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A Retrospective Interventional Cohort Study to Assess the Safety and Efficacy of Sandostatin LAR (octreotide acetate) for the treatment of Recurrent and/or Refractory Meningiomas in Adult Patients

THESIS

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in BIOMEDICAL AND TRANSLATIONAL SCIENCE

by

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DEDICATION

To

my mom

in recognition of her unconditional love and support

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ABSTRACT OF THE THESIS

A Retrospective Interventional Cohort Study to Assess the Safety and Efficacy of Sandostatin LAR (octreotide acetate) for the treatment of Recurrent and/or Refractory Meningiomas in Adult Patients

By

Emely Nhi Thi Ai Nguyen

Master of Science in Biomedical and Translational Science

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Associate Professor Daniela Bota, MD, PhD, Chair

Meningioma is the most common primary intracranial tumor in adults. Though the majority of tumors are slow growing, many patients fail first-line treatments with surgery and/or radiation. Others are poor surgical candidates for definitive surgical resection due to their age, tumor location or associated medical comorbidities. Few targeted therapies and biologics for meningioma are studied, and they have limited efficacy.

This study aims to estimate the overall survival, progression free survival, and safety of octreotide acetate (Sandostatin LAR) as a potential treatment for recurrent and/or refractory meningiomas. The retrospective chart review included patients over 18 years of age and diagnosed with meningioma who were administered Sandostatin LAR from 01/01/2010 until 06/01/2017 at the University of California, Irvine (UCI). The primary endpoints were overall survival (OS) and progression-free survival (PFS). The secondary endpoint was assessing safety.

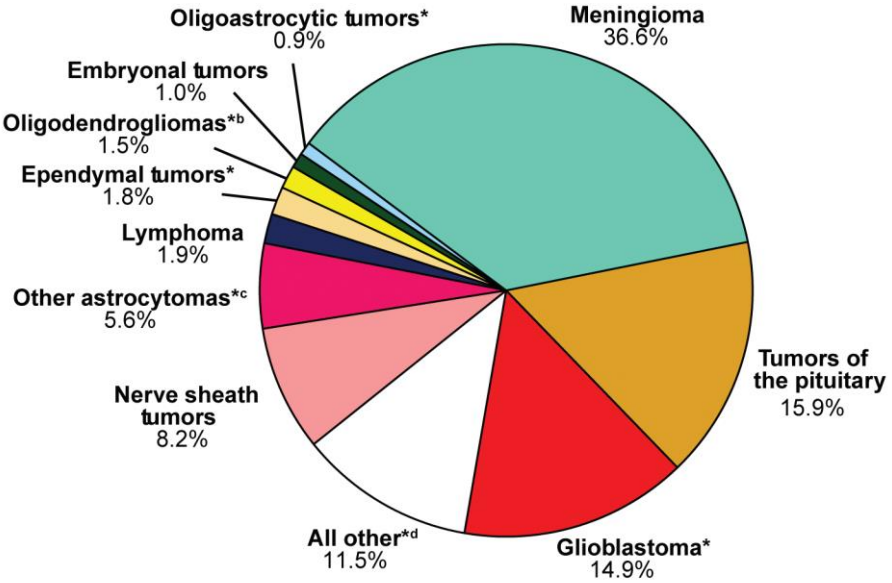
There were 43 patients included in the chart review. 14 patients experienced disease progression and 6 died. The overall survival times at 6 months, 1 year, and 3 years for all WHO grades was 94.8% (0.88-1.01), 88.1% (0.77-0.99), and 67.0% (0.36-0.98) respectively. Median time to progression for grade 1, 2, and 3 were 3.1, 2.38, and 0.21 years respectively. The most common AE was diarrhea which occurred in 19 out of 47 patients. Overall, Sandostatin LAR was well tolerated.

This is the largest reported cohort of meningioma patients treated with Sandostatin LAR and suggests that Sandostatin LAR can be a well-tolerated treatment and prolong overall survival and progression free survival.

Introduction

The meninges are a type of membrane that covers the brain and spinal cord. It serves as a protective barrier for the skull and spinal cord. It also provides space for cerebral spinal fluid and blood supply to the skull. The meninges is made of three layers that envelop the brain and spinal cord: the dura mater, arachnoid, and pia mater. Meningioma is a tumor in which there is an abnormal growth of the arachnoid layer. They are the most common type of Central Nervous System (CNS) tumors. According to the Central Brain Tumor Registry of the United States (CBTRUS) statistical report, meningiomas account for 36.6% of all primary brain tumors in the United States from 2009 – 2013 (Figure 1) and are the most common non-malignant tumors[30]. Most are found incidentally, and symptoms are dependent on the location of the meningioma. Since meningiomas are slow growing, it can be years before patients begin to experience any symptoms. Common symptoms depend on the tumor location, and can include loss of smell, loss of hearing, headaches, changes in memory, changes in mental status, seizures, changes in vision, and/or weakness in the arms or legs. Meningiomas are classified by the World Health Organization (WHO) into three grades according to the WHO Classification of Tumors of the Central Nervous System, Edition 4. Most meningiomas are very slow growing, are classified as grade I and account for approximately 90% of all meningiomas[21].

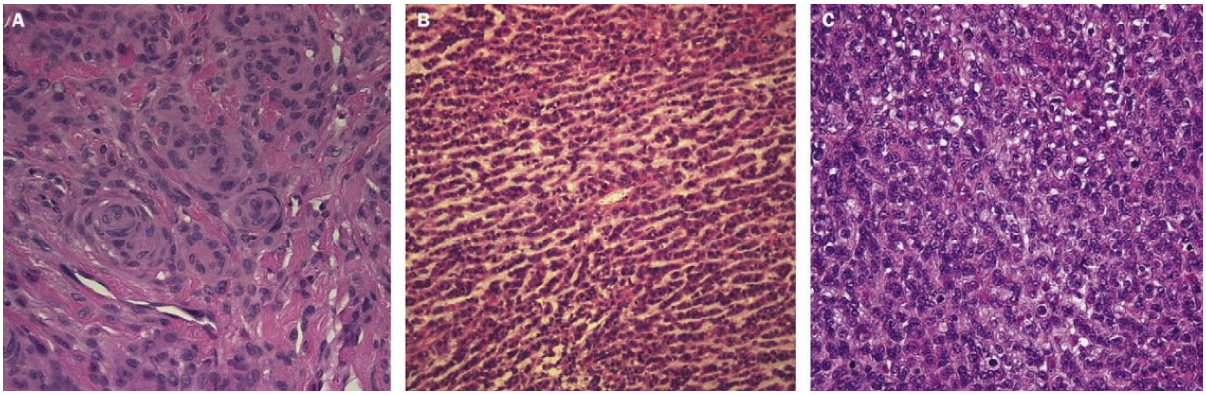
Figure 1.0 Distributions of All Primary Brain and Other CNS Tumors by CBTRUS Histology Groupings and Histology (N=368,117), CBTRUS Statistical Report: NPCR and SEER, 2009-2013.



Source: Quinn T. Ostrom, Haley Gittleman, Jordan Xu, Courtney Kromer, Yingli Wolinsky, Carol Kruchko, and Jill S. Barnholtz-Sloan, CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2009–2013, Neuro Oncol (2016) 18 (suppl 5): v1-v75

However, some meningiomas are diagnosed as atypical (grade II) or anaplastic (grade III). These rare types of meningiomas tend to be more often recurrent and are highly invasive. Grade II tumors make up 5-7% of meningiomas and grade III make up approximately 1-3% of meningiomas[21]. These grade types are differentiated from grade I tumors by several histological features. For the grade II/III tumors, a prominent nucleoli should be present, whereas, it is absent in grade I. The presence of a mitotic rate of at least four mitotic figures per ten high-power fields (hpf) is an important feature in differentiating grade II tumors from the others. Other histological features include 3 or more of the following: necrosis, small cells, increased cellularity, prominent nucleoli, sheeting, &/or brain invasion in an otherwise Grade I tumor[23]. Grade III tumors exhibit 20 or more mitoses per 10 hpf and/ often have characteristics that resemble carcinoma, sarcoma, or melanoma. Grade I tumors exhibit characteristics that are not described by grade II or grade III tumors.

Figure 2.0 Examples of meningiomas WHO histological grades I–III



A: transitional meningioma (grade I) showing characteristic cellular whorls; intranuclear pseudo-inclusions are visible in some cells. B: chordoid meningioma (grade II) with cohesive epithelial-like cords of cells; small foci of more typical arachnoidal differentiation are found in most of these tumors. C: anaplastic meningioma (grade III) consisting of pleomorphic arachnoidal cells with a high mitotic rate; foci of necrosis are widely distributed throughout most of these tumors
Source: Whittle, Ian R, et al. "Meningiomas." The Lancet, vol. 363, no. 9420, 2004, pp. 1535–1543.

Figure 2 shows examples of the different grades of meningioma. Compared to Grade I and II, Grade III meningiomas exhibit higher resistance to multiple lines of treatments and higher mortality rates.

Causes of meningioma are currently being investigated. There is limited research into what causes meningioma, however, several studies suggest that genetics, hormones, and previous radiation to the head are risk factors. Half of meningiomas have been found to have a loss of chromosome 22[31] which is normally involved in suppressing tumor growth. The neurofibromatosis type 2 (NF2) gene was also found to be mutated in meningiomas[32]. Mutated NF2 has been associated with complete loss of chromosome 22. Several studies have shown that hormones are associated with the risk of meningioma development since some meningiomas have estrogen, androgen, and progesterone receptors in both. Of the 510 tumor samples studied by researchers at the Department of Neurosurgery, University Hospital of Turku in Finland, 88% were progesterone receptor positive, 40% were positive for estrogen and 39% for androgen

receptors with no difference in expression of sex hormone receptors by sexes or age group[33]. The exact pathway for how genetics or hormones play a role in the development of meningioma remains to be explored.

Treatment options will depend on the location of the tumor, the grade, and patient preference. Grade 1 meningiomas are often slow growing, therefore, the standard of care for asymptomatic grade I tumors is often observation and monitoring. Patients will follow up with their physician and have periodic imaging tests done (usually MRI or CT) to track the growth of the tumor. For grade II and III, the rate of growth and the brain invasion precludes monitoring.

Resection is the most common treatment for symptomatic or aggressive or recurrent tumors and is often the only treatment needed for grade I tumors. Survival at 5, 10, 15, and 20 years was 92%, 81%, 63%, and 53%, respectively in an 11.5 year follow up study to assess long-term functional outcome and survival among patients age 4.5–84 years old with Grade 1 meningioma who have undergone resection[14]. Approximately 5% of completely resected benign meningiomas, 30% of partially resected benign meningiomas and 40% of atypical meningiomas recur within 5 years after surgery[8]. However, Grade II and III tumors tend to have higher rates of reoccurrence even after surgery.

Radiation therapy is also another option that is often used for malignant or recurrent tumors. There are two types of radiation therapy: external beam radiation therapy and stereotactic radiosurgery (SRS). External beam radiation therapy delivers radiation from outside the body using a machine called the linear accelerator. Stereotactic radiosurgery uses narrow beams of radiation coming from different angles to very deliver radiation to a brain tumor while saving the surrounding normal tissue. This method can also be delivered in fractions (called fractionated SRS) of small doses to reduce radiation induced toxicity. In a clinical study of 865

patients, tumor recurrence for all WHO grades combined after stereotactic radiation was 7.28%. Progression free survival was estimated at 95% at 1 year and 85% at 2 years[27]. Patients with WHO grade II or III have a higher rate of reoccurrence even after radiation therapy.

Some meningiomas are situated in areas that are difficult to access, and surgery is limited by the risk of severe neurological impairment. Other patients are poor surgical candidates at the time of recurrence due to their age or associated medical comorbidities, or refuse surgery/radiation due to their personal concerns. Some meningiomas can become aggressive (1-3% of meningiomas)[8] and will not respond well to first in line treatments (surgery, radiation). Chemotherapy or biologics are then considered as an alternate option. However, current drugs and biologics for meningioma have been limited due to lack of research, support for research in this area, and clinical trials since it is a rare tumor.

The National Comprehensive Cancer Network (NCCN) guidelines has defined three drugs that show activity in combating meningioma: vascular endothelial growth factor (VEGF) signaling pathway inhibitors, alpha-interferons, and somatostatin receptor agonists. However, literature for use of these agents are limited and often conducted in small sample sizes. Although these options are presented in the guidelines for treatment, there is no approved or effective drug for recurrent meningioma which also makes it difficult for patients to obtain the drug due to insurance approval and costs. There are other treatments that are being explored as potential agents as well for meningioma such as epidermal growth factor inhibitors (EGFR), hydroxyurea, immunotherapy, hormonal therapy, and platelet-derived growth factor receptor (PDGRF). EGFR was found to be overexpressed and in an activated state in meningiomas[28] which may be a potential option for targeted therapy. PDGF receptors are also found in meningiomas which has made it a potential option as well. Hydroxyurea is an inhibitor of ribonucleotide reductase which

induces apoptosis in meningioma cells in vitro and in mouse xenografts[29]. Another recent candidate for therapy is the use of estrogen and progesterone receptors. Progesterone receptors are found in approximately 70% of meningiomas, while fewer than 31% express estrogen receptors. There has been case studies in which tumor growth during pregnancy and change in size during menses were observed. Antiprogesterone and antiestrogen agents are presently being investigated as potential treatments for meningioma. These agents are potential candidates for therapy, however, clinical studies have had mixed results due to lack of research or small sample sizes. Full exploration of these and other chemotherapeutic agents as potential treatments for meningioma remain to be elucidated.

Due to the lack of research, patients with atypical, anaplastic, recurrent, or invasive meningiomas are often left with limited options. There is no FDA approved drug indicated specifically for meningioma. Additional research is needed in order to better understand meningioma and identify effective treatments. In this study, we retrospectively analyze patient medical records to estimate the overall survival (OS) and progression free survival (PFS) in patients with recurrent and/or refractory meningioma who were administered Sandostatin LAR. The safety profile of the drug was also assessed by analyzing any adverse events after administration of Sandostatin LAR. We compared our findings to that of other previous Sandostatin LAR studies and to other investigational treatments. We hypothesized that Sandostatin LAR has a longer OS and PFS than the previous clinical studies of other medical therapies. We also hypothesized that this could be a safer treatment option for recurrent and/or refractory meningioma compared to other drug and biological candidates.

Background

Naturally occurring somatostatin is an acyclic tetradecapeptide hormone that is secreted in the pituitary gland, the pancreas, and different areas of the nervous system. In the nervous

system, it is found most in hypothalamus, nervous tissue of the cortex, brainstem, and spinal cord which makes it a hormone of interest for potential treatment in meningioma. It binds to somatostatin receptors and receptor subtypes (SST 1-5) which are G protein-coupled. Somatostatin inhibits the release of several hormones: "acetylcholine, arginine vasopressin, cholecystokinin, epidermal growth hormone, glucagon, glucose-dependent insulinotropic peptide, gastrin, growth hormone, insulin, motilin, neurotensin, pancreatic polypeptide, secretin, serotonin, substance P, thyrotropin, vasoactive intestinal polypeptide"[2]. By doing so, it "decreases endocrine and exocrine secretion and blood flow, reduces gastrointestinal motility and gallbladder contraction, and inhibits secretion of most gastrointestinal hormones"[2]. Naturally occurring somatostatin has a very short half-life (less than 3 minutes) so it is not useful clinically. Instead, somatostatin analogs have been synthesized to counter the short half-life.

Meningiomas are found to express somatostatin receptor subtypes (SST 1-5) that can be targeted by somatostatin analogs. Somatostatin analogs can block cell division or inducing apoptosis depending on the SST subtype and cell type. SST2 is highly expressed in lymphomas, neuroblastomas, meningiomas, pituitary adenomas, small cell lung carcinomas, and breast tumors[19].

Somatostatin analogues have shown some activity in treating meningioma. The current types of somatostatin analogs available in the clinical practice include: lanreotide, pasireotide, and octreotide. *In vitro* studies done by *Graillon, T et. al*, looked at "effects of octreotide in a large series of 80 meningiomas, including 31 World Health Organization (WHO) Grade II and 4 WHO Grade III tumors, using fresh primary cell cultures to study the impact on cell viability, apoptosis, and signal transduction pathways"[9]. The study was conducted on meningiomas from 80 patients. 45 meningiomas were Grade I, 31 were Grade II, and 4 were Grade III. Cells from

these patients were cultured in well plates and treated with octreotide. SST2 mRNA expression was assessed on 50 meningiomas using real-time polymerase chain reaction (rtPCR). Expression and localization of SST2 were assessed by immunocytochemistry. 4 random tumors were selected for cell proliferation assays. They were treated with either 10-9 M octreotide, or 10-8 M octreotide, or no treatment at all. Both concentrations of octreotide were able to reduce the cell proliferations in all 4 tumors. In addition, they found that the level of SST2 mRNA was high in 74.5% of tested meningiomas. The results show that there was no correlation between SST2 mRNA levels and WHO tumor grades. This suggests that somatostatin analogs targeting SST2 may be a feasible research option for therapy.

Sandostatin LAR (Octreotide acetate) is another somatostatin analogue which has a similar biologic profile to somatostatin. It also has a longer half-life compared to somatostatin and can remain active for over 90 minutes. Sandostatin LAR (octreotide acetate) is a long acting, synthetic drug developed by Novartis for the treatment of excessive amounts of watery diarrhea associated with vasoactive intestinal peptide (VIP) secreting tumors and severe diarrhea/flushing episodes associated with metastatic carcinoid tumors. It can also be used to treat patients with acromegaly who did not have an effective response to radiotherapy and/surgery[44]. Octreotide acetate comes in doses of 10mg, 20mg, and 30mg and is administered intramuscularly in the gluteal region. It is administered at 4 week intervals. Hypersecretion of hormones such as serotonin and tachykinin can cause severe diarrhea and flush in patients with carcinoid tumors. Similarly, octreotide acetate can inhibit the excessive hormones that are released from carcinoid tumors by targeting somatostatin receptors and somatostatin receptor subtypes (sst1-5). Since octreotide acetate can also inhibit overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), it can be used to treat acromegaly. It was

observed that 73% of patients with cancer who were treated with octreotide for acromegaly also showed >30% tumor shrinkage[4] which suggests that octreotide acetate may have an anti-tumor effect. The mechanism in which octreotide acetate slows or even stops the proliferation of tumor cells is not well understood[5]. It is hypothesized that octreotide acetate binds to the somatostatin receptors of tumors which inhibits the cell cycle, induces apoptotic effects, and/or inhibits growth factor effects[5].

A case report published in February 2016 by Richard Rammo, MD in the Journal of Neurosurgery examines a 35 year old woman with malignant meningioma. In 1994, the woman had a right frontal mass that was resected and diagnosed as a Grade I tumor. Then in 1998, the patient had a minor recurrence which was treated by stereotactic radiosurgery. Tumor progression was observed in 2002 and in 2004 which was again treated using radiosurgery. In 2008, the tumor continued to progress to the right side of the falx and extending slightly across the midline, occluding the sagittal sinus. Eventually, the patient was admitted to the emergency room due to enlarging meningioma which caused left-sided weakness, headache, and blurry vision. The patient refused radiation at this point. After consultation with her oncologist, she was started on 30 mg octreotide acetate once every four weeks. In early 2010, her meningioma was diagnosed as Grade III and anaplastic. In 2011, octreotide acetate was increased to once every 3 weeks for 4 months. It was then increased to 40mg every 4 weeks, and she continued with this regimen without any other medications such as vitamins, herbal treatments, or other orally ingested agents. As of 2014, the patient has been stable and recurrence of the meningioma was delayed for a total of 3.5 years.

There have also been previous clinical studies in which octreotide acetate (Sandostatin LAR) was investigated for use in meningioma. Chamberlain, *et al* conducted a prospective pilot

study in 2007 to assess the PFS at 6 months in 16 patients who had recurrent meningiomas. 31% of patients demonstrated a partial radiographic response and 44% achieved progression-free survival at 6 months. Patients experienced minimal adverse events while on octreotide acetate (Sandostatin LAR) treatment. A phase II study was done by Johnson, *et al* in 2011 to evaluate the efficacy and safety of octreotide acetate (Sandostatin LAR) for the treatment of recurrent meningioma and meningeal hemangiopericytoma. The study included 12 patients and failed to produce objective tumor response. However, 2 patients experienced prolonged stability of previously progressive tumors, and the treatment was well tolerated. Also in 2011, Schulz, *et al* conducted a study using octreotide acetate (Sandostatin LAR) in 8 patients with recurrent or unresectable meningiomas of the skull base. 5 of 8 patients were on treatment continuously and had stabilized disease (median 115 months, range 48-180 months). The results from this study suggested that octreotide acetate (Sandostatin LAR) can delay progression of the disease.

There have been many other documented anecdotal or incidental cases and clinical studies in which octreotide acetate (Sandostatin LAR) demonstrated to be a potential treatment for meningioma, however, the studies are inadequately powered due to small sample sizes.

Our study provides more evidence to whether octreotide acetate (Sandostatin LAR) is a potential candidate for meningioma treatment. The primary objectives of this study are to estimate the overall survival (OS) and progression free survival (PFS) of octreotide acetate (Sandostatin LAR) treatment in patients with meningioma. The primary endpoints are to assess how long patients lived since being administered octreotide acetate (Sandostatin LAR) and how long patients lived (overall survival) or until their tumor progressed (progression free survival) to ultimately determine if this drug is effective or not. The secondary objective is to assess drug safety. Side effects of octreotide acetate (Sandostatin LAR) is assessed retrospectively by

classifying documented adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Results of those who previously received the drug are compared to previous studies and other agents.

Methods

This study is a retrospective, interventional cohort analyses of patient records. A chart review of patients seen at the University of California, Irvine (UCI) was conducted, and informed consent was obtained from all patients. The review included patients diagnosed with meningioma who were administered octreotide acetate (Sandostatin LAR) from 01/01/2010 until 06/01/2017. Patients were identified through the UCI Cancer Registry and medical records. All WHO grade meningiomas were included in the analyses. The sample size depended on the number of available cases at UCI. This study included 43 patients total. All information related to patient demographics, cancer type, response to treatment, therapies previously received, and Karnoksky performance scores (KPS) were collected. KPS scores quantifies cancer patients' general well-being and activities of daily life. KPS scores range from 0-100 and are scored in intervals of 10. Table 1.0 below describes the scores in detail.

Table 1.0 Karnofsky Performance Scoring

Karnofsky Status	**Karnofsky Score**
Normal, no complaints	100
Able to carry on normal activities. Minor signs or symptoms of disease	90
Normal activity with effort	80
Care for self. Unable to carry on normal activity or to do active work	70
Requires occasional assistance, but able to care for most of the patients' needs	60
Requires considerable assistance and frequent medical care	50
Disabled. Requires special care and assistance	40

Severely disabled. Hospitalization indicated though death nonimminent	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	20
Dying	10
Dead	0

Source: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Results from our treatment group were compared to results from previous published studies using octreotide acetate (Sandostatin LAR) for treatment of meningioma and compared to other studies using interferon-alpha, bevacizumab, sunitinib, vatalanib, imatinib, and erlotinib.

Progression free survival (PFS), overall survival (OS), and toxicity was assessed in all patients who received octreotide acetate (Sandostatin LAR). In order to protect patient confidentiality, subject identifiers were collected on a master list and medical information will be collected separately on separate forms with only a unique identifying number (UIN). No link was provided between the two sets of data to ensure confidentiality. Patients were included in the study if they met the inclusion criteria and signed the informed consent form. Patients were excluded from the study if they met the exclusion criteria.

Inclusion Criteria

1) Patients who were diagnosed with meningioma and who were 18 years and older
2) Presence of tumor expressing sandostatin receptors, as proven by a positive Octreotide PET and/or positive immunohistochemistry (IHC) analysis
3) Poor candidate for resection or radiation therapy (i.e. the meningioma was located around major blood vessels or high-risk areas, is difficult to access surgically, or the patient refuses surgery or radiation treatment) **or**
4) Their meningioma demonstrates tumor growth in which other treatment options have not been effective (already failed surgery and radiation)

Exclusion Criteria

1) Metastasis found on octreotide PET
2) Informed consent was not obtained

Treatment Plan

An ^{111}Indium (^{111}In)-octreotide positron emission tomography (PET) scan was done as standard of care in most patients to confirm meningioma and meningioma response to treatment with somatostatin analogues. For the few remaining patients that did not have ^{111}Indium (^{111}In)-octreotide PET imaging, positive pathology was obtained. For patients who agreed to start octreotide acetate (Sandostatin LAR), a MRI or CT scan was done prior to the first administration of the drug. Octreotide acetate (Sandostatin LAR) was administered every month via deep, intragluteal injection starting at 30mg for the first doses and escalated to 40mg if tolerated. After the first dose, a MRI or CT scan was done every 2-3 months to evaluate tumor status. Patients were followed for any adverse reactions to the drug. The treatment was stopped if the patient met any of the following criteria:

1) MRI or CT showed tumor progression
2) Patient choice to stop treatment
3) Death
4) Lost to Follow Up
5) Serious adverse event
6) Physician discretion

Statistical Methods

Statistical analyses were completed using IBM SPSS (PASW statistics v18.0) statistics. Demographics, disease, KPS score, and treatment characteristics for all patients were summarized in a table using descriptive statistics.

Overall survival (OS) was estimated by generating Kaplan Meir survival curves. It was defined as the number of days from the first date of administration of octreotide acetate

(Sandostatin LAR) to the date of death due to any cause. Subjects that have not died were censored at the last known date to be alive. The OS was compared between the WHO tumor grades and between ethnicities/race. The log-rank test was used to compare the survival distributions of the different groups. P-value ≤ 0.05 was considered significant.

Progression free survival (PFS) was estimated by generating Kaplan Meir survival curves. PFS was calculated from the first date of octreotide acetate (Sandostatin LAR) administration to the date of death or disease progression, whichever comes first. Patients who did not experience disease progression were censored. The PFS was compared between the WHO tumor grades and between ethnicities/race. The log-rank test was used to compare the survival distributions of the groups. P-value ≤ 0.05 for all analyses is considered significant.

Disease progression was determined based on the 2010 Response Assessment in Neuro-Oncology (RANO) criteria. Disease progression was determined by measuring tumor size on the MRI/CT image according to the RANO criteria. Tumor measurements were done by analyzing the MRI image at the baseline and every 2-4 months during the octreotide acetate (Sandostatin LAR) administration. Target tumor lesion response was based on the criteria in Table 2.0.

According to the RANO criteria, measurable lesions are defined as bi-dimensionally contrast-enhancing lesions with two perpendicular diameters $\geq$10 mm and clearly defined margins. They also need to be visible on two or more axial slices that are $\geq$ 5 mm apart with 0-mm skip. The largest lesion is targeted for measurement. Measurements do not include cysts, necrosis, or cavities.

Non-measurable diseases are classified as lesions that are small (less than 10 mm of two perpendicular dimensions, such as 12 x 8 mm), do not enhance, or have poorly defined margins

are considered as non-measurable disease. Lesions that do not fit the criteria for "measurable disease" are also considered non-measurable.

Table 2.0 Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
*Stable doses of corticosteroids include patients not on corticosteroids.
Source: *Journal of Clinical Oncology 28, no. 11 (April 2010) 1963-1972.*

Safety and tolerability of octreotide acetate (Sandostatin LAR) was assessed by looking at the reported adverse events (AE) in response to the drug. An adverse event is defined as any illness, symptom, sign, side effect, reaction, or untoward event that occurs during the treatment. The adverse event can be unrelated to the drug or clinically significant. For this study, adverse events were either reported by the patient or there were clinically significant abnormal findings on any examinations or laboratory tests. An abnormal laboratory value will be considered an AE if it is accompanied with clinical signs or symptoms, requires any treatment or therapeutic intervention, and/or is determined by the investigators to be clinically significant. An adverse event is also defined if there were any new or clinically significant abnormal lab results or if there was a worsening of a pre-existing condition or lab abnormality.

An adverse event or reaction was considered serious if it met the following:

- Results in death of the patient
- Is life-threatening
- Results in inpatient hospitalization or existing hospitalization is extended
- Results in a disability
- Results in a congenital anomaly/birth defect.
- Investigator determines the adverse event is serious

All patients who receive octreotide acetate (Sandostatin LAR) were evaluable for toxicity. Severity of adverse events were graded according to the NCI CTCAE v4.03. The NCI CTCAE is a set of standardized criteria for grading adverse event severity in oncology. Table 3.0 describes the NCI CTCAE grading scale in detail. Grade 1 adverse events are considered mild, grade 2 adverse events are considered moderate, grade 3 adverse events are considered serious, grade 4 adverse events are considered life threatening, and grade 5 adverse events is death.

Table 3.0 NCI CTCAE Grading Scale

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Source: Common Terminology Criteria for Adverse Events (CTCAE) v4.03

Adverse events were recorded from the first date of octreotide acetate (Sandostatin LAR) administration until death or 12 months of follow up. The relationship of the adverse event to the study drug was also evaluated. The following criteria were used to assess the relationship of the adverse event to the drug:

1) Related - There is evidence to suggest a causal relationship between the drug and the adverse event
2) Unrelated - The cause of the adverse event is more plausible due to an underlying disease or something that is biologically improbable.

Safety results were presented using descriptive statistics to show frequency, type, and severity of adverse events. The toxicity results were then compared to other clinical studies.

Results

A total of 43 patients were included in the study. Table 4.0 describes the patient population in our study. The majority of the patients were female (69.8%) and had WHO grade 1 meningiomas (73.3%). 5 patients had WHO grade II tumors and 7 had WHO grade III tumors. The majority of patients were white, Hispanic, and Asian. 17 patients were white, 11 were Hispanic, and 9 were Asian. The median age of patients in the study was 66 years old, and the majority had a KPS score between 70 and 90. The median KPS score was 80. Patients received a median of 8 octreotide acetate (Sandostatin LAR) treatments. Treatment numbers ranged from 1 to 25 injections. 74.4% of patients had prior resection before starting treatment. Previous treatments for meningioma was recorded. 24 patients with WHO grade I, 3 patients with WHO grade II tumors, and all patients with WHO grade III tumors had prior resection. 5 patients with WHO grade I, 1 patient with WHO grade II tumors, and no patients with WHO grade III tumors had prior chemotherapy. 12 patients with WHO grade I, 3 patients with WHO grade II tumors, and 6 patients with WHO grade III tumors had prior radiation therapy. Of the 43 patients in the study, 11 patients with WHO grade I tumors had no prior recurrences of meningioma. 6 patients with WHO grade II tumors had 1 prior reoccurrence, and 15 patients had 2 prior recurrences, and 7 patients had 3 or more prior recurrences. Of the 15 patients that had 2 recurrences, 10 patients had WHO grade I tumors, 2 had WHO grade III tumors, and 3 had WHO grade III tumors. Of the 7 patients that had 3 or more occurrences, 4 had WHO grade I tumors, 2 had WHO grade I tumors, and 7 patients had WHO grade III tumors.

Table 4.0 Baseline Characteristics (N=43)

Characteristics	**All Patients (N = 43)**
Median Age (years) (range)	66 (35-90)
Male, No. (%)	13 (30.2)
Female, No. (%)	39 (69.8)

Ethnicity/Race, No (%) • White • Hispanic • Asian • Pacific Islander • Black or African American • Iranian	17 (37.8) 11 (24.4) 9 (20.9) 2 (4.4) 2 (4.4) 2 (4.4)			
Median number of octreotide acetate (Sandostatin LAR) injections	8 treatments (1-25)			
Karnofsky Performance Scale (KPS) score at baseline, No. (%) • 50 • 60 • 70 • 80 • 90 • 100 • Median	1 (2.2) 3 (6.7) 10 (22.2) 15 (33.3) 12 (26.7) 4 (8.9) 80			
WHO Tumor Grade No. (%) • 1 • 2 • 3	32 (74.4) 5 (11.6) 6 (14.0)			
Prior Treatments No. (%)	WHO Grade 1	WHO Grade 2	WHO Grade 3	All Grades
• Resection • Chemotherapy • Radiation therapy	24 (54) 5 (11.4) 12 (27.3)	3 (6.8) 1 (2.27) 3 (6.8)	6 (13.6) 0 (0) 6 (15.9)	32 (72.7) 7 (15.9) 22 (50.0)
Previous Recurrences No. (%)	WHO Grade 1	WHO Grade 2	WHO Grade 3	All Grades
• 0 • 1 • 2 • 3≤	11 (25.0) 6 (13.6) 10 (22.7) 4 (9.0)	0 (0) 0 (0) 2 (4.5) 2 (4.5)	0 (0) 0 (0) 3 (6.8) 5 (11.4)	11 (25.6) 6 (13.6) 15 (34.0) 11 (25.6)

Throughout treatments for all patients, there were no grade 4 or 5 adverse events observed. Table 5.0 describes the reported adverse events that patients experienced while on octreotide acetate (Sandostatin LAR). Overall, octreotide acetate (Sandostatin LAR) was well tolerated by the patients. Two patients were discontinued on octreotide acetate (Sandostatin

LAR) due to adverse events. One patient experienced CTCAE grade 1 gall bladder stones and later, CTCAE grade 3 toxicity in which the patient was hospitalized and diagnosed with pancreatitis which was likely secondary to cholelithiasis. The other patient discontinued treatment due to CTCAE grade 2 vomiting. Other CTCAE grade 3 adverse events included nausea, vomiting, and weakness. The majority of the patients experienced CTCAE grade 1 diarrhea (27.91%) and CTCAE grade 1 headaches (27.91%).

Table 5.0 Treatment Related Adverse Events (N = 43)

Adverse Events	**CTCAE Grade 1 No. (%)**	**CTCAE Grade 2 No. (%)**	**CTCAE Grade 3 No. (%)**	**Total No. (%)**
Diarrhea	12 (27.91)	5 (11.63)	0	17 (39.5)
Loose Stools	5 (11.63)	0	0	5 (11.6)
Headache	12 (27.91)	3 (6.98)	0	15 (34.9)
local reactions from injection	5 (11.63)	0	0	5 (11.6)
flu like symptoms	3 (6.98)	1 (2.33)	0	4 (9.3)
Weakness	1 (2.33)	1 (2.33)	0	2 (4.7)
palmar redness	1 (2.33)	0	0	1 (2.3)
Gall bladder stones	1 (2.33)	0	0	1 (2.3)
Chills	1 (2.33)	0	0	1 (2.3)
Sweats	1 (2.33)	0	0	1 (2.3)
arthralgia	1 (2.33)	0	0	1 (2.3)
nausea/vomiting	3 (6.98)	2 (4.65)	0	5 (11.6)
Stomach pain	2 (4.65)	2 (4.65	0	4 (9.3)
insomnia/difficulty sleeping	3 (6.98)	1 (2.33)	0	4 (9.3)
Dizziness	4 (9.30)	0	0	4 (9.3)
Constipation	6 (13.95)	1 (2.33)	0	7 (16.3)
Anxiety	0 (0)	1 (2.33)	0	1 (2.3)
Fatigue	4 (9.30)	0	0	4 (9.3)
Pancreatitis	0	0	1 (2.33)	1 (2.3)
Cholelithiasis	0	0	1 (2.33)	1 (2.3)
Abdominal Bloating	1 (2.33)	0	0	1 (2.3)
Back pain	1 (2.33)	1 (2.33)	0	2 (4.7)
Fatigue	4 (9.30)	0	0	4 (9.3)

*Grading Based on CTCAE Version 4.03

Table 6.0 shows the progression free survival at 6 months, 1 year, 3 years, and the median progression free survival. Figure 3.0 shows the Kaplan Meier curves for overall progression free survival and Figure 3.1 shows progression free survival stratified by WHO grade. Progression free survival for all WHO grades at 6 months was combined was estimate at 77.50% (95% CI 2.83-3.38). At 1 year, it was 68.30% (95% CI 1.42-3.33), and at 3 years, it was 34.40% (95% CI 0.054-0.356). Progression free survival at 6 months, 1 year, and 3 years differed by WHO grade. For who grade 1 tumors, progression free survival at 6 months, 1 year, and 3 years was 85.90% (95% CI 0.73-0.99), 81.50% (95% CI 0.67-0.96), and 40.80% (95% CI 0.002-0.814) respectively. For WHO grade 2 tumors, progression free survival at 6 months, 1 year, and 3 years was 80.0% (95% CI 0.45-1.15), 60.0% (95% CI 0.17-1.03), and 30.0% (95% CI -0.17-0.77) respectively. For WHO grade 3 tumors, progression free survival at 6 months was 33.3% (0.53-1.1). Patients in this group did not survive past 6 months. The median progression free survival was 2.96 years (2.16-3.78 95) for all WHO grade tumors combined. For WHO grade 1, it was. 3.1 years (2.83-3.87), for WHO grade II, it was 2.38 years (1.42-3.33), and for WHO grade III, it was 0.205 years (0.054-0.356). The log rank test had a value of $p < 0.001$ which means that there is a statistically significant difference in PFS between the WHO groups.

The Kaplan Meier curve was also estimated for progression free survival between ethnicities/races to explore whether it had any impact on survival. However, no medians and other statistics were able to be computed due to all the patients being censored. The sample size for different ethnicities was too small to run any analysis.

Figure 3.0 Overall Progression Free Survival

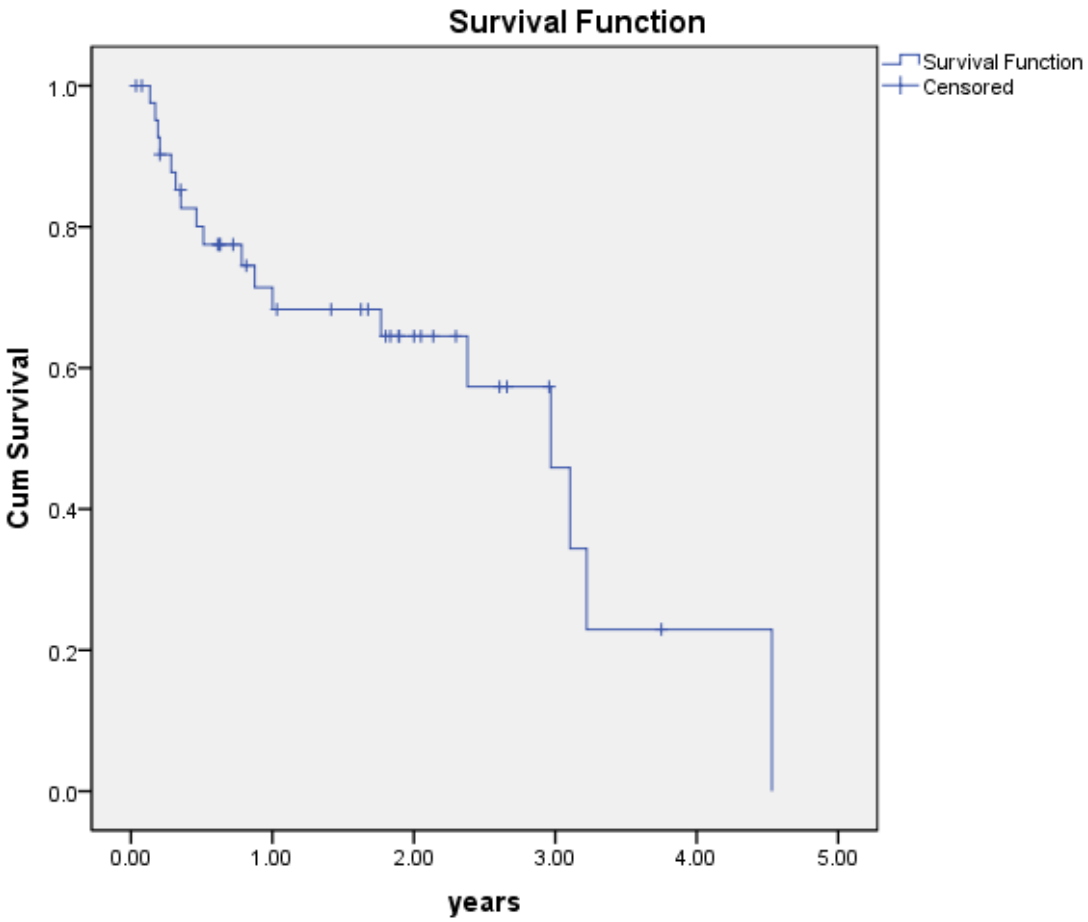


Figure 3.1 Progression Free Survival Stratified by WHO Grade

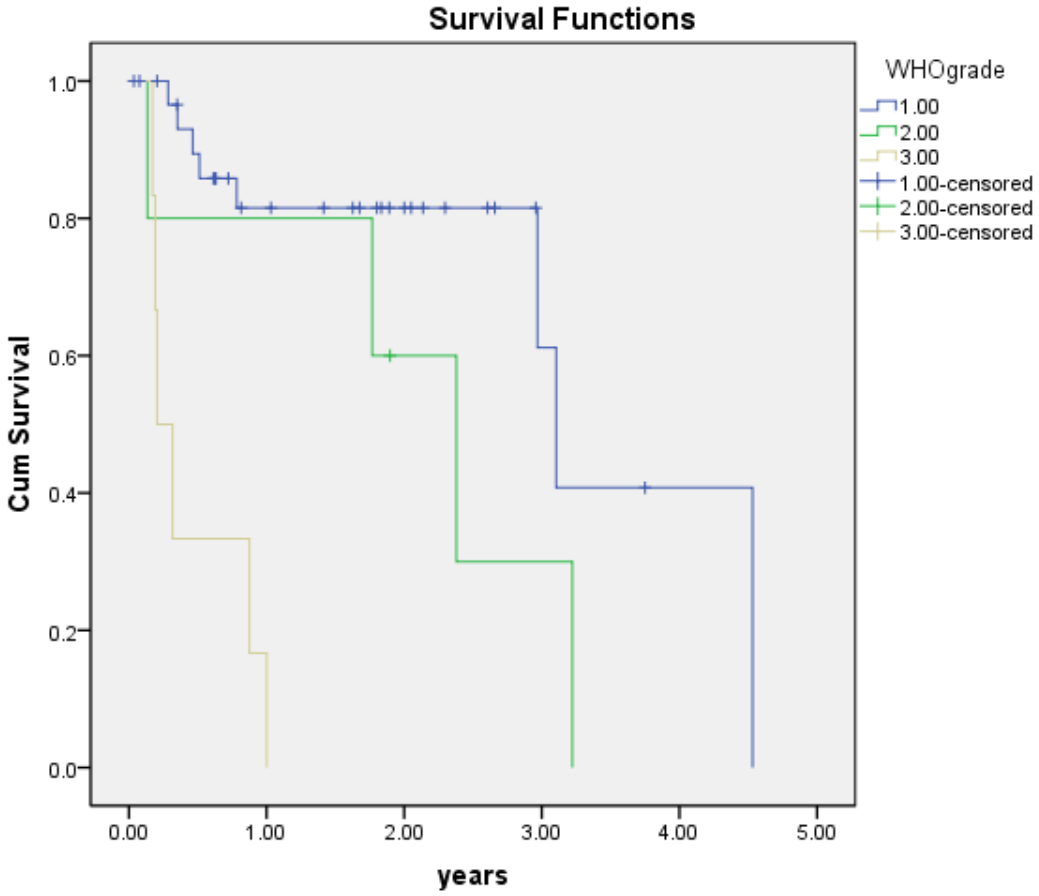


Table 6.0 Median Progression Free Survival and Progression Free Survival at 6 months, 1 year, and 3 years

PFS	WHO Grade 1 (CI 95%)	WHO Grade 2 (CI 95%)	WHO Grade 3 (CI 95%)	ALL (CI 95%)
6 months	85.90% (0.73-0.99)	80.0% (0.45-1.15)	33.3% (0.53-1.1)	77.50% (2.83-3.38)

1 year	81.50% (0.67-0.96)	60.0% (0.17-1.03)	--	68.30% (1.42-3.33)
3 years	40.80% (0.002-0.814)	30.0% (-0.17-0.77)	--	34.40% (0.054-0.356)
Median PFS	**WHO Grade 1 (CI 95%)**	**WHO Grade 2 (CI 95%)**	**WHO Grade 3 (CI 95%)**	**ALL (CI 95%)**
Median	3.1 years (2.83-3.87)	2.38 years (1.42-3.33)	0.205 years (0.054-0.356)	2.96 years (2.16-3.78 95)

Table 7.0 shows the overall survival at 6 months, 1 year, and 3 years by WHO grade.

Kaplan Meier curves were generated in Figure 4.0 and 4.1 to show overall survival and overall survival stratified by WHO grade.

Figure 4.0 Overall Survival for all WHO Grades Combined

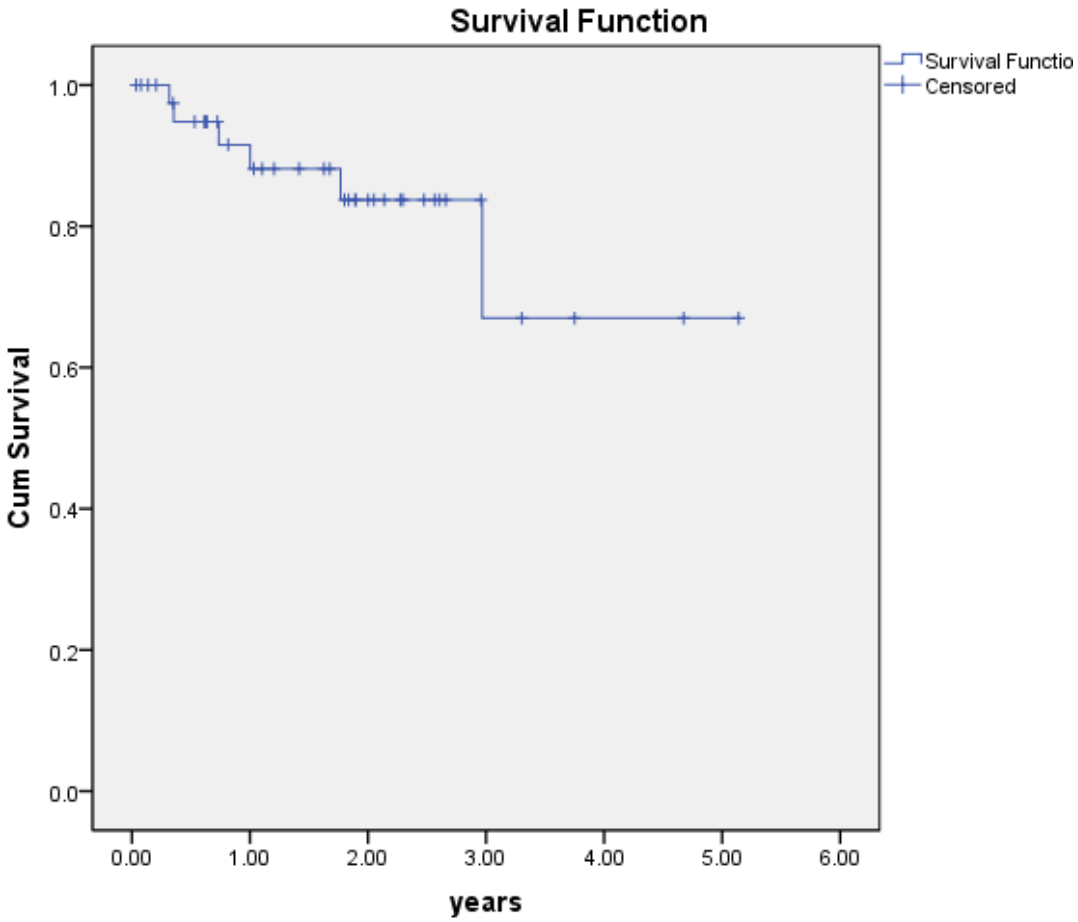


Figure 4.1 Overall Survival Stratified by WHO Grade

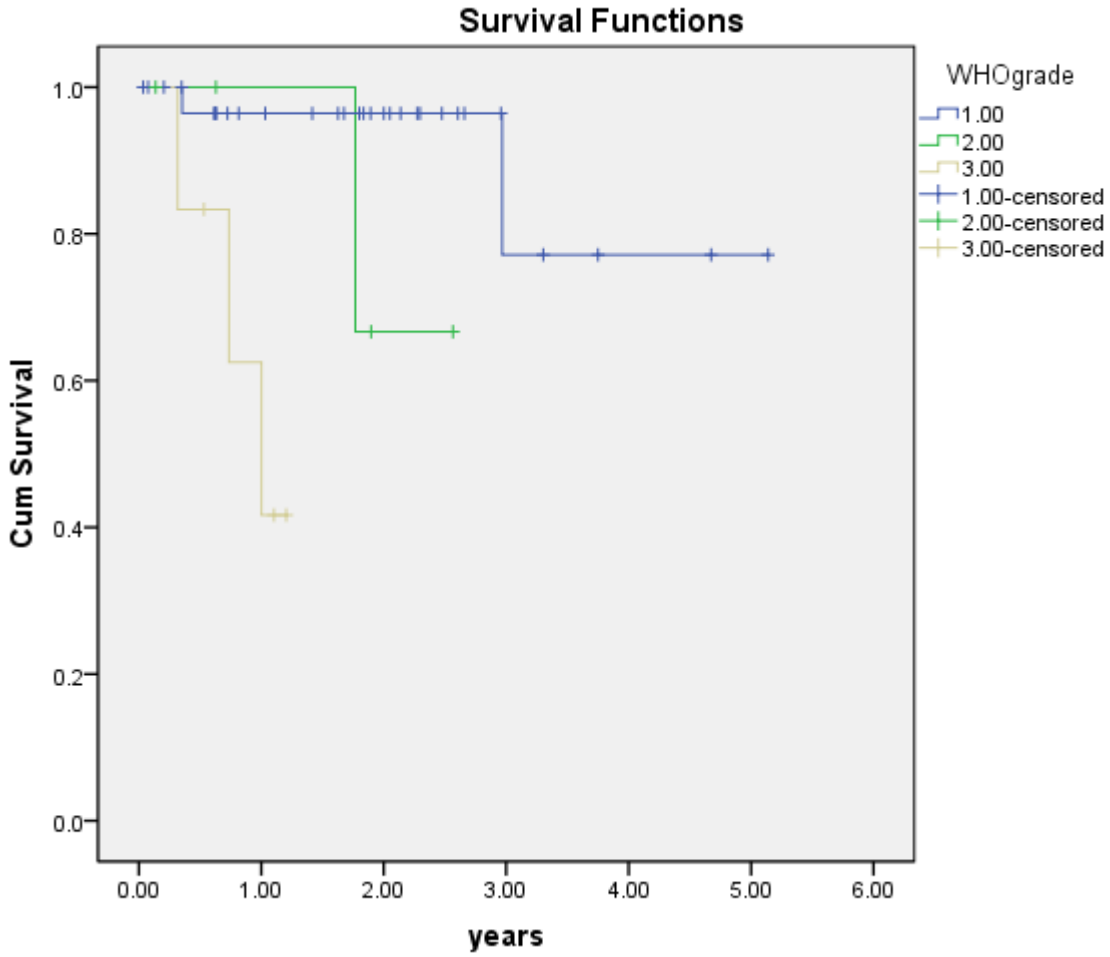


Table 7.0 Median Overall Survival and Overall Survival at 6 months, 1 year, and 3 years

OS	WHO Grade 1 (CI 95%)	WHO Grade 2 (CI 95%)	WHO Grade 3 (CI 95%)	ALL (CI 95%)
6 months	96.4% (0.895-1.03)	66.7% (0.134-1.2)	83.3% (0.536-1.13)	94.8% (0.88-1.01)
1 year	96.4% (0.895-1.03)	--	41.7% (0.018-0.085)	88.1% (0.77-0.99)
3 years	77. 1% (0.428-1.114)	--	--	67.0% (0.36-0.98)
Median OS	--	--	1.002 (0.448-1.56)	--

Table 7.0 shows results for overall survival at 6 months, 1 year, and 3 years. The median

overall survival has not yet been reached so it could not be reported. There was a low event rate in which half of the patients have not died. Overall Survival at 6 months was 94.8%, 88.1% at 1 year, and 67.0% at 3 years. The overall survival was also calculated for each WHO grade tumor. The overall survival for WHO grade I, II, and III at 6 months were 96.4%, 66.7%, and 77.1% respectively. The overall survival for WHO grade I, II, and III at 1 year, was 96.4%, 66.7%, and 41.7% respectively. The overall survival for WHO grade I, II, and III at 3 years, was 77.1%, 66.7%, and 41.7% respectively. The only median OS was able to be calculated for WHO grade III tumors which was 1.002 (0.448-1.56 95% CI). Figure 4.0 shows the Kaplan Meier curves for overall progression free survival and Figure 4.1 shows the overall survival stratified by WHO grade.

Discussion

Table 8.0 Comparison of Clinical Studies using octreotide acetate (Sandostatin LAR)

Study	N	WHO Grades	PFS-6	Median TTP	Median PFS	Median OS	Common Toxicities
Chamberlain (2007)[41]	16	--	44%	5 mos	--	7.5 mos	Diarrhea
Johnson (2011)[42]	12	I, II, III	--	4.25 mos	--	2.7 yrs	Diarrhea, Transaminitis
Schulz (2011)[43]	13	I	--	24 mos	--	--	--
Our study	43	I, II, III	94.9%	--	2.96 yrs (PFS)	4.09 yrs	Diarrhea, headache

- = not reported

Our study is the largest study to date that involves the use of octreotide acetate (Sandostatin LAR). We compared our results to other clinical studies that involved octreotide acetate (Sandostatin LAR) as an intervention. Table 8.0 shows the comparison of our study to other clinical studies. In the study by Chamberlain, et al., progression free survival at 6 months was 44%, median time to progression was 5 months, and median overall survival was 7.5 months

in the 16 patients that were studied. The meningioma WHO grades were not reported for this study. The most common toxicity patients experienced was diarrhea. The Johnson, et al., study included 12 patients with WHO grade I, II, and III meningiomas. The median time to progression was 4.25 months, and the median overall survival was 2.7 years. Progression free survival at 6 months was not reported in this study. Diarrhea and transaminitis were the most common toxicities reported. Schulz, et al, conducted a study in 13 patients with only WHO grade I meningiomas. Only the median time to progression was reported which was 24 months. Our study included patients with WHO grade I, II, III meningiomas and had a median overall survival of 4.09 years. Median progression free survival was 2.96 years and progression free survival at 6 months was 94.9%. Our data shows longer progression free survival and overall survival compared to the other clinical studies. Reported toxicities were consistent across the clinical studies and are expected adverse events.

Some studies showed octreotide acetate (Sandostatin LAR) was not a suitable option for treatment while other studies showed that it is. Most studies that have been reported have had less than 25 patients in their study which leads to low statistical power. Our clinical study provides additional evidence to support the rationale for a larger phase study to assess the efficacy of octreotide acetate (Sandostatin LAR). In table 9.0, octreotide acetate (Sandostatin LAR) had longer median progression free survival and progression free survival at 6 months compared to the drugs that targeted VEGF, VEGFR, interferon-alpha, and PDGFR. When the safety profiles of each drug was compared to octreotide acetate (Sandostatin LAR), it was observed that octreotide acetate (Sandostatin LAR) had safer profile. There were no observed CTCAE grade 4 or grade 5 adverse events and common toxicities were not as severe as the other drugs (Table 10.0). The most common adverse events that were observed in our study was

diarrhea, headache, and constipation. One patient on our study was hospitalized due to CTCAE grade 3 pancreatitis secondary to CTCAE grade 3 cholelithiasis. These adverse events were the only CTCAE grade 3 adverse events observed in our study. Octreotide acetate (Sandostain LAR) was subsequently discontinued for this patient. Erlotinib also demonstrated a favorable safety profile as well compared to all the other drugs, however, median progression free survival was lower than patients who were on octreotide acetate (Sandostatin LAR) compared to our study.

Table 9.0 Comparison of Drugs/Biologics under Investigation for Meningioma

Study	**Agent**	**Target**	**Tumor Grade**	**N**	**Median Age**	**KPS**	**Median PFS**	**PFS-6 (%)**
Nayak (2012)[33]	Bevacizumab	VEGF	II, III	15	55	--	4 months	44
Lou (2012)[34]	Bevacizumab	VEGF	I, II, III	14	53.5	~80	17.9 months	85.7
Kaley (2015)[35]	Sunitinib	VEGFR	II, III	36	61	80	5.2 months	42
Grimm (2014)[36]	Vatalanib	VEGFR	I, II, III	21	59	80	3.65 months	37.5
Wen (2009)[37]	Imatinib	PDGFR	I, II, III	22	58	80	2 months	29.4
Horak (2012)[38]	Imatinib	PDGFR	I, II, III	18	53.5	--	16 months	66.7
Norden (2010)[39]	Erlotinib	EGFR	I, II, III	25	57	90	2 months	25
Chamberlain (2008)[40]	Interferon-alpha	--	I	35	61	--	7 months	54
Our Study	Sandostatin LAR (octreotide acetate)	somatostatin	I, II, III	43	66	80	2.96 years	77.5

Table 10.0 Comparison of Drugs/Biologics under Investigation for Meningioma

Study	Agent	Target	Tumor Grade	N	Median Age	KPS	Common Toxicities	Grade 4 and/or 5 AE?
Nayak (2012)[33]	Bevacizumab	VEGF	II, III	15	55	--	Fatigue, intratumoral hemorrhage	NO
Lou (2012)[34]	Bevacizumab	VEGF	I, II, III	14	53.5	~80	Thrombocytopenia, proteinuria, craniotomy site cellulitis	YES
Kaley (2015)[35]	Sunitinib	VEGFR	II, III	36	61	80	Leukopenia, fatigue, thrombocytopenia	YES
Chamberlain (2008)[40]	Interferon-alpha	--	I	35	61	--	Fatigue, anemia, leukopenia	YES
Grimm (2014)[36]	Vatalanib	VEGFR	I, II, III	21	59.0	80	Fatigue, hypertension, elevated transaminases	YES
Wen (2009)[37]	Imatinib	PDGFR	I, II, III	22	58.0	80	--	YES
Horak (2012)[38]	Imatinib	PDGFR	I, II, III	18	53.5	--	--	--
Norden (2010)[39]	Erlotinib	EGFR	I, II, III	25	57.0	90	Diarrhea, rash	NO
Our Study	Sandostatin LAR (octreotide acetate)	somatostatin	I, II, III	43	66	80	Diarrhea, headache, constipation	NO

There are several limitations in our study. First, this is a retrospective study. In addition, we are aware and take into account that the comparison of our study to other drugs under investigation has many weaknesses. All the studies have different methodologies, sample sizes, patient population, WHO tumor grades, and some studies have different objectives which

prevents us from making a reliable comparison. In addition, our study did not include a control. Rather, we used previous results from studies using octreotide and other drugs under investigation as treatment for meningioma for our comparison analysis. Future studies would need a control in order to strengthen the study. Despite the limitations, our study is largest study to date and does provide rationale and support for further investigation into octreotide acetate (Sandostatin LAR) for the treatment of meningioma. Additional prospective, larger scale randomized trials are needed to validate octreotide acetate (Sandostatin LAR) use in meningioma. In addition, our study provides a diverse patient population. The CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2009–2013 only reports incidences of meningioma occurring higher in Blacks than in Whites. Whereas our study includes a diverse population where Hispanics made up 24.4% and Asians made up 20.9% of our patient population.

Conclusion

We compared octreotide acetate (Sandostatin LAR) to other drugs that are currently under investigation and found that it may be prolong overall survival and progression free survival. According to our data, it provided our patients longer overall survival and progression free survival while maintaining minimal to no adverse events. Overall survival for all WHO grades was 4.09 years, and progression free survival for all WHO grades was 2.96 years. This study provides additional support for further investigation into octreotide acetate (Sandostatin LAR) as a potential treatment option for patients with refractor and/or recurrent meningioma

References

1. Krejs, G. J. (1986). "Physiological role of somatostatin in the digestive tract: gastric acid secretion, intestinal absorption, and motility." Scand J Gastroenterol Suppl 119: 47-53. PMID: 2876506
2. Liddle, Rodger A. "Physiology of Somatostatin and Its Analogues." Physiology of Somatostatin and Its Analogues, www.uptodate.com/contents/physiology-of-somatostatin-and-its-analogues.
3. Rubin, J., et al. (1999). "Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome." J Clin Oncol 17(2): 600-606. DOI: 10.1200/jco.1999.17.2.600
4. Bevan JS, Atkin SL, Atkinson AB, et al. . Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size, J Clin Endocrinol Metab , 2002, vol. 87 (pg. 4554-4563)
5. C Susini, L Buscail; Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol* 2006; 17 (12): 1733-1742. doi: 10.1093/annonc/mdl105 https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdl105#1542731
6. Moazzam, A. A., et al. (2013). "Recent developments in chemotherapy for meningiomas: a review." Neurosurg Focus 35(6): E18. http://thejns.org/doi/abs/10.3171/2013.10.FOCUS13341?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&
7. Norden, A. D., et al. (2009). "Advances in meningioma therapy." Curr Neurol Neurosci Rep 9(3): 231-240.
8. American Brain Tumor Association. Meningioma. Meningioma, American Brain Tumor Association, 2017.
9. Graillon, T., et al. (2016). "Octreotide therapy in meningiomas: in vitro study, clinical correlation, and literature review." J Neurosurg: 1-10. https://www.ncbi.nlm.nih.gov/pubmed/27982767
10. Graillon, T., et al. (2016). "Octreotide therapy in meningiomas: in vitro study, clinical correlation, and literature review." J Neurosurg: 1-10. http://thejns.org/doi/pdf/10.3171/2016.8.JNS16995
11. Pyronnet, Stéphane, Corinne Bousquet, Souad Najib, Rania Azar, Hanane Laklai, and Christiane Susini. "Antitumor Effects of Somatostatin." Molecular and Cellular Endocrinology 286, no. 1-2 (2008): 230-37. doi:10.1016/j.mce.2008.02.002.
12. Peverelli, E., et al. (2017). "Dopamine receptor type 2 (DRD2) and somatostatin receptor type 2 (SSTR2) agonists are effective in inhibiting proliferation of progenitor/stem-like cells isolated from nonfunctioning pituitary tumors." Int J Cancer 140(8): 1870-1880.
13. Rammo, R., et al. (2016). "Anaplastic meningioma: octreotide therapy for a case of recurrent and progressive intracranial disease." J Neurosurg 124(2): 496-500. http://thejns.org/doi/pdf/10.3171/2015.1.JNS142260
14. van Alkemade, H., et al. (2012). "Impaired survival and long-term neurological problems

in benign meningioma." Neuro Oncol 14(5): 658-666. https://academic.oup.com/neuro-oncology/article/14/5/658/1079216/Impaired-survival-and-long-term-neurological
15. Cao, X., et al. (2015). "Survival rates, prognostic factors and treatment of anaplastic meningiomas." J Clin Neurosci 22(5): 828-833. http://dx.doi.org/10.1016/j.jocn.2014.11.022
16. Mangubat EZ, Byrne RW. Major intratumoral hemorrhage of a petroclival atypical meningioma: case report and review of literature. Skull Base 2010;20:469–73. V
17. Norden, A. D., et al. (2015). "Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma." Neurology 84(3): 280-286. https://www.ncbi.nlm.nih.gov/pubmed/25527270
18. Weckbecker, G., et al. (1993). "Somatostatin analogs for diagnosis and treatment of cancer." Pharmacol Ther 60(2): 245-264. https://www.ncbi.nlm.nih.gov/pubmed/7912834/
19. Reubi, J. C., et al. (1994). "Expression and localization of somatostatin receptor SSTR1, SSTR2, and SSTR3 messenger RNAs in primary human tumors using in situ hybridization." Cancer Res 54(13): 3455-3459. https://www.ncbi.nlm.nih.gov/pubmed/8012966/
20. “Meningiomas Pathology .” Meningiomas Pathology: Definition, Epidemiology, Etiology, 1 June 2016, emedicine.medscape.com/article/1744164-overview#a8.
21. Whittle, Ian R, et al. “Meningiomas.” The Lancet, vol. 363, no. 9420, 2004, pp. 1535–1543., doi:10.1016/s0140-6736(04)16153-9.
22. Commins, D. L., et al. (2007). "Review of meningioma histopathology." Neurosurg Focus 23(4): E3. http://thejns.org/doi/pdf/10.3171/foc-07/10/e3 histopathology Perry A, et al : Meningiomas, in Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. (eds): World Health Organization Classification of Tumours of the Central Nervous System, ed 4. Lyon: IARC, 2007, pp 164-172
23. K. Violaris, V. Katsarides and P. Sakellariou, "The Recurrence Rate in Meningiomas: Analysis of Tumor Location, Histological Grading, and Extent of Resection," *Open Journal of Modern Neurosurgery*, Vol. 2 No. 1, 2012, pp. 6-10. doi: 10.4236/ojmn.2012.21002.
24. RANO CRITERIA: DOI: 10.1200/JCO.2009.26.3541 Journal of Clinical Oncology 28, no. 11 (April 2010) 1963-1972.
25. Kim, Moinay, et al. “Analysis of the Results of Recurrent Intracranial Meningiomas Treated with Re-Radiosurgery.” Clinical Neurology and Neurosurgery, vol. 153, 2017, pp. 93–101., doi:10.1016/j.clineuro.2016.12.014.
26. Arnli, Magnus B. et al. “Expression and Clinical Value of EGFR in Human Meningiomas.” Ed. Paula Soares. *PeerJ* 5 (2017): e3140. *PMC*. Web. 3 July 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5374971/
27. Newton H B. Hydroxyurea chemotherapy in the treatment of meningiomas. Neurosurg Focus. 2007;23(4):E11. http://thejns.org/doi/abs/10.3171/FOC-07/10/E11?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
28. Quinn T. Ostrom, Haley Gittleman, Jordan Xu, Courtney Kromer, Yingli Wolinsky,

Carol Kruchko, and Jill S. Barnholtz-Sloan, CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2009–2013, Neuro Oncol (2016) 18 (suppl 5): v1-v75 doi: 10.1093/neuonc/nov207.
29. *Zang KD, Singer H Nature. 1967 Oct 7; 216(5110):84-5.*
30. Deletions on chromosome 22 in sporadic meningioma. *Ruttledge MH, Xie YG, Han FY, Peyrard M, Collins VP, Nordenskjöld M, Dumanski JP*. Genes Chromosomes Cancer. 1994 Jun; 10(2):122-30.
31. Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression. Korhonen K, Salminen T, Raitanen J, Auvinen A, Isola J, Haapasalo H. J Neurooncol. 2006 Oct; 80(1):1-7
32. Wahab, M, and F Al-Azzawi. "Meningioma and Hormonal Influences." Climacteric : the Journal of the International Menopause Society., U.S. National Library of Medicine, Dec. 2003, www.ncbi.nlm.nih.gov/pubmed/15006250.
33. Nayak, Lakshmi, et al. "Atypical and Anaplastic Meningiomas Treated with Bevacizumab." Journal of Neuro-Oncology, vol. 109, no. 1, 2012, pp. 187–193., doi:10.1007/s11060-012-0886-4.
34. Lou, Emil, et al. "Bevacizumab Therapy for Adults with Recurrent/Progressive Meningioma: a Retrospective Series." Journal of Neuro-Oncology, vol. 109, no. 1, 2012, pp. 63–70., doi:10.1007/s11060-012-0861-0.
35. Kaley, Thomas J., et al. "Phase II Trial of Sunitinib for Recurrent and Progressive Atypical and Anaplastic Meningioma." Neuro-Oncology, vol. 17, no. 1, June 2014, pp. 116–121., doi:10.1093/neuonc/nou148.
36. Raizer, Jeffrey J., et al. "A Phase II Trial of PTK787/ZK 222584 in Recurrent or Progressive Radiation and Surgery Refractory Meningiomas." Journal of Neuro-Oncology, vol. 117, no. 1, 2014, pp. 93–101., doi:10.1007/s11060-014-1358-9.
37. Wen, Patrick Y., et al. "Phase II Study of Imatinib Mesylate for Recurrent Meningiomas (North American Brain Tumor Consortium Study 01-08)." Neuro-Oncology, vol. 11, no. 6, Jan. 2009, pp. 853–860., doi:10.1215/15228517-2009-010.
38. Horak, Peter, et al. "Imatinib Mesylate Treatment of Recurrent Meningiomas in Preselected Patients: a Retrospective Analysis." Journal of Neuro-Oncology, vol. 109, no. 2, 2012, pp. 323–330., doi:10.1007/s11060-012-0896-2.
39. Norden, Andrew D., et al. "Phase II Trials of Erlotinib or Gefitinib in Patients with Recurrent Meningioma." Journal of Neuro-Oncology, vol. 96, no. 2, 2009, pp. 211–217., doi:10.1007/s11060-009-9948-7.
40. Chamberlain, Marc C., and Michael J. Glantz. "Interferon-α for Recurrent World Health Organization Grade 1 Intracranial Meningiomas." Cancer, vol. 113, no. 8, 2008, pp. 2146–2151., doi:10.1002/cncr.23803.
41. Chamberlain, M. C., et al. "Recurrent Meningioma: Salvage Therapy with Long-Acting Somatostatin Analogue." Neurology, vol. 69, no. 10, Apr. 2007, pp. 969–973., doi:10.1212/01.wnl.0000271382.62776.b7.
42. Johnson, Derek R. et al. "Phase II Study of Subcutaneous Octreotide in Adults with Recurrent or Progressive Meningioma and Meningeal Hemangiopericytoma." Neuro-Oncology 13.5 (2011): 530–535. PMC. Web. 16 Mar. 2018.

43. Schulz, Chris, et al. “Treatment of Unresectable Skull Base Meningiomas with Somatostatin Analogs.” Neurosurgical Focus, vol. 30, no. 5, 2011, doi:10.3171/2011.1.focus111.
44. Novartis. Sandostatin® Octreotide Acetate Injection Rx Only Prescribing Information. Sandostatin® Octreotide Acetate Injection Rx Only Prescribing Information. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/sandostatin_inj.pdf