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New Developments in Management of Meningioma

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Abstract

Introduction: The incidence of Meningiomas, indicating of the population-based studies, is approximately 13-26% of all primary intracranial tumors.

Methods: We searched PubMed for studies related to meningiomas published over the last 6 years (from May 2009) and retrieved 2104.

Results: Surgery remains the main choice of treatment at meningiomas and the combination with the endovascular treatment and/or Stereotactic radiosurgery provide a better and safer therapeutic strategy. In atypical and subtotal excised or recurrent meningiomas, conventional radiotherapy should be performed. Chemotherapeutic agents also, should be used in specific cases, because of questionable effectiveness and considerably side effects.

Conclusion: Even the recent technological developments, which give rise to better therapeutic options, the "gold standard" of meningiomas treatment, still remain challenging.

Keywords: Meningioma; Surgery; Chemotherapy radiotherapy; Endovascular treatment; Management

Introduction

The incidence of Meningiomas, indicating of the population-based studies, is approximately 13-26% of all primary intracranial tumors [1,2]. Has been estimated that the asymptomatic meningiomas account 2-3% of the population [3-6], although at some cases incidence approaches the 59,6% [7]. A Magnetic Resonance Imaging (MRI) study in the general population by Vernooij et al. reported a prevalence of 0,9% [8]. Their occurrence increases with age (peaks after the fifth decade of life) and affects women more frequently with 2:1 female:male ratio [1,3]. Contrary to commonly opinions, there is no evidence of an increased prevalence of meningiomas in cancer survivors [9]. Spinal meningiomas represents 25-46% of spinal tumors, affecting more commonly middle-aged women and having thoracic laterality [10,11].

Meningiomas most common arise from the arachnoid cap cells imbedded in the arachnoid vill [3], optic nerve sheath, choroids plexus and rare from unknown and progenitor cells origin [12,13]. According to Word Health Organization (WHO), they classified on the basis of the tissues involvement, dural site origin and histological type [14]. The vast majority of spinal meningiomas have thoracic localization 80%, with benign behavior and intradural extramedullary lateral appearance, whereas in 15-27% of cases have anterior manifestation and their surgical removal is difficult [15]. Meningiomas are the most common calcified intradural spinal tumors on CT scans and with low signal intensity on T2-weighted MRI associated with slower growth rate, but exhibit an uncommon totally ossification in only 1-5% of cases and more difficult resection than the usual type [16-18].

Although meningioma is typically benign and slow growing in approximately 92%, appearing mostly in the later decades of life, they can be exhibit an anaplastic (1.0 to 2.8%) or atypical (4.7 to 7.2%) behavior [19,20], with more common appearance in men [21].

However, more than 9% of all meningiomas are characterized by aggressive clinical behavior with increased risk of tumor recurrence [20], with 1,3 - 14,7% recurrence rate at the spinal cord meningiomas [11].

While asymptomatic meningiomas are traditionally managed conservatively until symptoms develop or lesion growth occurs, it is likely that patients at high risk for symptom development – most common young people because of the higher growth potential, may benefit from earlier clinical and radiological follow-up in order to decrease this possibility [4,6]. Also, many measurements are useful to determine the extent of the increase of meningiomas, such as the calcification evidence on CT scans and T2-weighted MRI, the depending of patient's age to the decision of operation, the symptomatology and comorbidities [17,21,22]. Furthermore, in surgical treatment of asymptomatic meningiomas, the morbidity rate was 4.4% in patients younger than 70 years of age and 9.4% in those 70 years of age or older [17,23].

The "gold standard" for symptomatic patients, is the complete tumor resection, although in elderly population the complications are more frequent [24,25]. Some studies proposed a stereotactic radiotherapy as an alternative method, with low toxicity and the lack of treatment-associated mortality [26]. In order to reduce the surgical complications in more aged patients with symptomatic meningiomas, Sacko et al. proposed a grading system to standardize the surgical indications [27]. On the other hand, for subtotal resected and recurrent meningiomas, radiotherapy (conventional or stereotactic) may be proposed. When all treatments (surgery and radiotherapy)

have failed; hormonal therapy or chemotherapy can be applied [28]. In the current study we reviewed the available treatment modalities for meningioma treatment.

Results

After investigation of 2104 articles, only 154 article were eligible. We found differences therapeutic strategies including surgery, Radiotherapy Stereotactic radiosurgery (SRS), Stereotactic Fractioned Radiotherapy (SFRT), Intensity-Modulated Radiotherapy (IMRT), Chemotherapy and Endovascular treatment. When meningiomas are symptomatic, surgery with radical excision, constitutes the first choice of treatment. Parasagittal meningiomas constitute a challenge for the surgeon; mainly when they arise from the middle. If meningiomas involve the optic canal, the decompression and removal of the tumor inside optimize visual recovery and prevent tumor recurrence. For parasellar and posterior fossa meningiomas, usual excision of the tumor followed by irradiation is advocated in order to reduce postoperative neurological injuries. Radiotherapy (RT), Stereotactic Radiosurgery (SRS) or Gamma Knife SRS constitute a supplementary and effective management to a surgery and conventional radiotherapy treatment. By the development of 3D Conformal Radiotherapy (CFRT), where the high-dose suits the target and avoids normal tissues, the effectiveness of radiotherapy has been improved. Traditional chemotherapeutic agents are not very effective against meningiomas. Hormonal manipulation is also under review in cases with untreatable tumors or those who are inappropriate for surgery. Angiography and more recently, selective intra-arterial injection of dilute MR contrast media, can be offer a better understanding and more clear view to the vascular blood supply of the meningiomas.

Discussion

Surgery

Surgery constitutes the first choice of treatment, when meningiomas are symptomatic, with more radical excision, because of latest approaches. Thus, the use of dorsolateral approach for foramen magnum meningioma [29], retrosigmoidal for petroclival [30] or skull base approach for giant anterior clinoidal meningiomas [31-33], usually offer very good results. Furthermore, microsurgical operation has given grate results and an effective resection [34-36]. The new imaging techniques also, allows a better preoperative planning. Meningiomas are well MR perfused tumors [37] and 3D-CTA helps to avoid vascular events, during surgical removal of the tumor [38]. Single Photon Emission Computed Tomography (SPECT) has showed promise for the differentiation between anaplastic and benign meningiomas [39,40] and Computed Tomography Venography (CTV) can provide a significant assistance at meningiomas located close to the Superior Sagittal Sinus (SSS) [41].

Recurrence rate has very well established and have been showed a depending on tumor's WHO grade and the extent of resection by Simpson criteria [42,43].

Many meningiomas cannot be totally resected because of their involving with vital neural, vascular (central veins) structures or are en plaque. Parasagittal meningiomas constitute a challenge for the surgeon; mainly when they arise from the middle and posterior third of SSS. If the sinus is partially or completely occluded, may be opened and a total tumor resection could be proposed, followed by venous reconstruction [32]. Also, an alternative plan is the outside of sinus tumor excision and coagulation of remnants or the use of radiation treatment [44]. The restore of flow, by venous reconstruction and maintenance of cortical veins, offer a very useful collateral drainage [45].

If meningioma involves the optic canal, the decompression and removal of the tumor, optimize visual recovery and prevent tumor recurrence [46,47]. The management of spheno-orbital meningiomas with diffuse orbital tumors and invasion of the optic canal, is a supraorbital-pterional approach and wide opening of the optic canal [48]. Surgical resection of spheno-orbital en plaque meningiomas is effective and safe (low morbidity and in about 2/3 of cases improving of the visual function) [49]. For lateral intraorbital tumors with invasion of the lateral aspect of the optic canal, a complete tumor resection offers good decompression of the optic nerve (via a less invasive lateral orbitocranial approach without craniotomy) [48]. For the cases of bilateral hyperostotic sphenoorbital meningiomas, which are quite rare, the proposed management includes pterional approach for surgical resection, in two stages (first treating the most impaired side), including the decompression of the optic nerve [50]. When cavernous sinus infiltration coexists, radiation therapy can be added [50].

For lateral sphenoid wing and olfactory groove meningioma, the complete resection is the goal [51]. Direct intratumoral hydrogen peroxide injection may reduce blood loss, the need of preoperative embolization and shorted resection times [52]. At sphenoid wing meningiomas, the tumors without cavernous sinus involvement had a more favorable visual outcome and overall prognosis, compared with tumors presenting cavernous sinus involvement [53]. For the olfactory groove meningiomas many approaches have been used depend on tumor size, location, origin and extension, with less morbidity rate and better access in bifrontal and frontolateral approaches [54,55].

For parasellar and posterior fossa meningiomas, usual excision of the tumor followed by irradiation is advocated in order to reduce postoperative neurological injuries [56]. In tuberculum and diaphragma sella meningioma, an early surgery using the subfrontal approach with better preoperative visual function and smaller tumor size is associated with better outcome [57]. Moreover, the management of tuberculum sellae meningiomas can include pterional [58] or frontolateral approach with microsurgical dissection of the Sylvian fissure, giving a quick access, safe and totally resection of the meningioma, with improvement of the vision and reduction of the morbidity [59]. The retrosigmoid approach for the management of the cerebellopontine angle (CPA) meningiomas, is a common and safe surgical procedure [60]. Large meningiomas of CPA, can compress the brainstem and may have a vascular and neuronal attachment. A combined retrosigmoid–transpetrosal–transcochlear approach can provide wide exposure to the CPA and easier surgical resection of large meningiomas [61]. In a case of a small residual tumor, it can be managed with radiosurgery for a long period free of tumor recurrence. The function of the facial nerve was preserved in 91% of cases with total resection, having a low recurrence rate (<1%) [60]. On the other hand, the retrolabyrinthine approach described in 1972 by Hitselberger and Pulec, allows an easier exposure in anatomical entities at this region with a better tumor resection and lateral sinus control [62].

Anterior clinoidal meningiomas constitute a more challenging tumor for surgery and many base approaches can be used with good results [63]. There are reports, showed that the pterional craniotomy is a satisfactory approach regardless of tumor size [64]. Other challenged

managing tumors are the foramen magnum meningiomas, mainly when they have anterolateral localization [65]. In difficult cases, a subtotal resection can be proposed; when they are asymptomatic. In elderly population with mild symptoms, the treatment is conservative. When they are small (<30 mm) and asymptomatics, radiosurgery offers very good results [65].

For giant meningiomas of the anterior cranial fossa, the extended anterior skull base approaches, using orbital osteotomies, have improved the possibility of gross-total tumor removal with minimal neurological morbidity [66]. Many techniques also, are spacialy beneficial for skull base meningiomas, in order to reduce thromboembolic events during surgery, such as an intraoperative leg-elevation, early (on the day of surgery) Low-Molecular-Weight Heparin (LMWH) (there were no elevated risk of post-operative hemorrhage), application of Intermittent Pneumatic Compression (IPC) and regular compression stockings [67]. In cases with large Intraventricular Meningiomas (IVM), the surgical resection can result in hydrocephalus, with difficulties in management [68]; using the transcortical parieto-occipital approach, temporal and transcallosal approach, can be achieved total surgical excision, with few neurological deficits and no recurrence [69]. In a small study of IVM, the lateral ventricular IVM were accessed by the posterior middle temporal gyrus or the superior parietal lobule approach, and the fourth ventricular IVM were accessed via midline suboccipital craniectomy [70]. Moreover, the parietooccipital route for lateral ventricular meningiomas is a safe surgical approach which may not necessarily been associated with postoperative visual deficits [71].

Petroclival meningiomas are other demanding tumors, with risk of postoperative neurological morbidity. The aim of 3D contrast-enhanced Magnetic Resonance Venography (MRV), is a more secure resection, mainly when the cavernous sinus drains into either inferior or superior petrosal sinus and patent sinus should be protected during operation [72]. In this region the near total tumor resection, considerably reduce the positivity of recurrence and the postoperative neurological deficits [73]. Recently, the use of computer-aided surgery and the transnasal endoscopic approach have been achieved a better outcome [74]. In meningiomas at the upper anterior third of the posterior fossa, a transcavernous approach with exposure of the lateral wall of the cavernous sinus and removal of the anterior clinoid process, leads to a better control to the upper basilar region. Furthermore, it can be offer a wide exposure of meningioma by removal of the posterior clinoid process and the petroclival osseous [75]. In case also, with sinus cavernosous involvement, a total tumor excision it's too difficult [76], and with poor outcome, mainly when the sinus is totally occluded [77]. In a young patient, the risk of brain infarction after a forceful excision is very high. The subtotal tumor removal with maintenance of vascular and neurological structures is now a most acceptable management, with residual tumor either observed by serial imaging or treated with radiation [68,78].

The management of meningiomas in children includes aggressive gross-total resection as first choice initial treatment. Radiotherapy has no benefit as initial treatment. Subtotal resection or WHO grade III tumors are in need of close observation [79,80].

In the elderly patients also, the decision for operating or not, is individual. Severe concomitant disease or high American Society of Anesthesiology (ASA) score advice not to undergo surgical therapy [81]. For elderly patients or asymptomatic with anterolateral meningiomas of the foramen magnum, conservative treatment is the recommendation [65].

Spinal meningiomas have more frequently intradural-extramedullar localization, with the majority of them to be extended laterally or posteriorly. Microsurgical techniques and MRI can be helpful for a better clinical outcome and early diagnosis [82-84]. An approximately 15-27% of spinal meningiomas, have an anterior to the spinal cord position, with difficult exposure [15]. In these challenging cases, can be used the transthoracic approach with a better tumor visualization, but is more invasive procedure and there is a need for verbectomy. Postero-lateral approach offers also, good results with radical resection. The less invasive posterior approach allows an incomplete resection. Additional, without intraoperative monitoring, used evoked potentials, surgeon's manipulations may damage the spinal cord [85,86]. Total exposure usually offers a neurological improvement, but the recurrence rate is 1,3-14% [84].

2. Radiotherapy

Radiotherapy (RT) recommended as an additional therapy in malignant or atypical meningiomas, mainly if incomplete surgical excision is performed [87,88]. Concerning atypical meningiomas, in same reports with gross total resected tumors without RT, the recurrence rate after 5 years was 28% [88]. In patients with high-grade atypical meningiomas, adjuvant radiotherapy improves patients' survival, only if there was brain involvement. The extent of resection, p53 overexpression, malignant progression, brain invasion and the adjuvant RT, constitute the prognostic factors for anaplastic meningiomas [89]. In benign meningiomas adjuvant radiotherapy is proposed, because of the delayed tumor growth and the reduces of likelihood for further surgery [90,91]. Furthermore, RT can be beneficial for high surgical risk or advanced age patients. Also, it can be helpful in cases with meningioma located in eloquent or surgical inaccessible areas [92,93]. High dose RT also, has a significant improvement in malignant meningiomas [94]. Most of the patients with Tentorial Fold (TF) meningiomas (TFM), after a total resection, suffer of permanent morbidity. They should be treated with radiotherapy [95].

3. Stereotactic radiosurgery (SRS)

Stereotactic radiosurgery (SRS) or Gamma Knife SRS constitute a supplementary and effective management to a surgery and convensional radiotherapy treatment, in patients with brain tumors [31]. In order to limit the side effects of radiation, especially in meningiomas, SRS allows smaller doses of radiation, improving survival and tumor control [96,97]. Either as initial or adjuvant therapy, SRS achieved a high rate tumor control (98% with WHO Grade I tumors, 50% in Grade II and 17% in Grade III tumors) and only in 5% after radiosurgery was necessary an extra resection. Results were better for small to medium-sized symptomatic and newly diagnosed or recurrent meningiomas [98]. The use of SRS in patients with recurrent or residual atypical and malignant meningiomas can improve survival, with 68% in 5-year local control rate in atypical meningiomas [99,100]. Three-dimensional conformal radiotherapy for atypical and anaplastic meningiomas produced 5-year actuarial local control rates of 38% and 52%, respectively [94]. Furthermore, SRS is safe and effective treatment option for radio-induced meningiomas such as typical ones [101-103].

Radiosurgery, is a good option for convexity, parasagittal, and falcine meningiomas as a primary or adjuvant therapy [104]. For parasagittal meningioma radiosurgery resulted in 60% 5-year control rates for recurrent and 93% for residual disease [105]. Gamma Knife

surgery can be used safely in small, minimally symptomatic or growing Foramen Magnum Meningiomas (FMMs). It is also useful and safe to use in residual tumors, after microsurgical removal [106]. In skull base meningiomas, the 5-year actuarial control rate was 87% for typical meningiomas, 49% for atypical and 0% for malignant lesions and the radiosurgery related complications occurred in 3% of patients [107,108]. SRS provided effective tumor control in patients suffering cavernous sinus meningiomas, but does not improve neuralgia, in most patients [109], while subtotal tumor resection does not reduce the effectiveness of the method [110].

The use of SRS in cerebellopontine angle (CPA) meningiomas, is possible to preserve cranial nerve function [111]. Gamma Knife radiosurgery shows satisfactory results in long-term disease control of benign meningiomas [112], with very low local tumor failure and treatment toxicity [91]. Other reports mentioned an 89% 5-year tumor control rate and 5% complication rate [113]. On the other hand, the use of radiosurgery in non-benign meningiomas is not effective enough. Results are better for small meningiomas under the condition of using higher doses and greater marginal [114].

Radiosurgery also, has been beneficial for the treatment of intradural spinal meningiomas, with a reduction of radiographic recurrence evidence [115].

4. Stereotactic Fractioned Radiotherapy (SFRT)

Stereotactic Fractionated Radiotherapy (SFRT) is the treatment of choice, for optic nerve sheath meningiomas. It is a safe option with low morbidity and satisfactory long-term results [116,117]. Furthermore, SFRT improves disease-free period after subtotal resection and offers excellent help in management of the skull base lesions, reducing post-surgical lesions of the optic nerve [118]. The restricted radiation tolerance of the visual pathways lesions is a great challenge and SFRS improves or stabilize visual deficit, in 89% of cases. The use is more meaningful before severe visual problems settle [119]. There are also reports, suggesting that multisession therapy can be an effective alternative to either surgery or radiotherapy for selected lesions immediately adjacent to short segments of the optic apparatus [120].

A single-fraction Stereotactic Radiosurgery provides a high rate tumor control, in cases of benign intracranial meningiomas [121]. In 317 patients with intracranial meningiomas, FSRS was used as primary treatment, after subtotal excision or biopsy and for recurrence disease. 4.5 years after SFRT, 22 patients (6.9%) had local tumor progression, depending of histology and tumor volume as prognostic factors [122].

Linear accelerator (LINAC) fractionated RT using the multiple noncoplanar dynamic rotation conformal paradigms can be offered to patients with meningiomas at the anterior visual pathways, an alternative to surgery or a primary treatment, with results similar to those reported for other stereotactic RT techniques [123]. Furthermore, LINAC is effective and safe method, with a relatively high local tumor control and low morbidity, at incompletely resected or recurrent malignant meningiomas [124].

Combined Stereotactic Radiosurgery and FSRS are both equally safe and effective in the management of symptomatic Cavernous Sinus Meningiomas (CSMs) [125].

5. Intensity-modulated radiotherapy (IMRT)

The development of 3D conformal radiotherapy (CFRT), where the high-dose suits the target and avoids normal tissues, has been improved the effectiveness of radiotherapy. IMRT is the most advanced form of CFRT. This technique is useful for irregularly shaped tumors and too large for stereotactic radiotherapy. For that reason meningiomas are an ideal candidate. A study that compared static Conformal Field (CF), IMRT and Dynamic Arcs (DA) for skull base meningiomas, reported that IMRT was more effective when the target volume was larger than 25 cm^3, because of a limited normal tissue sparing into the brain stem or temporal lobe [126,127].

IMRT is an effective method for treating meningiomas causing ophthalmologic deficits. Additionally, the toxicity is minimal [128]. The use of IMRT to treat grade II meningiomas with total initial margins (CTV + PTV) ≤1 cm, demonstrates efficacy and low risk of marginal failure with reduced margins [129]. In patients with skull base meningiomas IMRT leads to long-term tumor control with minimal side effects, but also with preservation of quality of life [130]. Furthermore, IMPT has the potential to overcome the lack of a framework for skull base tumors. Carbon ion plans offered considerably better dose distributions than proton plans in IMPT, but the differences were not clinically significant with traditional dose recommendation concepts [131]. In a study with complex-shaped meningiomas of the skull base (54.3% benign meningiomas, 9.6% atypical and 4.2% anaplastic) the use of IMRT as primary treatment or postoperative for residual disease and treatment after local recurrence, was an effective and safe cure modality for long-term local control. In 39.8% of the patients, neurologic deficits improved, and worsened or developed new symptoms in only six patients [132].

In a study where compared the effectiveness and limitations of Stereotactic Arc Therapy (SRS/T), Intensity-Modulated Radiotherapy (IMRT), Helical Tomotherapy (HT), cyberknife and Intensity-Modulated Multiple Arc Therapy (AMOA), on patients with benign brain tumors, including 5 meningiomas, all techniques provided good organs at risk sparing. HT providing the best combination of indices, and between AMOA and IMRT, target coverage was similar, but taking into account organs at risk, AMOA was considerably preferable [133].

6. Chemotherapy

While strong evidence exists for the standard therapy of meningiomas, inclusive of surgery and/or radiation therapy, for those tumors which recur, progress or are inoperable, the optimal medical therapies are yet to be elucidated. Traditional chemotherapeutic agents are not very effective against meningiomas. Hormonal manipulation is also under review in cases with untreatable tumors or those which are inappropriate for surgery [42,91,93]. A number of challenges are apparent with respect to the use of chemotherapy or targeted therapy for intracranial meningioma. There is very limited published literature that provides persuasive proof from which to establish appropriate treatment and there are a small number of clinical trials for patients with recurrent meningiomas [134].

Improved understanding of the molecular mechanisms driving meningioma tumorigenesis and malignant transformation has resulted in the targeted development of more specific agents for chemotherapeutic intervention in patients with nonresectable, aggressive, and malignant meningiomas [135].

Some studies analyze the potentials benefits from chemotherapeutics, including cytotoxic agents, biologic agents, targeted molecular agents and hormonal agents. Most data is about hydroxyurea and somatostatin, although further trials with combination and targeted molecular therapies are still underway [136].

Hydroxyurea is a modestly active agent against recurrent meningiomas and can induce long-term stabilization of disease in some patients [137]. It has been used for untreatable tumors, large residual tumors [91], benign meningiomas of the skull base or those involving the dural venous sinuses. On the other hand, in many reports mentioned a limited effect of this agent, in atypical or malignant recurrent meningiomas [138,139]. As for malignant meningioma, after total or subtotal resection and RT, adjuvant chemotherapy with cyclophosphamide, adriamicin and vincristine (CAV), has been used, with very good outcome (median survival 5,3 years) [140]. Further, combinations of andriamycin and dacarbazine or isosfamide and mensa provide a more effective treatment [141]. Mifepristone can be also performed for prolonged periods in patients with nonresectable meningioma, but have been reported many side effects, such as an irregular vaginal bleeding, endometrial thickening and biochemical hypothyroidism [142].

7. Endovascular treatment

The rapid technological developments in endovascular materials, allowed a micro catheterization and embolization of meningiomas [143]. Angiography and more recently, selective intra-arterial injection of dilute MR contrast media, can be offer a better understanding and more clear view to the vascular blood supply of the meningiomas [144]. Furthermore, angiographic embolization reduces the need of transfusion during operation [145].

Embolization is recommended, in order to decrease the volume of the tumor and the surgical blood loss [146]. Thus, may be beneficial in benign (grade I) meningiomas, preventing the atypical histological changes [147], eliminating the postoperative complications and shortening the operative time [148]. At inappropriate for surgery patients also, embolization can be used as an alternative treatment [149,150], with good results and tumor shrinkage in most cases [151].

On the other hand, the application or not of preoperative embolization in meningiomas, is still remaining controversial, due to the major complications, such as hemiparesis and tumor swelling [146]. There are reports also, performed the used of the temporary clipping of external carotid artery, as an alternative (effective and safe) method for very large convexity, parasagittal and temporal base meningiomas [152]. However, in patients whose tumor-feeding arteries run posteromedially toward the petrous apex or cavernous sinus is demanding more carefulness, since they are at increased risk of post-embolization cranial nerve palsy [153].

Conclusion

Surgery remains the main choice of treatment at meningiomas and in benign and total resected tumors, offer an excellent results and in most cases a completely therapy. The combination with the endovascular treatment, provide a better and safer therapeutic strategy. Stereotactic radiosurgery can be used as an alternative treatment to surgery. In atypical and subtotal excised or recurrent meningiomas, conventional radiotherapy should be performed. Chemotherapeutic agents also, should be used in specific cases, because of questionable effectiveness and considerably side effects. Even the recent technological developments, which give rise to better therapeutic options, the "gold standard" of meningiomas treatment, still remain challenging.

Methods

Search strategy for identification of studies

PubMed searches were performed using a wide array of terms pertinent to meningiomas. The exact search was done using the term – meningiomas and therapy- (last updated on January 2015). We included studies published over the last 6 years (from May 2009). The reference lists of eligible articles and pertinent reviews were scrutinized. Two independent investigators for eligibility evaluated retrieved articles and disagreements were solved by consensus after discussion with a third investigator.

Data extraction and definitions

This is a review study. From each eligible study we extracted the following information: author; journal; year; design; age of the study population; racial descent; whether analyses had been adjusted for multiple comparisons; whether analyses were acknowledged to be post hoc; and details on the definitions of all reported analyses.

From the 2104 related articles retrieved from the PubMed search, we excluded case reports analyzing less than four cases; non-English speaking publications and reports not related to humans; any study with less than four cases with spinal ependymomas. Information was captured on all analyses performed and reported in any format and in any level of detail in the text, figures, tables, or supplementary material.

Ethics Statement

This study has been approved by a suitably constituted Ethics Committee of the Institution within which this work was undertaken and conforms to the provisions of the Declaration of Helsinki.

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