS de 90. Los pacientes reoperados tuvieron una supervivencia global mediana superior (17 meses) en comparación con los no reoperados (14 meses) (*P*=0.018). Los factores asociados a una supervivencia global más larga dentro del grupo de pacientes reoperados fueron un tiempo transcurrido hasta la segunda progresión (TTP2) superior a 6 meses (*P*=0.013) y una progresión focal versus una multifocal (*P*=0.031). Progresión multifocal fue un predictor independiente de supervivencia. La segunda cirugía no se asoció con una mayor morbilidad.

Conclusiones: Cirugía confiere una supervivencia global más larga en comparación con los pacientes restringidos a la quimioterapia en pacientes con glioblastoma recurrente. Los pacientes con lesiones susceptibles de remoción total a la recurrencia deben someterse a una cirugía, que conduce a un mejor resultado.

Palabras Clave: Glioblastoma, Supervivencia, Reoperación, La Recurrencia, Pronóstico, Estudios Retrospectivos

INTRODUCTION

GBM, the most common form of primary brain cancer, is associated with high mortality and morbidity, and has a median survival of approximately 14 months with the current standard treatment, which consists in maximal surgical resection followed by concomitant radiotherapy and temozolomide. Extensive surgical tumor removal has an impact on survival and quality of life for newly diagnosis glioblastoma multiforme[1] but this was not yet proven in recurrent glioblastoma (GBM)[1-3]. Despite all aggressive treatments, recurrence is the rule, reaching almost all cases. Ninety percent of GBM tumors recur at the primary site[4].

It is well documented, that a maximal resection, as a first approach, improves the outcome and significantly increases the median survival, even though it is not used alone but always with radiation and chemotherapy[2]. However, due to its infiltrative nature and the high frequency of tumor *foci* in different regions of the brain, the cure becomes virtually impossible.

At the relapse there is no gold-standard or specific approach to follow but surgery, focal radiotherapy, chemotherapy, and anti-angiogenic drugs (like bevacizumab) are being used. Surgery has an effective palliation[4,5]. Improving and delaying the progression of symptoms, and a significant survival benefit of 3 months, as well as a better quality of life, have already been documented with maximal resection of the recurrent glioblastoma[6]. Nevertheless, there is no consensus of the role of surgery in recurrent glioblastoma and no randomized prospective studies have been done. Repeat surgery could be a definitive indication for recurrence[3].

We analyse retrospectively a cohort of patients from a central hospital, with a diagnoses of GBM, and compare the group of patients who went on an alternative chemotherapy treatment at the time of recurrence with the group of patients submitted

to a second surgery before the change of the chemotherapy regimen. We analysed the overall survival (OS) and the variables that may influence or alter the prognosis

MATERIALS AND METHODS

Patients

The patients with histologically proven glioblastoma treated during a period between 2009 and 2014 in a central hospital – Hospital de São João (HSJ), Oporto, were retrospectively reviewed. The database included 108 patients, 73 man and 35 women, with a median age of 67 years old at the time of diagnosis. All patients underwent the best therapeutic approach available after diagnosis, composed by radiotherapy, chemotherapy and/or maximal tumoral resection[4]. At relapse the patients were treated with second line therapy: surgery and chemotherapy (n=40 patients) or chemotherapy alone (n=68 patients); we used this group as control group.

A descriptive analysis of reoperated group patients (n=40) and the control group were, is summarized in Table 1 and Table 2 and include demographic, clinical and surgery variables. A comparative analysis is summarized in Table 3.

The data were collected reviewing all clinical information from the patients' medical records, anonymously and with the approval of the Hospital Ethical Council.

Prognostic variables

Three essential variables were created to compare the outcome between reoperated and non-reoperated patients: Overall Survival (OS – time from the first surgery until death), Time To First Progression (TTP1 – time from first surgery until first progression) and Time To Second Progression (TTP2 – time from second surgery until second progression), all measured in months. Demographic variables sex and age at the time of diagnosis, were included. We used clinical variables, KPS at diagnosis and after

first and second resection; imaging variables, eloquence and type of resection (subtotal, total) measured with MRI; and treatment variables, corticosteroid therapy before second surgery and second line chemotherapy[7].

Statistical Analysis

The statistical analysis were made using the IBM SPSS®19 program.

A descriptive analysis of both groups (reoperated and control group) was performed, for all demographic, clinical and surgical variables, and medians, ranges and frequencies.

To study the importance of the different prognostic factors in a multivariate analysis, considering a *P*-value <0.2 in univariate analysis, we used Cox proportional hazards modelling.

A univariate analysis with Kaplan-Meier plots and *P*-values with log-rank tests was done within the reoperated group, to evaluate the significance of the various variables studied. In order to compare variables as dichotomies, age, TTP1, KPS, number of surgeries and CCT (corticoid therapy) we used cut-off points based in the greatest generated hazard ratios between the two resulting groups, or in previous evidence[1,8-11]. Then, we studied the OS compared between both groups.

RESULTS

Reoperated patients

Forty patients were reoperated, 29 males (72.5%) and 11 females (27.5%). The median age of the reoperated patients was 55 years (range, 34-73 years). The median KPS, before second surgery was 90 (range, 50 to 100). 30 patients were on corticosteroids, 12 (40%) with a dose of 40 mg or higher and 18 (60%) with a dose lower than 40 mg. Before second surgery, 17 patients (42.5%) presented with headaches, 13

with de novo epilepsy (32.5%) and 16 (40%) presented new neurological deficits. Tumor involvement of eloquent areas were present in 16 patients. The median time to first progression was 5 months (range, 1-27 months) and the median time to second progression was 4 months (range, 1-23 months). The extension of resection was total in 24 patients in both first (61.5%) and second (66.7%) surgeries, and subtotal/partial in 15 patients (38.5%) in the first and 12 patients (33.3%) in the second surgery. In 32 patients (82.1%) occurred a focal tumoral progression and in 7 patients (17.9%) it was multifocal, after the first surgery. Six or more cycles of chemotherapy were completed in 14 patients (37.8%) and less than six in 23 patients (62.2%).

Control group

Sixty-eight patients were not reoperated, 44 males (64.7%) and 24 females (35.3%). The median age of the non-reoperated patients was 70 years (range, 48-80 years). The median KPS, before first surgery was 90 (range, 50 to 100). 27 patients (60.3%) have involvement of eloquent brain areas. The median time to first progression was 7.5 months (range, 1-40 months) and the median time to second progression was 4 months (range, 1-23 months). The extension of resection was total in 24 patients (35.3%) and subtotal/partial in 44 patients (64.7%). A focal tumoral progression was verified in 53 (85.5%) patients and a multifocal progression in 9 (14.5%) patients. Six or more cycles of chemotherapy were completed in 26 patients (40.6%) and less than six in 38 patients (59.4%).

Comparison between the two groups is summed in Table 3.

Survival Outcomes

The median overall survival (in months) of reoperated patients, calculated for each factor is summarized in Table 4.

Only three variables were found to have statistical significance (P<0.05) in improving OS in reoperated patients, TTP2 superior to 6 months, focal progression and

reoperation. The median survival of patients with a TTP2 superior to 6 months was 26 (SE = 3.864) months, compared with only 14 (SE = 1.677) for earlier progressions (*P*=0.013). Median survival for reoperated patients with multifocal progression was 14 months (SE = 4.988), compared with 18 months (SE = 1.635) in focal progression (*P*=0.031). When compared reoperated patients (2 or more surgeries) versus control group (only 1 surgery), the first one had a median survival of 17 months (SE = 1.327) in contrast with 14 months (SE = 1.062) in the second group (*P*=0.018).

Preoperative KPS in the second surgery of 80 or higher had a median OS of 18 months (SE = 4.163) and 12 months (SE = 1.789) if lower than 80 (*P* =0.093). With a TTP1 of more than 6 months, the median OS was 22 (SE = 1.465) compared to 16 months if less than 6 months (SE = 5.132) (*P*=0.251). Median OS of patients who underwent 6 or more cycles of chemotherapy was 23 months (SE = 3.430), compared to 12 months (SE = 2.830) with less than 6 cycles (*P*=0.055). The absence of headaches before second surgery was related with a median OS of 15 months (SE = 4.062), compared with 19 months (SE = 2.744) if present *(P*=0.074). Although no significance is observed for these variables, a tendency to a better survival could be noticed in all of them.

The median OS for eloquence was 16 months compared to 17 months in patients with no eloquence (*P*=0.482). Patients with TTP1 superior to 6 months had a median OS of 22 months, compared to 16 months if inferior (*P*=0.251). With CCT doses above 40 mg, median OS was 18 months, compared with 17 months for doses lower than 40 mg (*P*=0.505). Patients with de novo epilepsy had a median OS of 16 months compared to 18 months without it (*P*=0.490). Patients with an age at the time of diagnosis of more than 60 years had a median OS of 15 months compared to 18 months if less than 60 years (*P*=0.213). For both total resection in the first and second surgeries, the median OS was 17 months compared to 16 months with incomplete resection (*P*=0.433 and *P*=0.848, respectively).

Multivariate analysis was performed using Cox proportional hazards modelling for the variables preoperative KPS (second surgery), TTP1, number of chemotherapy cycles, type of progression and age (superior to 60 years). Forward stepwise modelling only confirmed the prognostic significance of multifocal progression (*P*=0.065; HR, 4.246; 95% CI, 0.152 to 0.975).

DISCUSSION

The aggressive behaviour of GBM and the invariable recurrence had motivating investigators to find new treatment options, but also creates the need to understand the real efficacy of the traditional surgery and chemotherapy. However, while there is no adequate alternative, surgery remains one of the main ways to treat and palliate the recurrence of the tumor. Still, there are not enough studies of patients validating the role of surgery in prolong survival after recurrence.

In this study, we study the OS and the outcome of patients with recurrent glioblastoma submitted to surgery and selected prognostic variables already determined to be significant on previous reports on recurrent glioblastoma surgery[9,11].

All the patients included are from the same hospital, and for all the choice of treatment was always the best option considered at the time of progression.

The main factor we intend to study is the number of surgeries, in a pool of patients with similar demographic and clinical features. All patients treated between 2009 e 2014 were included minimizing the selection bias. The group of reoperated patients included all patients with more than one resection and the control group included all patients submitted to one resection plus radio or chemotherapy. According to HSJ protocols, reoperation is chosen in single lesions if a complete resection is estimated or if relieving of symptoms is probable. All other cases were treated with chemotherapy.

The both groups were similar, as shown in Tables 1, 2 and 3. Sex, KPS, TTP1, eloquence, focal progression, and number of temozolomide cycles, all have similar frequencies in both groups. Patients median age (55 years in reoperated and 70 in control group) is within the median age range of diagnosis of GBM (45-70 years)[12]. This age difference between both groups can be explained by the preference of surgical treatment in younger patients, associated with their better clinical condition at the time of recurrence. Another important difference is the total resection in first surgery in reoperated patients of 61.5% comparing to only 35.3% in control group. As said before, patients with a planned maximal resection would have a better prognosis. In addition, to justify this difference, evidence shows a better overall survival with resection at recurrence, associated with a first maximal resection[1]. This was taken into account when choose to reoperated.

The type of adjuvant treatment at the time of recurrence was similar in both groups of patients. Most patients reoperated were simultaneously exposed to new cycles of chemotherapy, except for 10, who only had resection. The rest of them had treatment with temozolomide (13 patients), bevacizumab (10 patients) or PCV (procarbazine, lomustine, vincristine) (7 patients), depending on the first line used, the adverse effects and patient toleration, usually in that order of choice. The treatment of non-reoperated patients consisted in only chemotherapy, just the same of reoperated (temozolomide in first line, followed by bevacizumab and at last PCV), used in similar proportions.

Inside the group of reoperated patients, it was clear that a longer time to second progression, as well as focal progression were associated with a longer OS of 4 and 8 months, respectively. This can be a tool to predict benefit with reoperation. Other factors showed tendency to improve OS are preoperative KPS, absence of headaches, and temozolomide cycles. Even though not significant, there is evidence in other studies proving the prognostic importance of clinical status (with KPS). Barker et al[13], predicted longer survival periods after reoperation with a higher preoperative KPS scores (P=0.03).

In other study, Barbagallo et al.[11] had a KPS superior or equal to 90 associated with significant longer survival time after reoperation (29 weeks versus 18 weeks).

Resection extension, proven to improve overall survival with resections superior to 80%, by Oppenlander et al.[14], was not significant, probably due to the reduced number of patients studied. Multifocal progression, when evaluated in a multivariable analysis, predicted a bad outcome with reoperation, as an independent variable. This suggests that if recurrence is multifocal, patients do not benefit with resection.

The main goal of this work is to find evidence supporting the benefit or disadvantage of reoperation in recurrence and for that, we compared both groups of patients. The median OS in reoperated patients was 17 months, 3 months higher versus non-reoperated patients (P=0.018). Barker et al.[13] reported an identic OS benefit of 3 months, although with inferior OS in both groups, 9 months in reoperated patients compared to 6 months with only resective surgery. McNamara et al.[15] reported higher rates of success with reoperation, with a OS of 20.8 months versus 9.9 months with primary surgery alone ($P < 0.001$).

We studied and grouped the patients by variables related to the tumor prognosis, as verified and validated by Park et al.[7]; other variables not studied could also influence response to treatment. The reduced number of 40 reoperated patients included, although similar to most studies of this kind (Park et al.[7] with 55 patients Barker et al.[13] with 46 patients), represent a statistical limitation and maybe another bias, also explaining why there was no significance in some of the variables with a tendency to be associated with a better prognosis (preoperative KPS, absence of headaches, and temozolomide cycles).

CONCLUSION

This data alone is not enough to validate the use of reoperation in every recurrence, neither to establish reoperation as the best treatment for it. Nevertheless, we can conclude that surgery confers a longer median overall survival when compared to patients with only best chemotherapy in patients with recurrent glioblastoma. With our results we can predict the benefit of surgery for an important group of patients, including all that underwent the best therapeutic approach available after diagnosis, with maximal tumoral resection and focal progression at recurrence.

Still, many factors independent from surgery may influence the prognosis of this tumor, and more research is necessary, in order to find a way to maximize the benefits of reoperation and improve the OS, as well as the quality of life of these patients.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

TABLES

Table 1: Demographic, Clinical and Surgery Related Variables of Reoperated Patients of Hospital de São João

Variable		No	%
Age of diagnosis, years			
	Median	55	
	Range	34-73	
Sex			
	Male	29	72.5
	Female	11	27.5
KPS, preoperative (2nd surgery)			
	Median	90	
	Range	50-100	
	100	13	32.5
	90	8	20
	80	3	7.5
	70	6	15
	60	3	7.5
	50	6	15
CCT, dose (mg)			
	≥40	12	40
	<40	18	60
Headaches			
	Yes	17	42.5
	No	23	57.5
Epilepsy			
	Yes	13	32.5
	No	27	67.5
Time To First Progression, months			
	Median	5	
	Range	1-27	
Time To Second Progression, months			
	Median	4	
	Range	1-23	
Eloquence			
	Yes	16	40
	No	24	60
Resection extention (1st surgery)			
	Total	24	61.5
	Subtotal	6	15.4
	Partial	9	23.1
Resection extention (2nd surgery)			
	Total	24	66.7
	Subtotal	7	19.4
	Partial	5	13.9
Type of Progression			
	Focal	32	82.1
	Multifocal	7	17.9
Chemotherapy , no. of cycles completed			
	≥6	14	37.8
	<6	23	62.2

Abbreviation: KPS, Karnofsky performance status; CCT, corticoid therapy.

Table 2: Demographic, Clinical and Surgery Related Variables of the Control Group of Patients of Hospital de São João

Variable		No		%
Age of diagnosis, years				
	Median		70	
	Range		48-80	
Sex				
	Male	44		64.7
	Female	24		35.3
KPS, preoperative (1st surgery)				
	Median		90	
	Range		50-100	
	100	15		28.3
	90	22		41.5
	80	7		13.2
	70	5		9.4
	60	3		5.7
	50	1		1.9
Time To First Progression, months				
	Median		7.5	
	Range		1-40	
Eloquence				
	Yes	27		39.7
	No	41		60.3
Resection extention (1st surgery)				
	Total	24		35.3
	Subtotal	23		33.8
	Partial	21		30.9
Type of Progression				
	Focal	53		85.5
	Multifocal	9		14.5
Chemotherapy , no. of cycles completed				
	≥6	26		40.6
	<6	38		59.4

Abbreviation: KPS, Karnofsky performance status; CCT, corticoid therapy.

Table 3: Comparison table of Demographic, Clinical and Surgery Related Variables between both Reoperated and Control groups

	Frequencies in both groups	
	1 Surgery	≥2 Surgeries
Sex, male	64.70%	72.50%
Age at diagnosis, years (median)	70	55
KPS, preoperative (median)	90	90
TTP1, months (median)	7.5	5
Eloquence	39.70%	40%
Total Resection (1st surgery)	35.30%	61.50%
Focal Progression	85.50%	82.10%
≥ 6 cycles of Chemotherapy	40.60%	37.80%

Abbreviation: KPS, Karnofsky performance status; TTP1, time (from the first surgery) to first progression.

Table 4: Univariate Analysis of Prognostic Factors

	Median survival (months)		
Factor	Yes	No	*P*
KPS, preoperative (2nd surgery) ≥ 80	18	12	0.093
Eloquence	16	17	0.482
TTP1, > 6 meses (1st Surgery)	22	16	0.251
TTP2, > 6 meses (2nd Surgery)	26	14	0.013
CCT ≥ 40 mg, preoperative (2nd surgery)	18	17	0.505
Headaches	15	19	0.074
Epilepsy	16	18	0.490
Age > 60	15	18	0.213
Total Resection (1st surgery)	17	16	0.433
Total resection (2nd surgery)	17	16	0.848
≥ 6 Cycles of Chemotherapy	23	12	0.055
Multifocal Progression	14	18	0.031
Reoperation	17	14	0.018

Abbreviation: KPS, Karnofsky performance status; TTP1, time (from the first surgery) to first progression; TTP2, time (from second surgery) to second progression; CCT, corticoid therapy.

FIGURES

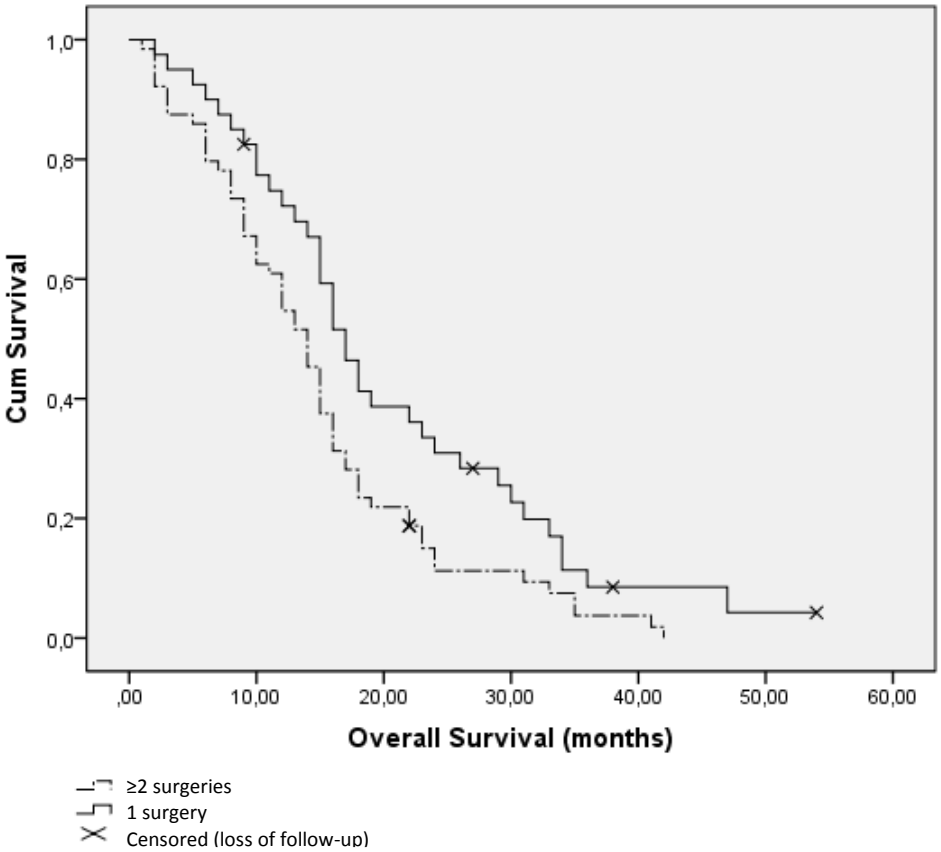

Figure 1: Kaplan-Meier Plot of Number Of Surgeries, found to be significantly associated with Overall Survival.

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ANEXOS

- Normas para escrita de artigo da Revista de la Sociedad Española de Neurocirugía

Neurocirugía
Revista de la Sociedad Española de Neurocirugía

INSTRUCCIONES PARA LOS AUTORES

Julio de 2012

CONSIDERACIONES GENERALES

Neurocirugía (www.elsevier.es/neurocirugia) de periodicidad bimestral considerará para su publicación trabajos científicos originales de contenido clínico y experimental relacionados con la neurocirugía y otras ciencias neurológicas afines, así como artículos solicitados de expertos, casos clínicos, artículos de opinión y cualquier otra información de interés para los neurocirujanos. *Neurocirugía* acepta trabajos tanto en castellano como en inglés.

La revista está indexada en *Science Citation Index Expanded*, *Journal of Citation Reports*, *Scopus* y *Science Direct*.

Todos los manuscritos se someten a una valoración efectuada por revisores expertos *(peer review)*, ajenos al Comité de Redacción de la revista y realizada de forma anónima.

Los manuscritos deben elaborarse siguiendo los requisitos de uniformidad para manuscritos presentados para la publicación en revistas biomédicas, elaborados por el Comité Internacional de Directores de Revistas Médicas, disponibles en http://www.icmje.org, y ajustarse a las siguientes instrucciones para los autores.

ENVÍO DE MANUSCRITOS

Los manuscritos deben remitirse por vía electrónica a través del *Elsevier Editorial System* (EES) en la dirección http://ees.elsevier.com/neurocirugia, donde se encuentra la información necesaria para realizar el envío. La utilización de este recurso permite seguir el estado del manuscrito a través la página web.

El manuscrito se debe acompañar de una carta de presentación (véase más adelante) redactada en la sección **Enter Comments** del EES. A través de esta plataforma, además de cargar la carta, los autores deberán declarar si el trabajo ha tenido algún tipo de financiación, si tienen algún conflicto de intereses, el cumplimiento de las responsabilidades éticas y transferir todos los derechos sobre el artículo.

El texto del manuscrito (salvo la primera página o página del título), el resumen/*abstract*, las palabras clave/*key words*, las referencias, las tablas, las leyendas y los pies de figuras se incluirán en un único fichero, y cada una de las figuras en ficheros separados. Estos documentos se grabarán en la sección **Attach Files.**
Consulte las instrucciones generales de uso del EES en su tutorial para autores:
http://epsupport.elsevier.com/al/12/1/article.aspx?aid=1562&bt=4

CARTA DE PRESENTACIÓN

Todos los manuscritos deben ir acompañados necesariamente de una carta de presentación (véase el apartado "*Obligaciones del autor*") que se incluirá en la sección **Attach Files** del EES, en la que, además de incluir el título del trabajo, se indique:

1) La sección de la revista en la que se desea publicar el trabajo.
2) La declaración de que el trabajo es original y no se encuentra en proceso de evaluación por ninguna otra revista científica.
3) La explicación, en un párrafo como máximo, de cuál es la aportación original y la relevancia del trabajo en el área de la revista.
4) La declaración de que los autores han tenido en cuenta las "Responsabilidades éticas" incluidas en estas normas y, entre ellas: *a)* que los procedimientos seguidos en la investigación se han realizado conforme a las normas éticas del comité de experimentación humana o animal responsable (institucional o regional) y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki; *b)* que garantizan el derecho de sus pacientes a la privacidad y confidencialidad conforme a lo descrito en el apartado correspondiente de esas normas y que en el artículo se ha evitado cualquier tipo de dato identificativo en texto o imágenes y, en cualquier caso, *c)* que están en posesión del consentimiento informado de los pacientes para la participación en el estudio y la publicación de los resultados en formato de libre acceso en Internet en la revista *Neurocirugía* y que así lo han declarado en el EES.
5) La declaración de cualquier beca (técnica o económica) de una institución.
6) La confirmación de que los autores firmantes cumplen los requisitos de autoría (es opcional declarar el grado de participación) conforme a lo recogido en el apartado de "Autoría" de estas normas y conforme con lo han declarado en el EES.

7) En el supuesto de que parte del artículo hubiera sido previamente publicado en otra revista (publicación redundante o duplicada), se deberán especificar aquí los detalles y declarar que se está en posesión de los permisos de publicación necesarios por parte del autor y el editor de la misma (véase también el apartado "Garantías y cesión de derechos de propiedad intelectual").
8) La declaración en este punto por cada uno de los autores de la existencia o no de conflicto de intereses y la confirmación de su declaración en la sección **Additional Information** del EES.
9) Deberá hacerse constar si el trabajo o parte del mismo ha sido presentado en la Reunión Anual de la SENEC o en otras reuniones o congresos.

Los autores podrán proponer a personas que consideren cualificadas para realizar la revisión crítica del manuscrito. Los revisores sugeridos no deben haber sido colaboradores o coautores en los tres años anteriores ni deben haber contribuido con una crítica sustancial del manuscrito. Pueden hacer sus sugerencias a través del EES, en la sección **Suggest Reviewers.**

SECCIONES

Originales. Trabajos empíricos relacionados con cualquier aspecto de la investigación en el campo de la neurocirugía que tengan forma de trabajo científico, con los siguientes apartados: resumen, introducción, material y métodos, resultados y discusión. La extensión del texto será ilimitada, incluyendo un resumen estructurado, palabras clave y referencias bibliográficas. Además del texto, se admitirán figuras y tablas. El número de autores recomendado es de 6, aunque se permitirá un máximo de 8.

Para la elaboración de ensayos clínicos controlados deberá seguirse la normativa CONSORT (JAMA.1996;276:637-9). Disponible en: http://www.consort-statement.org/ y para el metaanálisis la normativa QUOROM (http://www.consort-statement.org/QUOROM.pdf). Los manuscritos que presenten resultados de estudios sobre validez de pruebas diagnósticas deberán incluir el diagrama de flujo STARD (http://www.consort-statement.org/stardstatement.htm).

Casos clínicos. Casos que supongan una aportación importante al conocimiento de la fisiopatología, etiología u otros aspectos de un proceso clínico. La extensión máxima del texto será de 1.500 palabras, 5 DIN-A4, incluyendo un resumen sin estructurar de 150 palabras y un máximo de 15 referencias bibliográficas. La estructura de estos trabajos será la misma que la de los originales (introducción, métodos, resultados y discusión), Resumen, Introducción, Caso o Casos Clínicos, Discusión, y Conclusiones y podrá incluirse hasta un máximo de 3 tablas y/o figuras. El número de autores recomendado es de 4, aunque se permitirá un máximo de 6.

Revisiones. Este tipo de manuscritos será encargado específicamente por el Comité Editorial. Los autores que espontáneamente deseen colaborar en esta sección deberán consultar previamente a los editores de la revista. Serán trabajos de revisión sobre temas relevantes y de actualidad en neurocirugía con la siguiente estructura: Resumen, Introducción, Desarrollo y Conclusiones La extensión máxima del texto será de 16 DIN-A4, en cuya extensión se incluirá un resumen y un *abstract* de 150 palabras si no está, y las palabras clave correspondientes. También se incluirán 50 referencias bibliográficas como máximo. Es aconsejable que el número de firmantes no sea superior a 3. Además del texto, se admitirán hasta 4 figuras o tablas.

Artículos de opinión. Esta sección tiene como objetivo publicar temas relevantes y de actualidad en neurocirugía que contengan componentes novedosos para la especialidad. No es necesario que el texto se estructure formalmente, pero deberá guardar la lógica narrativa (introducción, desarrollo de la experiencia y conclusiones). La extensión máxima del texto será de 10 DIN-A4, en cuya extensión se incluirá un resumen y un *abstract* de 150 palabras sin estructurar o de 250 si está estructurado) y las palabras clave correspondientes. También se incluirán 15 referencias bibliográficas como máximo. Además del texto se admitirán hasta 2 figuras o tablas.

Cartas al director. Harán referencia a trabajos publicados en la revista y aportarán opiniones, observaciones o experiencias que por sus características puedan ser resumidas en un texto breve. La extensión máxima será de 2 DIN-A4 de texto, sin resumen, incluyendo un máximo de 5 referencias bibliográficas. El número máximo de autores será 4. Se admitirá 1 figura o 1 tabla.

Otras secciones. La revista incluye otras secciones (Editoriales y Artículos especiales, entre otras) cuyos artículos encarga el Comité Editorial. Los autores que espontáneamente deseen colaborar en alguna de estas secciones deberán consultar previamente a los editores asociados de la revista.

PRESENTACIÓN GENERAL DEL MANUSCRITO

Los manuscritos, que podrán estar escritos en español o en portugués, tendrán el formato de papel tamaño DIN-A4 a doble espacio con un tipo de letra de 11 caracteres por pulgada. Las páginas deben estar numeradas correlativamente. Las abreviaturas se introducirán tras el término completo al que representa en el primer uso que se haga de ellas en el artículo a excepción del título. Las unidades de medida se expresarán preferentemente en unidades del sistema internacional. Las cifras decimales se separarán de las unidades mediante una coma y los millares se indicarán mediante un punto.

1. Página del título

Constará de la siguiente información:

- El título del artículo (en castellano y en inglés para el *abstract*) debe describir adecuadamente el contenido del trabajo. Será breve, claro e informativo y sin acrónimos.
- El nombre y el primer apellido de los autores (o los dos apellidos unidos mediante guión). Se recomienda que los autores definan su "apellido bibliográfico" mediante el uso de un solo apellido o, en su defecto, los dos apelli-

dos unidos mediante un guión, para evitar confusiones en las bases de datos bibliográficas.
- En el nombre del (los) departamento(s) y la(s) institución(es) a los que el trabajo debe ser atribuido no se incluirá el cargo académico o profesional.
- Se incluirá el nombre completo, número de teléfono, correo electrónico y la dirección postal completa del autor al que se dirige la correspondencia, que será el responsable de la corrección de las pruebas.

La primera página debe presentarse en un archivo separado del resto del manuscrito.

2. Resumen y palabras clave (2ª página)

Es el apartado que sirve de presentación del trabajo en bases de datos, tanto nacionales como internacionales; por eso es de vital importancia su redacción. Debe realizarse en español y en inglés. Será de 150 palabras y sin estructurar en el caso de las "Revisiones" y las "Revisiones breves" con Introducción, Desarrollo y Conclusiones. El de los "Originales" será de 250 palabras y estructurado en los siguientes apartados: *Objetivo*, señalando el propósito fundamental de la investigación; *Material y método*, la manera de llevarla a cabo: explicando el diseño del estudio, los criterios de valoración de las pruebas diagnósticas y la dirección temporal (retrospectivo o prospectivo). Se mencionará el procedimiento de selección de los pacientes, los criterios de entrada, y el número de los pacientes que comienzan y terminan el estudio; *Resultados*, hará constar los resultados más relevantes y significativos del estudio, así como su valoración estadística; *Conclusiones*, se mencionarán las que se sustentan directamente en los datos junto con su aplicabilidad clínica. Habrá que otorgar el mismo énfasis a los hallazgos positivos y a los negativos con similar interés científico.

Al final del resumen deben figurar 6 palabras clave de acuerdo con las incluidas en el *Medical Subject Headings* (MeSH) del *Index Medicus*/MEDLINE, disponible en inglés en: http://www.nlm.nih.gov/ mesh/ meshhome.html y traducirlas al castellano.

A continuación del resumen y palabras clave se redactará el *title*, el *abstract* y se añadirán las *key words*. El *abstract* debe ser una traducción completa y correcta del resumen al inglés.

3. El texto (3ª página y siguientes)

En la redacción del texto se recomienda la forma impersonal. Conviene dividir claramente los trabajos en apartados, siendo de desear que el esquema general sea el siguiente:

1) *Introducción*. Será breve y debe proporcionar sólo la explicación necesaria para que el lector pueda comprender el texto que sigue a continuación. Se deben citar sólo aquellas referencias estrictamente necesarias según criterios de actualidad y relevancia en relación con los objetivos del estudio. No debe contener tablas ni figuras. Debe incluir un último párrafo en el que se exponga de forma clara el o los objetivos del trabajo.
2) *Material y métodos*. Se referirá el centro donde se ha realizado la investigación, el período o duración, las características de los pacientes y el criterio de selección y las técnicas utilizadas, describiendo con precisión cómo se llevó a cabo el estudio, el tipo de diseño utilizado, los criterios de inclusión y exclusión, las pautas de tratamiento, el análisis estadístico, etc., proporcionando los detalles suficientes para que la experiencia pueda repetirse sobre la base de la información aportada. Cuando sea aplicable, deben describirse brevemente las normas éticas seguidas por los investigadores tanto en estudios observacionales como experimentales o cuasi experimentales. Los estudios en seres humanos deben contar con la aprobación expresa del comité local de ética y de ensayos clínicos, y así debe figurar en el manuscrito (véanse "Responsabilidades éticas"). Se debe exponer concisamente el tipo de diseño y, en referencia a los métodos estadísticos empleados, describir con detalle aquellos que no sean habituales en la investigación en neurocirugía. En las revisiones, en el apartado de fuentes, se describirá dónde y cómo se ha realizado la búsqueda de la información.
3) Los resultados deben ser concisos y claros, e incluirán el mínimo necesario de tablas y figuras, de acuerdo con el tipo de trabajo. Se presentarán de tal modo que no exista duplicación y repetición innecesaria de información en el texto y en las figuras y tablas.
4) *Discusión*. Los autores tienen que exponer sus propias opiniones sobre el tema. Destacan aquí: *a)* el significado y la aplicación práctica de los resultados; *b)* las consideraciones sobre una posible inconsistencia de la metodología y las razones por las que pueden ser válidos los resultados y sus limitaciones, relacionándolas con otros estudios importantes; *c)* la relación con publicaciones similares y la comparación entre las áreas de acuerdo y desacuerdo, y *d)* las indicaciones y las directrices para futuras investigaciones.

4. Información incorporada por la editorial

En este punto la editorial añadirá la información relativa a las *"Obligaciones del autor"* declaradas en el EES en relación a las *"Responsabilidades Éticas"*, en concreto lo relativo a: *a)* la protección de personas y animales; *b)* la confidencialidad, y *c)* el derecho a la privacidad y el consentimiento informado; la financiación; el grado de participación de los autores (opcional) y las declaraciones de cada uno de ellos en relación con la existencia o no de un conflicto de intereses.

5. Agradecimientos

Sólo se expresarán a aquellas personas que hayan contribuido claramente a hacer posible el trabajo, pero que no puedan ser reconocidos como autores. Todas las personas mencionadas específicamente en *"Agradecimientos"* deben conocer y aprobar su inclusión en dicho apartado. La ayuda técnica debe ser expresada en un párrafo distinto al dedicado a reconocer las ayudas económicas y materiales procedentes de instituciones, que deben reconocerse en *"Financiación"* y dan lugar a un potencial conflicto de intereses.

6. Bibliografía

Los nombres de las revistas deben abreviarse de acuerdo con el estilo usado en el Index Medicus: consultar la «List

of Journals Indexed» que se incluye todos los años en el número de enero del Index Medicus.

Las referencias bibliográficas se identificarán en el texto mediante llamada en números arábigos en superíndice y numeración consecutiva, según su orden de aparición en el texto, tablas y figuras. En los casos que la cita se coloque junto a un signo de puntuación, la cita precederá al signo (por ejemplo, a diferencia de trabajos previos[6-9], los resultados muestran…).

Se evitará en lo posible la inclusión como referencias bibliográficas de libros de texto y de actas de reuniones.

En lo posible se evitará el uso de frases imprecisas como referencias bibliográficas; no pueden emplearse como tales «observaciones no publicadas» ni «comunicación personal», pero sí pueden citarse entre paréntesis dentro del texto.

Las abreviaciones de las revistas se ajustarán a las que utiliza el *Index Medicus* de la *US National Library of Medicine,* disponibles en: http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi

Las citas bibliográficas deben comprobarse comparándolas con los documentos originales, indicando la página inicial y la página final, señalando sólo los dígitos que difieran de la página inicial (por ejemplo, 34-9 y no 34-39; 136-41 y no 136-141). La exactitud y veracidad de las referencias bibliográficas es de la máxima importancia y debe ser garantizada por los autores. Las citas tendrán el formato propuesto por el Grupo de Vancouver. A continuación se dan unos ejemplos de citas correctas para diferentes tipos de documentos (para formatos no incluidos en esta relación pueden consultarse más ejemplos en la página web: http://www.icmje.org).

Artículo de revista

Apellido e iniciales del nombre separados por comas. Se citarán todos los autores si son 6 o menos de 6, colocando solamente una coma entre ellos, y un punto tras el último autor; si son 7 o más, relacionar sólo los 6 primeros y se añadirá la expresión et al. A continuación se incluye el título del trabajo en el idioma original y un punto al final, abreviatura del nombre de la revista, seguido también de punto, año de publicación seguido de punto y coma, número de volumen, tras el que se pondrán dos puntos, y la primera y última página del trabajo separadas por un guión.

Artículo de revista estándar con menos de 6 autores

Castle M, Barrena C, Samprón N, Arrese I. Remote cerebellar haemorrhage after lumbar arthrodesis: case report and literature review. Neurocirugia (Astur). 2011;22: 574-8.

Artículo de revista estándar con más de 6 autores

Álvarez-Salgado JA, Ruiz-Ginés JA, Fuentes-Ventura CD, Gonzales-Sejas AG, Belinchón de Diego JM, González-Llanos Fernández de Mesa F, et al. Intracranial tuberculoma simulating a malignant tumor: case report and literature review. Neurocirugia (Astur). 2011;22:600-4.

Artículo en prensa

Barrow DL, Tindall GT. Visual loss following transephenoidal surgery. Neurosurgery. En prensa 2011.

El autor es una organización

Grupo de Estudios de Enfermedades Cerebrovasculares de la SEN. Enfermedad carótida de origen aterotrombótico: hacia un consenso en la prevención. Neurología. 2004;19:193-212.

Individuo y organización, ambos son autores

Vallancien G, Emberton M, Harving N, Van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1274 European men suffering from lower urinary tract symptoms. J Urol. 2003;169:2257-61.

Sin autor

The entry of NEUROCIRUGIA in the Index Medicus/MEDLINE database. Neurocirugia (Astur). 2002;13:4-5.

Suplemento de un volumen

Magni F, Rossoni G, Berti F. BN-52021 protects Guinea pigs from heart anaphylaxis. Pharmacol Res Comoun. 1988;20 Suppl 5:75-8.

Suplemento de un número

Pou A. Enfermedades de las neuronas motoras. Estado actual. Neurología. 1996;11 Suppl 5:1S-6S.

Parte de un volumen

Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. Int J Psychoanal. 2002;83 (Pt 2):491-5.

Parte de un número

Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumors. J Vasc Interv Radiol. 2002;13(9 Pt 1):923-8.

Número sin volumen

Baumeister AA. Origins and control of stereotyped movements. Monogr Am Assoc Ment Defic. 1978;(3):352-84.

Sin volumen ni número

Outreach: bringing HIV-positive individuals into care. HRSA Careaction. 2002 Jun:1-6.

Libro

Autores como editores

Diener HC, Wilkinson M, editores. Drug-induced headache. Nueva York: Springer-Verlag; 1988.

Autor(es) personal(es) (no editores)

Jennett B, Teasdale G. Management of Head Injuries. Philadelphia; FA Davis Company; 1981.

Autores y editores distintos

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2ª ed. En: Wieczorek RR, editor. White Plains: March of Dimes Education Services; 2001.

Organización como autor

Royal Adelaide Hospital; University of Adelaide, Department of Clinical Nursing. Compendium of nursing research and practice development, 1999-2000. Adelaide: Adelaide University; 2001.

Capítulo de libro
Rhoton AL. Microsurgical anatomy of the third ventricular region. En: Apuzzo MLJ, editor. Surgery of the third ventricle. Baltimore; Williams & Wilkins; 1987. p. 92-166.

Actas de reuniones
Vivian VL, editor. Child abuse and neglect: a medical community response. Actas de First AMA National Conference on Child abuse and neglect; 1984, marzo 30-31; Chicago, American Medical Association, 1985.

Tesis
Gómez López PA. Hemorragia subaracnoidea aneurismática: Análisis de los factores que influyen en la aparición de isquemia cerebral y en la evolución final [tesis]. Madrid: Facultad de Medicina. Universidad Autónoma; 1991.

Documentos en formato electrónico
Artículo estándar en formato electrónico
Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis. [revista electrónica] 1995;1 [consultado 5 Jun 1996]: Disponible en: http://www. cdc. gov/ncidod/EID/eid.htm

CD-ROM:
Anderson SC, Poulsen KB. Anderson's electronic atlas of haematology [CD-ROM]. Filadelfia: Lippincott Williams & Wilkins; 2002.

Sitio en internet (página)
Cancer-Pain.org [página en internet]. Nueva York: Association of Cancer Online Resources, Inc.; c2000-01 [actualizada 16 May 2002; citada 9 Jul 2002]. Disponible en: http://www.cancer-pain.org/

Otros materiales publicados
Libro de resúmenes de congreso (Conference proceedings)
Harnden P, Joffe JK, Jones WG, editores. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 13-15 septiembre 2001; Leeds, UK. Nueva York: Springer; 2002.

7. Tablas

Se presentarán en hojas aparte dentro del archivo de texto e incluirán: *a)* numeración de la tabla con números arábigos, y *b)* el título correspondiente. Se presentará una sola tabla por hoja y se procurará que sean claras y que su comprensión sea posible sin hacer referencias al texto. Las siglas y abreviaturas se acompañarán siempre de una nota explicativa al pie. Si una tabla ocupa más de una página, se repetirán los encabezamientos en la hoja siguiente. La revista admitirá tablas que ocupen hasta un máximo de una página impresa. A pie de tabla se hará constar el grado de significación estadística, si no se hubiera incluido en el texto de la tabla.

8. Figuras

Se considerarán figuras las fotografías, gráficos de datos y esquemas. Cada figura irá en un archivo aparte. Se identificarán con números arábigos que coincidan con su orden de aparición en el texto. Es muy importante que las imágenes sean de calidad inmejorable para poder obtener así buenas reproducciones; se presentarán de manera que los cuerpos opacos (huesos, sustancias de contraste) aparezcan en blanco. El Comité de Redacción de la Revista se reserva el derecho de rechazar, previa información a los autores, las figuras que no reúnan la calidad necesaria para conseguir una buena reproducción. Las fotografías se enviarán preferiblemente en formato JPG o TIFF, con una resolución de 300 puntos por pulgada (dpi). Las fotografías se publicarán en blanco y negro en la versión impresa de la revista mientras que se mantendrá el color en la versión electrónica.
Si se reproducen fotografías o datos de pacientes, éstos no deben ser identificativos del sujeto. En todos los casos, los autores deben haber obtenido el consentimiento informado escrito del paciente que autorice su publicación, reproducción y divulgación en soporte papel y en Internet en la Revista.
Las gráficas y esquemas se realizarán cuidando que el formato de las mismas sea de 9 × 12 cm o un múltiplo. La resolución de gráficas y esquemas será de 500 puntos por pulgada (dpi), mientras que para los casos en los que se combinen en una misma figura gráficos y fotografías se recomienda una resolución de 1000 dpi.
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El autor, a partir del número de registro que recibirá junto con el acuse de recibo, podrá consultar el estado de su artículo a través del EES.
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Neurocirugía
Revista de la Sociedad Española de Neurocirugía

INSTRUCTIONS FOR AUTHORS

February 2012

GENERAL ASPECTS

Neurocirugía (www.elsevier.es/neurocirugia), a bi-monthly Journal, will consider original scientific and experimental works of clinical content associated with neurosurgery and other related neurological sciences, as well as articles requested from experts, clinical cases, opinion articles, and any other information of interest to neurosurgeons. *Neurocirugía* accepts articles in Spanish and in English.

The Journal is indexed in Science Citation Index Expanded, Journal of Citation Reports, Scopus and in Science Direct.

All manuscripts are subjected to anonymous peer review, independent of the Editorial Committee of the Journal.

The manuscripts must be prepared according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors, available at: http://www.icmje.org, and adapted to the following Instructions for Authors.

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Manuscripts must be submitted electronically through the Elsevier Editorial System (EES) to the address, http://ees.elsevier.com/neurocirugia, where the information required to make the submission will be found. The use of this resource enables the status of the manuscript to be followed via the web page.

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SECTIONS

Originals. Empirical studies associated with any aspect of research in the field of Neurosurgery that is in the form of a scientific article, with the following sections: abstract, introduction, Material and methods, Results, and Discussion. The length of the text will be unlimited, including a structured abstract, key words and literature references. Besides the text, Figures and Tables will be accepted. It is recommended that the number of authors does not exceed 6, although a maximum of 8 will be allowed.

For the preparation of controlled clinical trials the CONSORT (JAMA. 1996;276:637-9) guidelines should be followed. Available at: http://www.consort-statement.org/, and for a meta-analysis, the QUOROM guidelines (http://www.consort-statement.org/QUOROM.pdf). Manuscripts that present study results on the validity of diagnostic tests should include the STARD flow diagram (http://www.consort-statement.org/stardstatement.htm).

Clinical cases. Cases that make an important contribution to the knowledge of the pathophysiology, aetiology or other aspects of a clinical process. The maximum length of the text will be 1,500 words on 5 DIN-A4, including an unstructured abstract of 150 words and a maximum of 15 literature references. The structure of these articles will be the same as Originals (Introduction, material and methods, Results, and Discussion). Abstract, Introduction, Clinical Case or Cases, Discussion, and Conclusion, and may include up to a maximum of 3 Tables and/ or Figures. The recommended number of authors is 4, although a maximum of 6 will be allowed.

Reviews. These types of manuscripts will be specifically commissioned by the Editorial Committee. Authors who wish to collaborate spontaneously in this section should previously consult the Journal Editors. These will be review articles on relevant and current topics in Neurosurgery with the following structure:, Abstract, Introduction, Development and Conclusions. The maximum length of text will be 16 DIN-A4 pages, in this length the abstract/ *resumen* of 150 words, if it is unstructured, (in English and Spanish) will be included, as well as the corresponding key words. Up to a maximum of 50 literature references will also be included. It is advisable that the number of signing authors does not exceed 3. Besides the text, up to 4 Figures or Tables will be accepted.

Opinion articles. This section has as its purpose to publish relevant and current topics in Neurosurgery that contain novel aspects for the specialty. The text does not need to be formally structured, but should maintain the narrative logic (introduction, development of the experience and conclusions). The maximum length of text will be 10 DIN-A4 pages, which will include an unstructured *resumen*/ abstract (in Spanish and in English) of 150 words (or 250 if this is unstructured) plus the corresponding key words. Up to a maximum of 15 literature references will also be included. Besides the text, up to 2 Figures or Tables will be accepted.

Letters to the Editor. These will refer to works published in the Journal and will contribute opinions, observations or experiences which due to their characteristics may be summarised in a short text. The maximum length will be 2 DIN-A4 pages of text, with no abstract, including a maximum of 5 literature references. The maximum number of authors will be 4. One Figure or Table will be accepted.

Other sections. The Journal includes other sections (including Editorials and Special Articles), which are commissioned by the Editorial Committee. Authors who wish to collaborate spontaneously in any of these sections should previously consult the Editors associated with the Journal.

GENERAL PRESENTATION OF THE MANUSCRIPT

The manuscript, which can be written in Spanish or Portuguese, will have a format on size DIN-A4 paper, with double spacing and a font size of 11 characters per inch. The pages must be numbered consecutively. Abbreviations must be introduced after the complete term it represents when first use is made of them in the article, except in the title. The measurement units will be preferably expressed using the International System of Units. Decimal numbers should be separated by a point and thousands will be indicated with a comma.

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- In the name of the department(s) and the institution(s) to which the work should be attributed, it should not include the academic or professional position.
- It will include the full name, telephone number, e-mail address and the full postal address of the author for correspondence, who will be responsible for correcting the proofs.

The first page must be submitted in a separate file from the rest of the manuscript.

2. Abstract and key words (2nd page)

This is the section that represents the work in the national and international data bases, for this reason its wording and phrasing is of vital importance. It should be written in English and Spanish. It will contain 150 words, and will be unstructured for "Reviews" and "Short Reviews" with and Introduction, Development and Conclusions. That of the "Originals" will contain 250 words and structured into the following sections: *Objective,* indicating the fundamental purpose of the investigation; *Material and method,* the way it will be carried out: explaining the design of the study, the evaluation criteria of the diagnostic tests and the time direction (retrospective or prospective). It will mention the patient screening procedure, the entry criteria, and the number of patients who started and finished the study; *Results,* it will mention the most relevant and significant results of the study, as well as their statistical assessment; *Conclusions,* those conclusions that are directly supported by the data together with their clinical applicability should be mentioned. The same emphasis must be given to the positive and negative findings with similar scientific interest.

There must be 6 key words at the end of the abstract in accordance with those included in the Medical Subject Headings (MeSH) of *Index Medicus*/MEDLINE, available in English at: http://www.nlm.nih.gov/ mesh/ meshhome. html and translate them into Spanish.

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4) *Discussion*. The authors must express their own opinions on the subject. Emphasise here: *a)* the significance and practical application of the results; *b)* thoughts on a possible inconsistency of the methodology, and the reasons why the results may be valid and their limitations; comparing them with other important studies; *c)* relationship with similar publications and a comparison between the areas of agreement and disagreement, and *d)* the indications and directions for future investigations.

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5. Acknowledgements

Only those persons who have made a clear contribution to make the work possible, but cannot be recognised as authors, will be mentioned. All persons specifically mentioned in the "*Acknowledgements*" must be aware of this and approve their inclusion in this section. Technical help must be mentioned in a separate paragraph from that dedicated to acknowledge financial and material assistance from institutions, which must be mentioned in "*Funding*" and give rise to a potential conflict of interests.

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The names of the Journals must be abbreviated in accordance with the style used in Index Medicus, consult the "List of Journals Indexed" which is included every year in the January edition of Index Medicus.

The literature references must be identified in the text using Arabic numerals in superscript and numbered consecutively, in the order that they appear in the text, Tables and Figures). Where the quote is placed next to a punctuation sign, this number will precede the sign (e.g., unlike in previous works[6-9], the results show…).

Wherever possible avoid including text books and meeting minutes as literature references.

Avoid the use of vague phrases as literature references; those such as "unpublished observations" or "personal communication" may not be used, but they may be quoted between inverted commas within the text.

The abbreviations of the journals will be adapted to those used in the *Index Medicus* of the US National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi

The literature references must be checked by comparing them with the original documents, indicating the initial and final page, indication only the digits that differ from the initial page (for example, 34-9 and not 34-39); 136-41 and not 136-141). The accuracy and veracity of the literature references are of utmost importance and must be guaranteed by the authors. The references will be in the format proposed by the Vancouver Group. Some examples of correct references are shown below for the different types of documents (for formats not included in this list, consult more examples on the web page: http://www.icmje.org).

Journal Article

Surname and initials separated by commas. List all the authors if there are 6 or less than 6, placing only a coma between them, and a full stop after the last author; if there are 7 or more, list the first 6 and add the expression "et al". The title of the article is then included (in the original language) followed by a full stop, abbreviation of the journal name, also followed by a full stop, year of publication followed by a semi-colon, volume number, after which is placed a colon, then the first and last page of the reference separated by a hyphen.

Standard journal article with less than 6 authors

Castle M, Barrena C, Samprón N, Arrese I. Remote cerebellar haemorrhage after lumbar arthrodesis: case report and literature review. Neurocirugia (Astur). 2011;22:574-8.

Standard journal article with more than 6 authors

Álvarez-Salgado JA, Ruiz-Ginés JA, Fuentes-Ventura CD, Gonzales-Sejas AG, Belinchón de Diego JM, González-Llanos Fernández de Mesa F, et al. Intracranial tuberculoma simulating a malignant tumor: case report and literature review. Neurocirugia (Astur). 2011;22:600-4.

Article In press

Barrow DL, Tindall GT. Visual loss following transsphenoidal surgery. Neurosurgery. In press 2011.

The author is an organisation

Grupo de Estudios de Enfermedades Cerebrovasculares de la SEN. Enfermedad carotida de origen aterotrombitico: hacia un consenso en la prevencion. Neurología. 2004;19:193-212.

Individual and Organisation, both are authors

Vallancien G, Emberton M, Harving N, Van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1274 European men suffering from lower urinary tract symptoms. J Urol. 2003;169:2257-61.

No author

The entry of NEUROCIRUGIA in the Index Medicus/MEDLINE database. Neurocirugia (Astur). 2002;13:4-5.

Supplement of a volume

Magni F, Rossoni G, Berti F. BN-52021 protects Guinea pigs from heart anaphylaxis. Pharmacol Res Comoun. 1988;20 Suppl 5:75-8.

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Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. Int J Psychoanal. 2002;83 (Pt 2):491-5.

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Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumors. J Vasc Interv Radiol. 2002;13(9 Pt 1):923-8.

Number without a volume

Baumeister AA. Origins and control of stereotyped movements. Monogr Am Assoc Ment Defic. 1978;(3):352-84.

No volume or number

Outreach: bringing HIV-positive individuals into care. HRSA Careaction. 2002 Jun:1-6.

Book

Authors as Editors

Diener HC, Wilkinson M, Editors. Drug-induced headache. New York: Springer-Verlag; 1988.

Personal author(s) (no editors)

Jennett B, Teasdale G. Management of Head Injuries. Philadelphia; FA Davis Company; 1981.

Different Authors and Editors

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. In: Wieczorek RR, Editor. White Plains: March of Dimes Education Services; 2001.

Organisation as Author

Royal Adelaide Hospital; University of Adelaide, Department of Clinical Nursing. Compendium of nursing research and practice development, 1999-2000. Adelaide: Adelaide University; 2001.

Book chapter
Rhoton AL. Microsurgical anatomy of the third ventricular region. In: Apuzzo MLJ, Editor. Surgery of the third ventricle. Baltimore; Williams & Wilkins; 1987. pp. 92-166.

Meeting Minutes
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COVER LETTER

The Role of Reoperation in Recurrent Glioblastoma

Our intention is to publish this work in scientific investigation section in your Journal.

We hereby confirm that this work is original, made with data from solely Hospital de São João, and it is only being sent to your editorial.

The aim of this work is represented in its title, to validate “The Role of Reoperation in Recurrent Glioblastoma”. So, it will contribute to the field of neurosurgery, namely in the choice of treatment of this tumor, showing if surgery is still a good option.

All the clinical information in this study was collected from the hospital clinical records with the proper authorization of the Neurosurgery Department of Hospital de São João. Data was analysed, processed and worked in accordance with the ethical guidelines of the Hospital Ethical Committee and in compliance with the World Medical Association and the Helsinki Declaration.

It is guaranteed the preservation of patients’ rights, privacy and confidentiality. In addition, it was also avoided any type of identification data in text or images in the article and in any event.

The committee is also informed of the publication of our results in the Journal of Neurocirugia in free access form on the Internet, and according as declared *Elsevier Editorial System*.

No type of financial grant was obtained from any institution, however computer assistance was provided in the Neurosurgery Department.

All the signing authors who participated meet the requirements of authorship (in the conception, design, as well as in the acquisition, analysis and interpretation of the data gathered that has resulted in the article in question; participated in writing the text and its possible revisions; approved the version that will finally be published).

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There are no conflicts of interest to declare.

At the time of submission of this work and writing of the cover letter, the work was not presented in the SENEC (Spanish Society of Neurosurgery) Annual Meeting nor other meetings or conferences.