https://doi.org/10.47822/bn.v14i1.1121
ISSN 2526-6349 *On-line version*
ISSN 2175-1943 *Print version*

Review article

Use of mifepristone for the treatment of unresectable meningiomas: systematic review and meta-analisis

Uso de mifepristona para o tratamento de meningiomas irressecáveis: revisão sistemática e metanálise

Marcelo José da Silva de Magalhães[1] | Nathalia Cristina Freitas Souza[1] | Heick Damasceno Batista[1]

[1]*University Center of Northern Minas, Montes Claros, MG, Brazil.*

Abstract

Objective: to conduct a systematic review and meta-analysis on the treatment of unresectable meningiomas using mifepristone (RU-486). **Materials and Methods:** the search descriptors were Meningiomas, Hormonal treatment, Mifepristone, Progesterone antagonist, Unresectable tumors, Systematic review, Meta-analysis, Central Nervous System neoplasms, Clinical efficacy, and Endocrine therapy. The search was performed on March 30, 2024, using PubMed, Medline, and Cochrane. The quality of the included studies was assessed using the Qualis and JBI tools, and the study was registered in PROSPERO - International Prospective Register of Systematic Reviews (registration number CRD42024550741). **Results:** five studies were eligible for this systematic review and meta-analysis, only one of which was in phase III. The studies included 219 patients with unresectable meningiomas, of whom 135 were initially assigned to receive mifepristone. All studies analyzed a daily dosage of 200 mg. The meta-analysis revealed that 58% of treated patients achieved at least maintenance or reduction in tumor volume, as shown on imaging exams such as CT and MRI, with statistical significance. However, therapeutic responses varied according to clinical and histological subgroups, indicating the need for future studies to refine its indications. The drug showed good long-term tolerance, reinforcing its potential as an adjuvant therapy. **Conclusion:** mifepristone appears promising for male and female patients of reproductive age. Given the exhaustion of other therapeutic options, mifepristone treatment is a reasonable consideration.
Keywords: Meningioma. Mifepristone. RU-486.

Resumo

Objetivo: realizar uma revisão sistemática e metanálise sobre o tratamento de meningiomasirressecáveis por meio do uso de mifepristona (RU-486). **Materiais e Métodos:** os descritores da busca foram *Meningiomas,Hormonaltreatment, Mifepristone, Progesteroneantagonist, Unresectabletumors, Systematic review, Meta-analysis, Central Nervous System neoplasms, Clinicalefficacy, Endocrinetherapy*. A data da busca foi 30/03/2024. As plataformas escolhidas para a pesquisa foram PubMed, Medline e Cochrane. A qualidade dos trabalhos incluídos foi avaliada pelas ferramentas Qualis e JBI. O trabalho foi registrado no PROSPERO-*Internationalprospectiveregisterofsystematic reviews* com o número: CRD42024550741.**Resultados:** após análise dos resultados, restaram 5 estudos elegíveis para esta revisão sistemática e metanálise, apenas um deles na fase III. Os trabalhos avaliaram um total de 219 pacientes portadores de meningiomas irressecáveis, dos quais 135 foram inicialmente destinados a receber mifepristona. Todos os trabalhos encontrados estudaram a posologia diária de 200 mg. A metanálise revelou que 58% dos pacientes tratados apresentaram pelo menos manutenção ou redução do volume tumoral nos exames de imagem, como tomografia e ressonância magnética do crânio, com significância estatística. **Conclusão:** a mifepristona parece promissora em pacientes do sexo masculino e feminino em idade fértil. Frente ao esgotamento das opções terapêuticas, é razoável considerar o tratamento com mifepristona.
Palavras-chave: Meningioma. Mifepristona. Mifepristona. RU-486.

Corresponding auhtor: Marcelo José da Silva de Magalhães | marcelo7779@yahoo.com.br
Received: 06|24|2024. Approved: 06|05|2025.
Assessed by the double blind review process.

How to cite this article: Magalhães MJS, Souza NCF, Batista HD. Uso de mifepristona para o tratamento de meningiomas irressecáveis: revisão sistemática e metanálise. Revista Bionorte. 2025 jan-jun;14(1):691-708. https://doi.org/10.47822/bn.v14i1.1121

Introduction

Meningiomas are tumors of the Central Nervous System (CNS) that originate from the proliferation of arachnoidea meningothelial cells (MECs)[1]. Criteria established by the World Health Organization (WHO), in 2021, classified these tumors into 15 subtypes, grouped into three degrees, being grade I benign, grade II atypical and grade III malignant and anaplastic as shown in table 1[2,3].

Table 1. Classification of Meningiomas according to the World Health Organization.

Grade I Meningiomas
Angiomatous
Fibrous
Rich in lymphocytes and plasma cells
Meningothelial
Metaplastic
Microcystic
Psammomatous
Secretory
Transitional
Grade II Meningioma
Clear cells
Chordoid
Atypical: More than four mitoses per 10 high-power fields or at least three of the following: increased cellularity, small cells with high nuclear-to-cytoplasmic ratio, prominent nucleoli, patternless or sheetlike growth, necrosis.
Grade III Meningioma
Rhabdoid
Papillary
Anaplastic: number of mitoses equal to or greater than 20 per 10 high-power fields and/or malignant characteristics*

*Similar to sarcoma, carcinoma or melanoma, such as: loss of typical growth patterns, abundant mitoses with atypical forms, brain invasion, multifocal necrosis. Adapted from: Merrit, Tratado de Neurologia, Guanabara Koogan LTDA, 2018.

This is the most common primary neoplasia in the CNS, corresponding to 37.6% of all primary tumors of the CNS and 53.3% of benign tumors of the CNS[1]. About 90% of these tumors present benign behavior; the remaining 10% are atypical, malignant or anaplastic[2]. The prevalence of this diagnosis increases with age, being more common in females and in Afro-descendent[1,4].

The usual treatment for symptomatic, exfoliating or growing tumors is surgical. Radiotherapy is reserved for unresectable meningiomas or as complementary therapy for patients undergoing partial resection[2].

The presence of estrogen and progesterone receptors in some histological types of meningiomas is well-established in the literature[5]. The idea that these hormones can influence the

rate of tumor growth is supported by clinical-radiological evidence. It is known that many of these tumors have accelerated growth in the second and third trimesters of pregnancy, as well as in the luteal phase of the menstrual cycle, physiological situations that determine the increase of plasmatic progenes[5]. A 1931 case report describes the appearance of visual symptoms in primigesta with complete resolution after delivery; in the second pregnancy, the patient evolved with total amaurosis and again with complete disappearance of symptoms after delivery; in 1935, more details were published of the same patient, in which parasselar meningioma was discovered[6]. Given this information, preclinical studies point to the possibility of using progesterone receptors (PR) as a target for possible pharmacological treatment.

Therefore, the possibility of an endocrine treatment based on progesterone antagonists is object of academic interest. Among the drugs tested for this purpose, mifepristone (RU-486) seems to be the most promising. It is an oral progesterone antagonist, discovered in France in 1982, initially used to induce abortion. Among the pharmacological properties of the drug, we highlight: affinity for PR, five times greater than that of the endogenous hormone, ability to freely transpose the blood-brain barrier (BBB) and low affinity for the glycocorticoid receptor[7-9].

In an experimental study conducted in 1987, fragments of human meningioma were transplanted into six rats and 10 mg/kg/day of mifepristone was administered for three months. After the end of the study, the authors reported tumor growth rates higher than those observed in the control group compared to the test group[10].

The systematic review and meta-analysis proposed are justified by the need to evaluate the efficacy of mifepristone in the treatment of unresectable meningiomas, given the academic and clinical interest in exploring endocrine treatments based on progesterone antagonists. Therefore, the systematic review and meta-analysis will seek to consolidate clinical evidence of mifepristone use by providing a comprehensive analysis of studies published between 1990 and 2024, and to contribute to the definition of more effective therapeutic protocols for unresectable meningiomas.

The objective of this work is to make a systematic review and meta-analysis to evaluate the clinical results of the use of mifepristone in the treatment of unresectable meningiomas.

Materials and Methods

For this systematic review and meta-analysis, the authors conducted extensive bibliographical research on the platforms "PubMed", "Medline" and "Cochrane". The guiding question was: "What is the efficacy of mifepristone for the treatment of patients with unresectable meningiomas?"

The description of PICO:

Population: patients with meningiomas whose surgical treatment is no longer possible due to their volume.

Intervention: use of mifepristone for the treatment of unresectable meningiomas.

Control: patients with unresectable meningiomas who received placebo.

Outcome: evaluation of the volume of the meningioma after the use of mifepristone.

The languages used for the research in the databases were Portuguese, English and Spanish. Chart 1 shows the descriptors used.

Chart 1. Descriptors used in the systematic review and meta-analysis.

Spanish	1. *Meningiomas* 2. *Tratamiento hormonal* 3. *Mifepristona* 4. *Antagonista de progesterona* 5. *Tumores irresecables* 6. *Revisión sistemática* 7. *Metanálisis* 8. *Neoplasias del Sistema Nervioso Central* 9. *Eficacia clínica* 10. *Terapia endocrina*
English	1. Meningiomas 2. Hormonal treatment 3. Mifepristone 4. Progesteroneantagonist 5. Unresectabletumors 6. Systematic review 7. Meta-analysis 8. Central Nervous System neoplasms 9. Clinicalefficacy 10. Endocrinetherapy
Portuguese	1. *Meningiomas* 2. *Tratamento hormonal* 3. *Mifepristona* 4. *Antagonista de progesterona* 5. *Tumores irressecáveis* 6. *Revisão sistemática* 7. *Metanálise* 8. *Neoplasias do Sistema Nervoso Central* 9. *Eficácia clínica* 10. *Terapia endócrina*

Chart 2 describes the inclusion and exclusion criteria.

Chart 2. Inclusion and exclusion criteria used in the systematic review and meta-analysis.

Inclusion Criteria:	1. **Type of Study:** Clinical studies (randomized controlled trials, cohort studies, case-control studies) published between January 1990 and November 2024. 2. **Population:** Patients diagnosed with unresectable meningiomas regardless of histogical grade. 3. **Intervention:** Use of mifepristone as a treatment, administered alone or in combination with other therapies. 4. **Outcomes:** Studies reporting data on clinical efficacy, including tumor shrinkage rate, tumor growth control, overall survival, progression-free survival, and treatment-related adverse events. 5. **Language:** Articles published in English, Portuguese or Spanish. 6. **Access:** Articles with full text available.
Exclusion Criteria:	1. **Type of Study:** Preclinical studies, narrative reviews, isolated case reports, letters to the editor, and expert opinions. 2. **Population:** Patients with meningiomas who have undergone complete resection or who have resectable meningiomas. 3. **Intervention:** Studies that use hormonal treatments other than mifepristone or that do not detail the mifepristone regimen used. 4. **Outcomes:** Studies that do not provide specific data on relevant clinical outcomes or that do not report the efficacy of mifepristone treatment. *5.* **Language:** Articles published in languages other than English, Portuguese or Spanish. *6.* **Quality:** Studies with inadequate methodology, insufficient sample or inconclusive data that compromise the validity of the results.

The search strategies used in the databases were:

a) In Portuguese:
(("Meningiomas" OR "Neoplasias do Sistema Nervoso Central" OR "Tumores Cerebrais") AND ("Tratamento Hormonal" OR "Mifepristona" OR "Antagonista de Progesterona") AND ("Revisão Sistemática" OR "Meta-análise" OR "Eficácia Clínica" OR "Taxa de Redução Tumoral" OR "Sobrevida Global" OR "Sobrevida Livre de Progressão" OR "Efeitos Adversos"))

b) In English:
(("Meningiomas" OR "Central Nervous System Neoplasms" OR "Brain Tumors") AND ("Hormonal Treatment" OR "Mifepristone" OR "Progesterone Antagonist") AND ("Systematic Review" OR "Meta-analysis" OR "Clinical Efficacy" OR "Tumor Reduction Rate" OR "Overall Survival" OR "Progression-Free Survival" OR "Adverse Effects"))

c) In Spanish:
(("Meningiomas" OR "Neoplasias del Sistema Nervioso Central" OR "Tumores Cerebrales") AND ("Tratamiento Hormonal" OR "Mifepristona" OR "Antagonista de Progesterona") AND ("Revisión Sistemática" OR "Metanálisis" OR "Eficacia Clínica" OR "Tasa de Reducción Tumoral" OR "Supervivencia Global" OR "Supervivencia Libre de Progresión" OR "Efectos Adversos"))

The quality of the works was evaluated by the tools "QUALIS" and "Joanna Briggs Institute" (JBI).

The works were identified separately by the two researchers using the same search strategy in the databases, taking into account the inclusion and exclusion criteria in the databases indicated by the methodology of the work. In case of doubt as to the selection of a particular article, the author MJSM was responsible for the evaluation of the article and decision making for its inclusion in the systematic review.

For the preparation of the meta-analysis, the fixed effect model and heterogeneity test were used. Regarding the heterogeneity analysis, the Q test of Cochran and the I^2 test were used.

To calculate the weight or contribution of each study, fixed effects models were used. The confidence interval used was 95% and significant p-value <0.05. The control group of the meta-analysis was constituted by the controls groups present in the studies. The intervention groups were constituted by the groups of patients who received the drug mifepristone as a form of control of meningioma.

The calculations for the preparation of the meta-analysis graphs were processed by means of the Meta-mar version 3.5.1 tool.

This work was registered in the PROSPERO-International prospective register of systematic reviews with the number: CRD42024550741.

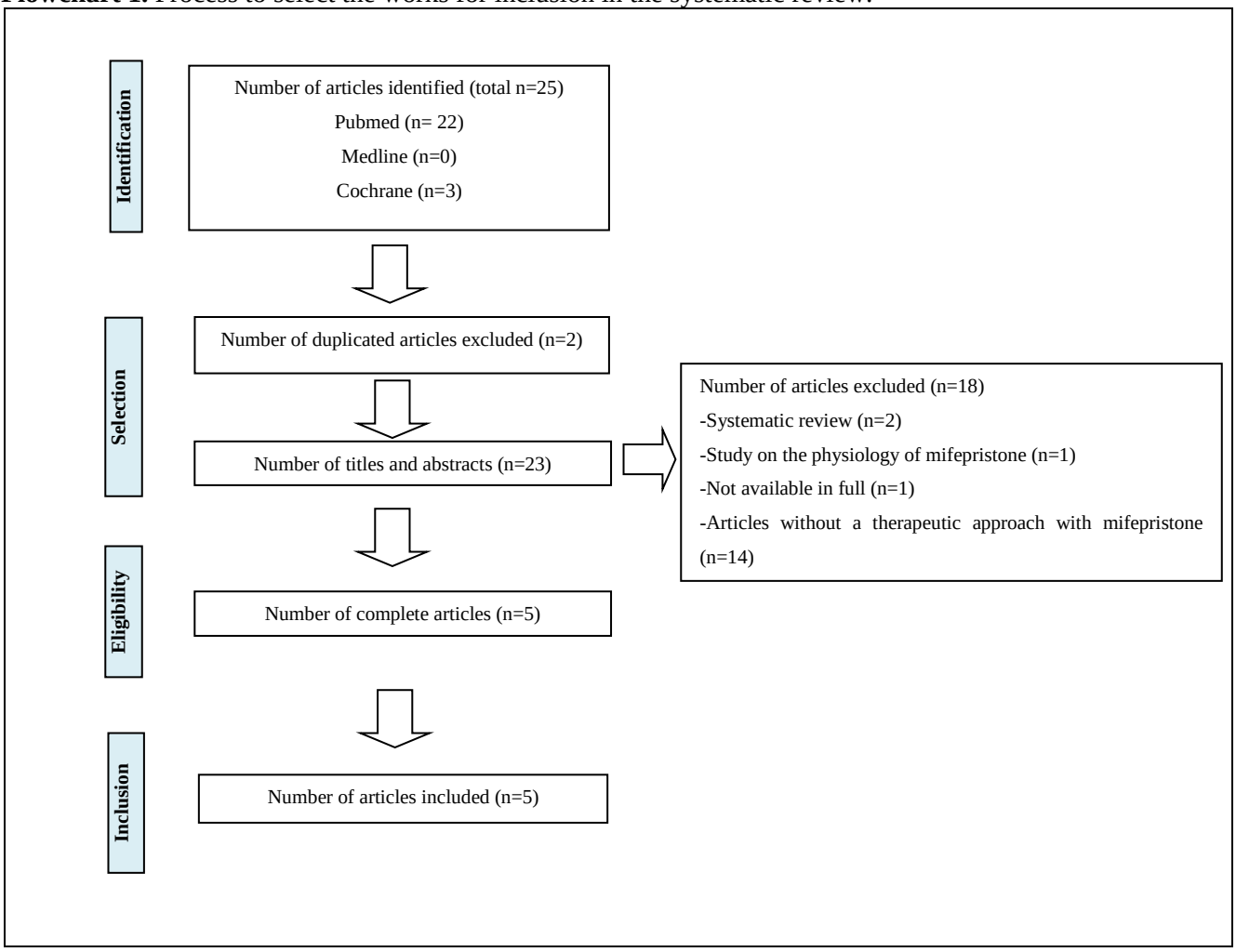
Results

As shown in Flowchart 1, 22 papers were identified on the PubMed platform, 0 on Medline and 3 on Cochrane, totaling 25 papers identified by the aforementioned descriptors. Of these, two publications were deleted for duplicity. After reading the title and abstract of the remaining 5 papers, they were separated for the full evaluation.

Of the 18 excluded works, two were systematic reviews; one was discarded due to complete unavailability in the database; another for addressing the physiology of mifepristone action and 14 for not aligning with the proposed theme. No study was eliminated due to conflicts of interest. Of the 5 articles fully evaluated, all were included in this systematic review. Flowchart 1 illustrates the selection process of the articles used in the study.

The authors evaluated four clinical trials, with three studies of level II[11-13] and one study of level III[14] (Chart 3). One of the studies was carried out in the Netherlands [12], three of the studies were carried out with the population of the United States of America (USA) and one in France[11-15].

Flowchart 1. Process to select the works for inclusion in the systematic review.



The analyzed studies included a total of 219 patients, of whom 135 were treated with mifepristone at a dose of 200 mg/day and 84 patients were initially assigned to receive placebo. It is possible that up to 12 patients were double-counted, by a presumptive repetition of patients between the works of Grunberg et al (1991) and (2006)[11,13].

For the evaluation of the quality of the papers and inclusion in this review, the tools Qualis and JBI were used. Three of the found papers were published in journals that had A1 classification, and one work in journal with A4 classification by the Qualis classification (Chart 4).

Chart 3. Works used to prepare the systematic review on the treatment of patients with unresectable meningioma using Mifepristone.

Authors	Year	Patients	Objective	Outcome	Adverse effects	Authors' conclusion
Grunberg *et. al.*[11]	1991	14 patients, 6 men and 8 women, two premenopausal	To verify the efficacy of mifepristone in unresectable meningiomas	5 patients developed tumor regression and/or clinical improvement, 5 patients remained stable, 3 patients developed disease progression and 1 patient subsequently refused therapy.	Amenorrhea, gynecomastia, hot flashes, fatigue.	Mifepristone therapy may be effective in controlling some unresectable meningiomas.
Lamberts *et al.*[12]	1992	10 patients, 3 men and 7 women, 1 of reproductive age, 12 tumors in total.	To investigate the effect of mifepristone therapy in patients with unresectable meningiomas presenting progressive growth	4 tumors in 3 patients evolved with transient tumor reduction, 3 tumors in 3 patients remained stable and 5 tumors in 4 patients showed growth. 4 patients reported symptomatic improvement.	Nausea, vomiting, anorexia, fatigue.	Mifepristone therapy results in control of tumor growth in some patients with unresectable meningiomas.
Grunberg *et. al.*[13]	2006	28 patients, 9 men, 19 women, 5 premenopausal	To verify the clinical efficacy of long-term therapy with mifepristone in meningiomas	8 patients showed clinical and radiological improvement	Fatigue, hot flashes, gynecomastia, mood swings, rash, partial alopecia, lower limb edema and reduced libido.	The use of mifepristone for unresectable meningiomas may be promising in selected patient groups, such as men and premenopausal women, and especially for progesterone receptor-positive tumors.
Touat et al.[15]	2014	3 female patients.	To verify the clinical efficacy of mifepristone therapy in meningiomas	In 3 patients, tumor size remained stable after 5 to 9 years of use.	Subclinical hypothyroidism in 1 patient and endometrial thickening in 1 patient.	The use of mifepristone appears to be an effective drug in the control of inoperable meningiomas.
Ji Y. *et al.*[14]	2015	164 patients, 48 men and 116 women, 33 premenopausal. 80 assigned to receive mifepristone and 84 to receive placebo.	To determine the role of mifepristone in the treatment of growing unresectable meningioma	The test group presented 1 partial response, 1 unconfirmed response, 44 patients evolved with stable disease and 25 with disease progression. In the control group, 1 presented partial response, 44 stable disease and 28 disease progression.	Fatigue, alopecia, hot flushes, weakness due to motor neuropathy, nausea, gynecomastia.	Mifepristone was unable to control the disease.

Chart 4. Qualis classification of eligible studies

Authors	Qualis Classification
Grunberg*et al.* 1991	A1
Lambertset *al.* 1992	A1
Grunberg*et. al.* 2006	A4
Touat *et al.* 2014	A1
Yongli Ji *et al.* 2015	A1

By the JBI tool, the appropriate sample questions were evaluated, considering the target population, selection and sample size, sample detailing, evaluation of results with adequate sample coverage, valid methods for identification of the condition, appropriate statistical analysis and if there was adequate response rate (Chart 5).

Chart 5. Critical assessment of the methodological quality of the included studies using the JBI tool

JBI	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Grunberg*et. al.* 1991	Y	Y	N	Y	Y	Y	Y	Y	Y
Lambertset *al.* 1992	Y	Y	N	Y	Y	Y	Y	Y	Y
Grunberg*et. al.* 2006	Y	Y	N	Y	Y	Y	Y	Y	Y
Touat*et al.* 2014	Y	Y	N	Y	Y	Y	Y	NA	Y
Ji *et al.* 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y

Caption: Y= Yes, N= No, NC= Not clear, NA= Not applicable.

Q1- Was the sampling frame appropriate to address the target population?
Q2- Were the study participants sampled appropriately?
Q3- Was the sample size adequate?
Q4- Were the study subjects and setting described in detail?
Q5- Was the data analysis performed with sufficient coverage of the identified sample?
Q6- Were valid methods used to identify the condition?
Q7- Was the condition measured in a standard and reliable way for all participants?
Q8- Was there appropriate statistical analysis?
Q9- Was the response rate adequate and, if not, was the low response rate managed appropriately?

The dosage of mifepristone adopted was 200 mg per day, administered orally, in all clinical studies found[11-15]. The authors usually justified the choice of this dosage by showing good inhibition of progestogen activity with low anti-glucocorticoid effects. Most of the authors adopted precautions, such as the use of informative bracelets for the risk of acute adrenal insufficiency and the recommended dose of glucocorticoid to reverse the condition, in addition to pregnancy tests for patients in menarche before starting treatment and use of oral glucocorticoids in the first days.

The most reported side effect was asthenia. The occurrence of nausea, vomiting, anorexia, subclinical hypothyroidism, endometrial hypertrophy, amenorrhea in premenopausal women, sensitive and palpable gynecomastia in male patients was described, Discrete changes in serum cortisol levels and thyroid hormones[11-15]. The effects with the greatest statistical difference in favor

of the test group were: fatigue, alopecia, heatwaves and weakness due to motor neuropathy (Chart 6). None of the studies reported life-threatening side effects.

Chart 6. Non-neurological and neurological adverse effects in the test and control groups of Ji *et al.*(2015)[14].

Adverse Effect	Mifepristone (80 patients)	Placebo (84 patients)
Non-neurological		
Fatigue	60	46
Hot flashes	31	22
Nausea	25	21
Alopecia	22	9
Menstrual changes	14	12
Gynecomastia	13	9
Neurological		
Headache	36	35
Weakness due to motor neuropathy	23	14
Dizziness	23	20
Ataxia	21	17
Change in mood or consciousness	19	16
Pain	16	11
*80 patients; **84 patients. Adapted from: Ji et al. 2015[14]		

Regarding the evaluation of tumor growth during treatment, most authors chose to evaluate tumor evolution by clinical and radiological methods. The neuroimaging methods used for tumor volume evaluation were computed tomography and magnetic resonance imaging of the skull. In a study published in 1992, tumor dimensions were evaluated at regular intervals with computed tomography. These images were obtained from the same apparatus and the slices were kept at 3 mm; the tumor volume was calculated by planimetry, from the same image, by two independent professionals and an agreement rate of 95%[12].

In two studies, published respectively in 1991 and 2006, a neurological clinical examination was performed monthly in the first year and quarterly in the second year, in addition to objective measurements of tumors twice a year with computed tomography, magnetic resonance or visual field exams[11,13]. A clinical study evaluated patients by means of monthly neurological and gynecological clinical examination in the first year and quarterly in the second year, quarterly and semi-annual serum examinations, visual and annual neuroimaging exams[14]. Finally, a study in 2014 used magnetic resonance imaging as a form of radiological control[15].

In a study conducted in 1991, the authors reported the experience of using mifepristone in 14 patients with unresectable meningiomas for one year[11]. The study was conducted with eight women, two of them in reproductive age and six menopausal and six men. As for histological characteristics, eight tumors were of the meningothelial or cell type, two were of the fibrous type, two were malignant and two had not been submitted to biopsy - for technical reasons and patient safety. Among the 14

eligible patients, five patients progressed with tumor regression and/or clinical improvement, five patients remained stable, three patients progressed with disease progression and one refused treatment[11].

In a study conducted in 1992, the experience with the use of mifepristone for one year was evaluated in ten patients with growing unresectable meningiomas. Of the 10 patients, there were 7 women and 3 men with 12 tumors in total. Five patients showed subjective improvement during treatment. Among the evaluated patients, four presented tumor growth, in three patients, the tumors remained stable and three patients presented transient tumor regression. A patient evolved with considerable reduction in the palpable tumor[12].

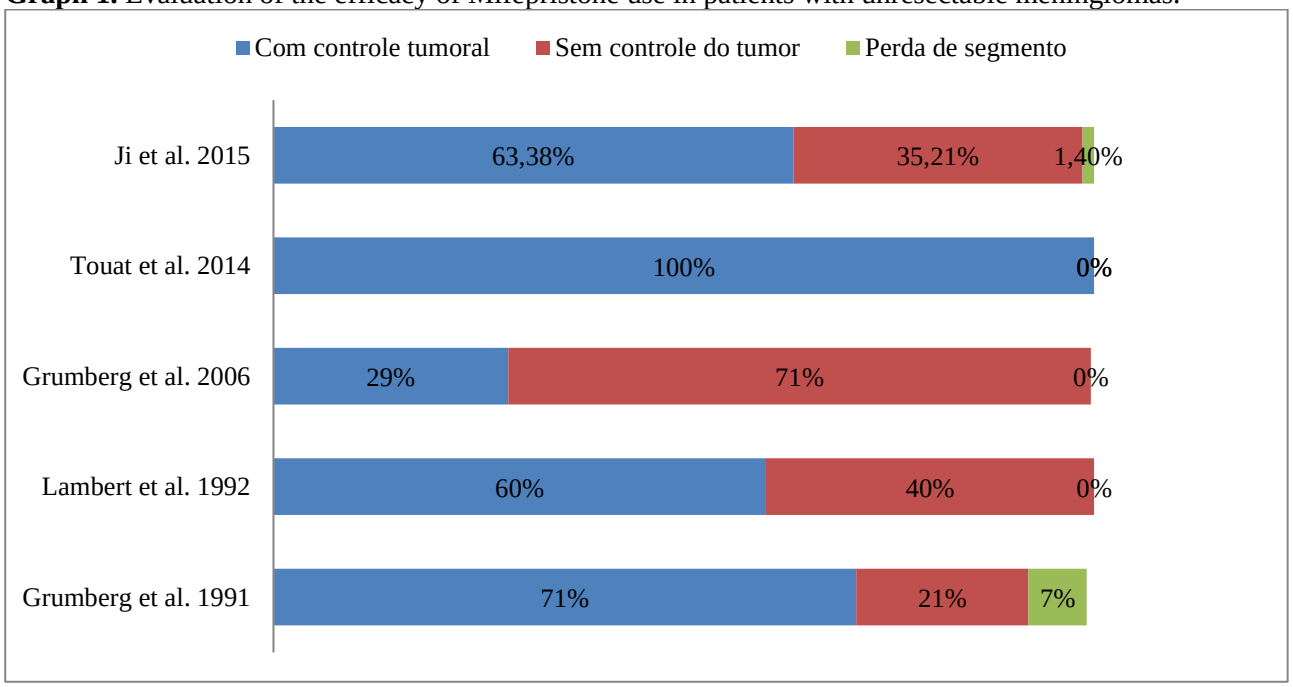
In 2006, a study was published that evaluated the use of mifepristone in 28 patients with unresectable meningiomas, some of whom possibly belonged to the 1991 study group. Of the 28 patients, 20 remained in treatment for at least 12 months; seven of these for 120 months. The study group included five premenopausal women, 14 postmenopausal women and nine men. As for histology, 13 were meningothelial, four were fibroblastic, two malignant, five cell without other specification and four were not biopsied. Regarding the results and clinical efficacy, there was no detailed description; it was only mentioned that of the 28 patients, eight presented benefits related by the author to the use of the drug, with clinical and radiological improvement. Among these patients with benefit described by the study, four were premenopausal women, one was postmenopausal woman and three were men[13].

In a randomized, double-blind, phase III clinical trial evaluating response to mifepristone treatment in 164 patients over a two-year period, the patients were randomly separated into test and control groups of 80 and 84 patients respectively. According to the authors, these groups were balanced according to basal characteristics - sex, age, ethnicity, menopause status, radiotherapy history, histology and disease status. Of the 80 patients assigned to receive mifepristone, 24 received treatment for at least two years, 34 stopped treatment due to disease progression or recurrence, eight due to drug intolerance and 14 for various reasons. Of these, 71 patients were evaluated for the clinical response, of which one presented partial response, one presented unconfirmed response by second evaluation, 44 presented stable disease and 25 had progress of the disease. Of the 84 patients assigned to placebo, 73 patients were evaluated, of which one presented a partial response; 44, stable disease and 28, progressive disease[14].

In a series of cases published in 2014, three women with multiple meningiomas who were treated with mifepristone at the dose of 200mg/day, there was control of the disease in all 3 cases. Only subclinical hypothyroidism and endometrium thickening were observed as side effects of medication. The cases showed a long-term follow-up, between 3 and 5 years[15].

Graph 1 shows the overall view of the 5 studies used in the meta-analysis regarding the efficacy of mifepristone in controlling the size of meningiomas. The blue color shows patients who presented reduction or maintenance of the tumor size during the treatment period.

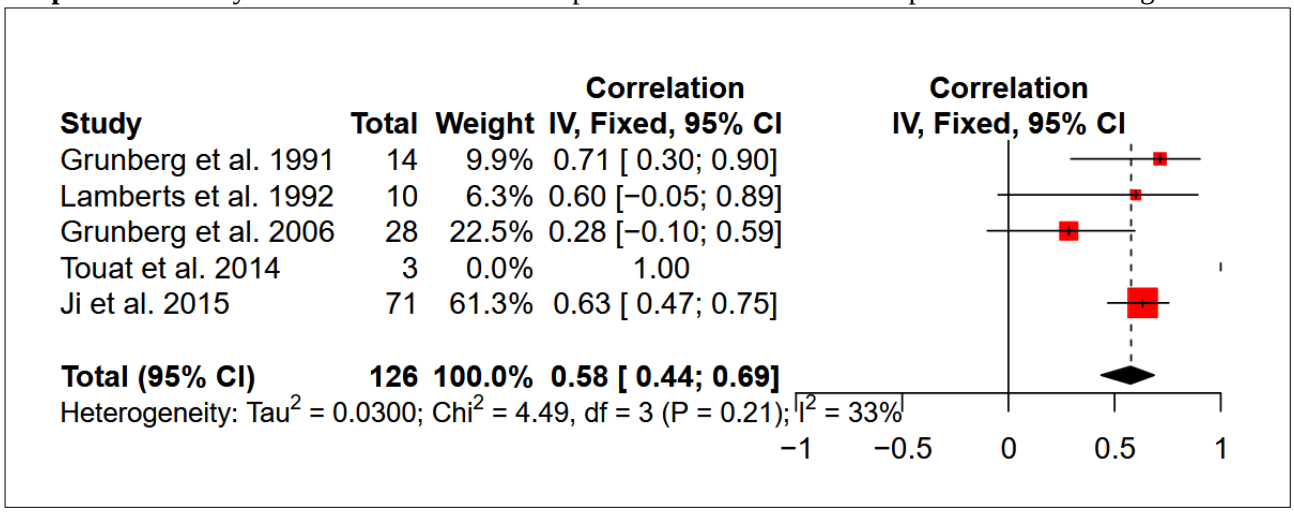
Graph 1. Evaluation of the efficacy of Mifepristone use in patients with unresectable meningiomas.



Translation of graph 1: Blue - with tumor control. Red - without tumor control. Green - Loss of follow-up. Ji *et al.* 2015 - 63.38%; 35.21%; 1.40%. Touat *et al.* 2014 - 100%; 0%; 0%. Grumberg *et al.* 2006 - 29%; 71%; 0%. Lambert *et al.* 1992 - 60%; 40%; 0%. Grumberg *et al*. 1991 - 71%; 21%; 7%.

The meta-analysis of the five studies revealed that the average radiological control by reducing or maintaining the size of patients' tumors was 58% with statistical significance and heterogeneity of 33%, as shown in graph 2.

Graph2. Meta-analysis of studies that used mifepristone for the treatment of patients with meningiomas.



Discussion

As already mentioned, there is a well-founded relationship between the emergence and growth of meningiomas and exposure to endogenous and/or exogenous female hormones[4,16-18]. The presence of estrogen receptors is known in approximately 31% of tumors and progesterone (PR) in approximately 70% of meningioms[2,14,19]. It is assumed that the action of progesterone on the PR of meningiomas increases the sensitivity of cells to the action of epidermal growth factor and other mitogenic stimuli[11,20]. However, the exact mechanisms by which progestogen may contribute to tumor growth are not yet fully elucidated in the literature. Due to its PR-antagonist effect, mifepristone is believed to inhibit the tumor response to mitogenic stimuli, slowing progression.

Concerning the therapeutic response, it should be pointed out that meningiomas are diverse in terms of histology, aggressiveness and anatomical location[21-23], thus it would be unlikely that a single chemotherapy would be effective for this variety of clinical contexts. Thus, it is sensible to evaluate the drug response in specific clinical and/or histological groups. Unfortunately, the most robust of the publications included in this bibliographical research does not detail the response evaluation in specific subgroups of patients, which compromises more detailed analyses of its results.

A 2006 study suggested that the premenopausal female population and the male population would be the groups with the highest probability of response[13]. Given the possible mechanism of control of tumor growth by mifepristone, it can also be inferred that patients whose tumors are known to express PR have a greater propensity to clinical responsives[24]; other similar, it is intuitive to expect better response in populations with elevated plasma levels of progesterone.

In relation to sex, among all the individuals studied in the 5 exposed studies, 66 were men and 153 were women[11-15]. In the subgroup of women, there were 41 in reproductive age and 112 in postmenopausal. Of the 66 men, it was possible to evaluate whether or not there was a response to the drug in 18 of them. Of these, five (27.7%) presented improvement in symptoms or tumor regression. In the female population, of 153 women, 37 were subject to evaluation and, of these, 6 (20.6%) of 29 postmenopausal patients and 6 (75%) of 8 premenopausal patients presented tumor reduction or clinical improvement. Despite an apparent noticeable response among premenopausal women, the sample group is still small and these numbers are possibly conflicting with data found in a study published in 2015 that did not discriminate the response by sex[14].

From a histological point of view, only two studies published in 1991 and 2006 respectively discriminated the tumors evaluated and only the 1991 publication details the response in specific histological types. In these two studies, with a total of 42 patients, 26 were meningothelial or cellular (most of them meningothelial), 4 were fibroblastic, 2 were fibrous, 4 malignant and 6 had not been

submitted to biopsies[11,13]. In the 1991 publication, among the 5 meningothelial tumors studied, 2 (40%) evolved with tumor reduction or clinical improvement, 2 (40%) remained stable and 1 (20%) presented volume increase or clinical worsening during treatment with mifepristone; 2 (66%) of the 2 cell tumors presented tumor reduction or clinical improvement, and the other could not be evaluated by discontinuation of treatment; the 2 fibrous tumors remained stable; for the 2 patients with malignant tumors, the disease continued to progress; 1 tumor that was not biopsied remained stable and the other presented a return[11]. In a study published in 2015, it included 17 atypical meningiomas, 8 in the test group and 9 in the placebo group, and 147 meningiomas without other specification, 72 and 75 in the test and control groups, respectively[14]. None of the included studies reported any positive response to treatment with mifepristone in known malignant tumors. There is insufficient data to evaluate the therapeutic response in specific histological groups. A further study of 2014 specified one patient with transitional meningioma who presented clinical response with reduced tumor size and clinical control of symptoms[15].

In the study groups, of the 135 patients who received mifepristone, 80 could not be evaluated regarding the treatment time due to lack of available data. Of the remaining 55, 8 received treatment for less than 6 months; 44 for at least 6 months; 37 for at least 1 year; 20 for at least 2 years and 7 for at least 10 years. In the evaluated studies, not enough information was found to relate therapeutic response to treatment time. The studies included in this review are consistent with the findings published by a study published in 2005 that analyzed the long-term side effects of the use of mifepristone[24]. A study published in 2005 positively assessed the long-term clinical tolerance of the drug after rigorous analysis on a cut of 1,620 patient-months, some of whom have used the drug for more than a decade. The work of this team drew attention only to the need to annually perform thyroid function evaluation and ultrasonography to evaluate endometrial thickening in women with mifepristone-induced amenorrhea[24].One study from this review presented as an adverse effect, subclinical hypothyroidism and thickening of the endometrium[15].

The study published in 2006 evaluated the clinical tolerance of various dosages of mifepristone - controlled studies for the treatment of oncological, gynecological and endocrine conditions - and also found consistent results for the dose of 200 mg/day. It also revealed that the risk of severe acute adrenal insufficiency is related only to the use of higher doses - 5 - 25 mg/kg/day tested for the treatment of Cushing syndrome[13].

Among the limitations of this study, it is possible to identify that the criteria adopted by each of the authors to evaluate the disease progression, although similar, have divergences that may hinder the comparative analysis of the results obtained in each of the studies. In one of the papers, which was published in 2006, the authors discussed the rigor of the criteria adopted in the study and

recognize that the criteria for evaluating tumor progression are mild when compared to most studies with chemotherapy, which consider as a partial response a reduction greater than 50% of the tumor volume[13]. However, they argue that in the closed space of the skull or spinal canal, small volumetric oscillations can cause large clinical alterations. In addition, a rapid reduction in mostly benign tumors cannot be expected as that expected in responsive maligns[13]. Mifepristone therapy was never intended to replace conventional treatments, neurosurgery and radiotherapy, but rather to be an adjuvant that can control the growth of masses with surgically inaccessible localization. The authors consider that stabilization or reduction of tumor growth rate are encouraging results.

Conclusion

The proposed treatment has a credible and reasonable mechanism of action, in addition to favorable and promising in vitro and in vivo studies. The preliminary results, three phase II clinical studies, showed satisfactory results with stable disease, clinical improvement and/or tumor regression. However, the only randomized double-blind multicenter clinical trial published so far was not able to detect any change in the progression of disease related to the use of mifepristone, although the meta-analysis revealed a radiological control by maintaining the size or reduction of tumors in 58% of patients, with statistical significance. Given the conflicting results between the published works and the scarcity of available studies, the authors report the need for more studies on the subject, to better elucidate the clinical indications of mifepristone in the control of unresectable meningiomas.

In order to define precise clinical indications, it is necessary to discriminate the response in specific populations, especially those with a higher probability of response: premenopausal women and men. In addition, new in vitro studies can facilitate the design of future clinical trials by discriminating response by specific histological groups.

Evaluating the evidence found, the profile of side effects of the drug and the possible prognosis of the disease, it should be considered the treatment with mifepristone for symptomatic benign meningiomas against the exhaustion of other therapeutic options.

Author contributions

Marcelo José da Silva de Magalhães: Conception and design of the research; data collection; analysis and interpretation of the data; writing of the manuscript; critical revision of the manuscript in terms of intellectual content and final presentation. **Nathalia Cristina Freitas Souza e Heick Damasceno Batista:** Conception and design of the research; data collection; analysis and interpretation of the data; writing of the manuscript. The authors approved the final version of the manuscript and declared themselves responsible for all aspects of the work, including guaranteeing its accuracy and integrity.

Conflict of interests

The authors declare no conflicts of interest.

References

1. Ogasawara C, Philbrick B, Adamson DC. Meningioma: A Review of Epidemiology, Pathology, Diagnosis, Treatment, and Future Directions. Biomedicines. 2021 Mar 21;9(3):319. Available from: https://doi.org/10.3390/biomedicines9030319

2. Louis ED, Mayer SA, Rowland LP. Merritt Tratado de Neurologia. 13th ed. Rio de Janeiro: Guanabara Koogan LTDA; 2018. ISBN 978-85-277-3389-2.

3. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A *et al.*The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol. 2007 Aug;114(2):97-109. Available from: https://doi.org/10.1007/s00401-007-0243-4

4. Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: a review. J Neurooncol. 1996 Sep;39(3):197-205. Avaliable from: https://doi.org/10.1007/BF00165649

5. Cahil DW, Bashirelahi N, Solomon LW, Dalton T, Salcman M, Ducker TB. Estrogen and progesterone receptors in meningiomas. J Neurosurg. 1984 May;60(5):985-993. Available from: https://doi.org/10.3171/jns.1984.60.5.0985

6. Bickerstaff ER, Small JM, Guest IA. The relapsing course of certain meningiomas in relationto pregnancy and menstruation. J Neurol Neurosurg Psychiatry. 1958 May;21(2):89-91. Available from: https://doi.org/10.1136/jnnp.21.2.89

7. Sitruk-Ware R, Spitz IM. Pharmacological properties of mifepristone: toxicology and safety in animal and human studies. Contraception. 2003 Dec;68(6):409-420. Available from: https://doi.org/10.1016/S0010-7824(03)00171-9

8. Baulieu EE. Contragestion and Other Clinical Applications of RU 486, an Antiprogesterone at the Receptor. Science. 1989 Sep 22;245(4919):1351-1357. https://doi.org/10.1126/science.2781282

9. Matsuda Y, Kawamoto K, Kiya K, Kurisu K, Sugiyama K, Uozumi T.Antitumor effects of antiprogesterones on human meningioma cells in vitro and in vivo. J Neurosurg. 1994 Mar;80(3):527-534. Available from: https://doi.org/10.3171/jns.1994.80.3.0527

10. Olson JJ, Beck DW, Schlechte JA, Loh PM. Effect of the antiprogesterone RU-38486 on meningioma implanted into nude mice. J Neurosurg. 1987 Apr;66(4):584-587. Available from: https://doi.org/10.3171/jns.1987.66.4.0584

11. Grunberg SM, Weiss MH, Spitz IM, Ahmadi J, Sadun A, Russell CA, *et al.* Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. J Neurosurg. 1991 Nov;74(6):861-866. Available from: https://doi.org/10.3171/jns.1991.74.6.0861

12. Lamberts SW, Tanghe HL, Avezaat CJ, Braakman R, Wijngaarde R, Koper JW*et al.* Mifepristone (RU 486) treatment of meningiomas. J Neurol Neurosurg Psychiatry. 1992 Jun 1;55(6):486-490. Available from: https://doi.org/10.1136/jnnp.55.6.486

13. Grunberg SM, Weiss MH, Russell CA, Spitz IM, Ahmadi J, Sadun A, *et al*. Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. Cancer Invest. 2006 Dec;24(8):727-733. Available from: https://doi.org/10.1080/07357900601062339

14. Ji Y, Rankin C, Grunberg S, Sherrod AE, Ahmadi J, Townsend JJ, *et al.* Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005. J Clin Oncol. 2015 Dec;33(35):4093-4098. Available from: https://doi.org/10.1200/JCO.2015.61.6490

15. Touat M, Lombardi G, Farina P, Michel Kalamarides M, Sanson M. Successful treatment of multiple intracranial meningiomas with the antiprogesterone receptor agent mifepristone (RU486). Acta Neurochir.2014;156:1831–1835.Available from: https://doi.org/10.1007/s00701-014-2188-4

16. Jhawar BS, FuchsCS, Colditz GA, Stampfe MJ. Sex steroid hormone exposures and risk for meningioma. J Neurosurg. 2003 Nov;99(5):848-853. Available from: https://doi.org/10.3171/jns.2003.99.5.0848

17. Schoenberg BS, Christine BW, Whisnant JP. Nervous system neoplasms and primary malignancies of other sites. The unique association between meningiomas and breast cancer. Neurology. 1975 Aug;28(8):705-712. Available form: https://doi.org/10.1212/WNL.25.8.705

18. Longstreth WT Jr, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD. Epidemiology of intracranial meningioma. Cancer. 1993 Aug 1;72(3):639-48. Available from: https://doi.org/10.1002/1097-0142(19930801)72:3<639::AID-CNCR2820720304>3.0.CO;2-P

19. Wahab M, Al-Azzawi F. Meningioma and hormonal influences. Climacteric. 2003 Dec;6(4):285-92. Available from: https://pubmed.ncbi.nlm.nih.gov/15006250/

20. Koper JW, Foekens JA, Braakman R, Lamberts SW. Effects of progesterone on the response to epidermal growth factor and other growth factors in cultured human meningioma cells. Cancer Res. 1990 May 1;50(9):2604-7. Available from: https://pubmed.ncbi.nlm.nih.gov/2183929/

21. Nasrallah MP, Aldape KD. Molecular classification and grading of meningioma. J Neurooncol. 2023 Jan;161(2):373-381. Available from: https://doi.org/10.1007/s11060-022-04228-9

22. Maas SLN, Stichel D, Hielscher T, Sievers P, Berghoff AS, Schrimpf D, *et al.* Integrated Molecular-Morphologic Meningioma Classification: A Multicenter Retrospective Analysis, Retrospectively and Prospectively Validated. J Clin Oncol. 2021 Dec 1;39(34):3839-3852. Available from: https://doi.org/10.1200/JCO.21.00784

23. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV. An overview of meningiomas. Future Oncol. 2018 Sep;14(21):2161-2177. Available from: https://doi.org/10.2217/fon-2018-0006

24. Spitz IM, Grunberg SM, Chabbert-Buff N, Lindenberg T, Gelber H, Sitruk-Ware R. Management of patients receiving long-term treatment with mifepristone. FertilSteril. 2005 Dec;84(6):1561-1844. Available from: https://doi.org/10.1016/j.fertnstert.2005.05.056