# *Metastatic pituitary tumors: an institutional case series*

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# Title: Metastatic Pituitary Tumors: An Institutional Case Series

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## ABSTRACT

*Purpose*

Pituitary carcinomas are a rare entity that respond poorly to multimodal therapy. Patients follow a variable disease course that remains ill-defined.

*Methods*

We present an institutional case series of patients treated for pituitary carcinomas over a 30-year period from 1992 to 2022. A systematic review was conducted to identify prior case series of patients with pituitary carcinomas.

*Results*

Fourteen patients with a mean age at pituitary carcinoma diagnosis of 52.5 years (standard deviation [SD] 19.4) met inclusion criteria. All 14 patients had tumor subtypes confirmed by immunohistochemistry and hormone testing, with the most common being ACTH-producing pituitary adenomas (n = 12). Patients had a median progression-free survival (PFS) of 1.4 years (range 0.7-10.0) and a median overall survival (OS) of 8.4 years (range 2.3-24.0) from pituitary adenoma diagnosis. Median PFS and OS were 0.6 years (range 0.0-2.2) and 1.5 years (range 0.1-9.6) respectively upon development of metastases. Most patients (n = 12) had locally invasive disease to the cavernous sinus, dorsum sellae dura, or sphenoid sinus prior to metastasis. Common sites of metastasis included the central nervous system, liver, lung, and bone. In a pooled analysis including additional cases from the literature, treatment of metastases with chemotherapy or a combination of radiation therapy and chemotherapy significantly prolonged PFS (p = 0.02), while failing to significantly improve OS (p = 0.14).

*Conclusion*

Pituitary carcinomas are highly recurrent, heterogenous tumors with variable responses to treatment. Multidisciplinary management with an experienced neuro-endocrine and neuro-oncology team is needed given the unrelenting nature of this disease.


**Keywords:** pituitary neuroendocrine tumors, metastatic, pituitary carcinoma, outcomes, pituitary adenoma

## INTRODUCTION

Pituitary carcinomas are pituitary adenomas that have shown evidence of metastasis within or outside the central nervous system (CNS). Pituitary carcinomas, like primary adenomas, can be functional or silent, with around half producing adrenocorticotropic hormone (ACTH) or prolactin (PRL) [1]. Although only representing 0.1-0.2% of pituitary tumors, pituitary carcinomas are associated with a poor prognosis, with 5-year survival ranging from 28.6-56.2% [2-7]. The typical patient diagnosed with a pituitary carcinoma experiences a long course of treatment defined by multiple surgeries, rounds of radiation therapy, and cycles of chemotherapy [8, 9]. The European Society of Endocrinology has issued clinical practice guidelines that endorse temozolomide (TMZ) monotherapy as the primary adjuvant treatment for pituitary carcinomas and emphasize the importance of a multidisciplinary approach to the management of these complex patients [10]. However, even with multi-modal treatment outcomes remain poor.

In this study, we present the disease course, treatment, and outcomes of an institutional cohort of 14 patients diagnosed with pituitary carcinomas over a 30-year period.

## METHODS

An institutional database query was performed from 1992 to 2022. To meet inclusion criteria, patients required radiographic evidence of metastasis from the initial site of the pituitary adenoma (**Fig. 1**). Patients with insufficient follow-up data were excluded. Chart review was conducted to collect information related to treatment course and outcomes including: date of primary pituitary adenoma and carcinoma diagnoses; dates of recurrence(s); lesion location and size; presenting symptoms; treatment at each timepoint including dose, duration, and surgical approach; side effects of treatment; radiographic response to treatment; tumor pathology; available genomic analyses; pituitary adenoma to carcinoma latency; progression-free survival (PFS) defined as the time from index treatment to subsequent tumor growth; and overall survival (OS). PFS and OS were reported from both primary pituitary adenoma and carcinoma diagnosis. This study was approved by the Mass General Brigham Institutional Review Board (Protocol #2015P002352).

A systematic literature review was conducted in PubMed to identify patients diagnosed with pituitary carcinomas. Searches were conducted using keywords “metastatic pituitary neuroendocrine tumor,” “pituitary carcinoma,” and “aggressive pituitary tumor” for manuscripts published from 1999-2022. Studies published before 1999, when TMZ received FDA approval in the United States, were excluded. Inclusion criteria included

studies that contained outcome and treatment data on at least one patient diagnosed with a pituitary carcinoma. Exclusion criteria consisted of: studies that were not in English; studies with repeat authorship (to avoid patient duplication); commentaries or review articles that did not include original data; or studies with data derived from national registries. After identification of studies for final review, the following data were retrieved from each study: pituitary carcinoma subtype; site of metastasis; pituitary carcinoma treatment; OS; and PFS. If unavailable, OS and PFS were calculated for all cases with complete survival data.



**Fig. 1.** 72-year-old woman (Case 10) initially diagnosed with a 5.7 cm, growth-hormone positive pituitary adenoma that progressed to a pituitary carcinoma 6 years later. **a,** Sagittal contrast-enhanced T1-weighted magnetic resonance (MR) image of the initial 5.7 cm × 4.9 cm × 3.8 cm pituitary adenoma. **b,** Sagittal contrast-enhanced T1-weighted MR image of the 1.2 cm × 0.8 cm × 0.8 cm dural pituitary carcinoma at the level of the foramen magnum.

Kaplan-Meier curves with log-rank significance testing among subgroups were generated in Prism (GraphPad Software, New York, NY, USA). Cox proportional hazards models were employed to compare OS across continuous variables including age and latency between primary and metastatic disease. A Mann Whitney U test was employed to compare Ki-67 indices between primary and metastatic lesions across all patients. All statistical analyses were conducted in RStudio IDE (RStudio, PBC, Boston, MA, USA). Significance was set as a p-value $< 0.05$. All figures were generated or compiled in Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

## RESULTS

*Presentation and management prior to metastasis*

Fourteen pituitary carcinoma patients met inclusion criteria **(Table 1)**. The cohort was 64.3% female and had a mean age at initial pituitary adenoma diagnosis of 44.8 years (standard deviation [SD] 19.8). The mean follow-up period was 10.2 years (SD 5.8) and 2.4 years (SD 2.6) after primary pituitary adenoma and carcinoma diagnosis respectively. All patients were symptomatic at initial presentation reporting vision changes (n = 9, 64.3%), headaches (n = 5, 35.7%), symptoms of Cushing syndrome (n = 3, 21.2%), oligomenorrhea/amenorrhea (n = 3, 21.2%), sexual dysfunction (n = 3, 21.2%), and facial pain or numbness (n = 2, 14.3%).



| Case | Age, Gender | Subtype | Initial Ki-67 (%) - PA | Initial Ki-67 (%) - PC | PA to PC Latency (years) | Site of Initial Metastasis | No. PA/PC Recurrences | PC Therapy at Diagnosis | PC Therapy at Recurrence | Current Status | PFS PA/PC | OS PA/PC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *1* | 11F | ACTH | | 27.5 | 20.4 | Femoral head, liver, rib | 4/1 | Surgery, THAL, TMZ | | Deceased | 10.0/2.0 | 24.0/3.6 |
| *2* | 61F | ACTH† | | | 19.9 | Frontal lobe, parafalcine dura, planum sphenoidale | 5/0+ | | | Lost to Follow-Up | 2.4/- | 20.0+/0.1+ |
| *3* | 14F | ACTH† | 4.1 | 10.1 | 4.9 | Clivus, cerebellum | 2/2+ | Surgery | RT, SRS | Surveillance | 1.4/0.7 | 14.5+/9.6+ |
| *4* | 53M | ACTH | | | 8.5 | Prepontine cistern | 1/2 | TMZ | SRS, surgery, TMZ | Deceased | 5.3/1.9 | 13.9/5.4 |
| *5* | 33F | ACTH† | | | 7.0 | Liver, iliac bone | 2/1 | TMZ | RT | Deceased | 3.0/2.2 | 10.0/3.4 |
| *6* | 18F | ACTH | 8.4 | | 5.8 | Liver | 1/1+ | RT | RT | Surveillance | 1.4/1.1 | 9.1+/3.3+ |
| *7* | 49F | Null Cell# | | | 8.0 | Frontal lobe, cerebellum | 2/0 | Surgery | | Deceased | 3.0/0.0 | 8.4/0.4 |
| *8* | 63F | ACTH# | | | 6.2 | Clivus | 2/0 | TMZ | | Deceased | 3.8/0.0 | 7.7/1.5 |
| *9* | 49M | ACTH | | 5.9 | 6.2 | Iliac bone, vertebral bodies | 4/0 | CIS/ET | | Deceased | 1.0/- | 7.6/1.4 |
| *10* | 72F | GH, PRL | | | 5.9 | Foramen magnum | 1/1 | RT, surgery | | Deceased | 0.7/0.1 | 7.4/1.5 |
| *11* | 43M | ACTH# | | | 6.0 | Nasal cavity, maxilla | 2/2 | Surgery | CAPE, CTX, GEM, T/P | Deceased | -/0.5 | 7.0/1.3 |
| *12* | 35F | ACTH | | 5.1 | 5.6 | Frontal lobe, prepontine cistern, olfactory groove | 1/0+ | Surgery, TMZ | | Surveillance | 1.2/1.4+ | 7.0+/1.4+ |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *13* | 57M | ACTH | >70.0 | 3.7 | Mesial temporal lobe | 1/2 | Surgery | BVZ, PEM | Deceased | 1.0/0.3 | 4.6/0.9 |
| *14* | 67M | ACTH # | | 2.2 | Liver, lung | 1/0 | | | Deceased | 1.0/0.0 | 2.3/0.1 |

**Table 1.** Overview of Mass General Brigham cohort of patients diagnosed with a pituitary carcinoma between 1992 and 2022. Patients are ordered by overall survival since pituitary adenoma diagnosis.
+ indicates since last follow-up.
† Indicates that the tumor was initially nonfunctioning and became functioning at recurrence.
# Indicates that the tumor was nonfunctioning at last follow-up.
ACTH, adrenocorticotropic hormone positive tumor; BVZ, bevacizumab; CAPE, capecitabine; CIS/ET, cisplatin/etoposide; CTX, cyclophosphamide; GEM, gemcitabine; GH, growth hormone positive tumor; OS, overall survival; PA, pituitary adenoma; PC, pituitary carcinoma; PEM, pembrolizumab; PFS, progression-free survival; PRL, prolactin hormone positive tumor; RT, radiotherapy; SRS, stereotactic radiosurgery; THAL, thalidomide; TMZ, temozolomide; T/P, trametinib/palbociclib.

All 14 patients initially underwent an endoscopic transnasal transsphenoidal (TNTS) tumor resection, of which seven were subtotal resections and seven were unknown. Three patients received adjuvant radiotherapy after initial TNTS. All 14 patients had tumor subtypes confirmed by immunohistochemistry (IHC) laboratory testing and hormone testing. Transcription factor analyses were not available for this cohort. Six patients had functional ACTH-positive adenomas, six patients had nonfunctional ACTH-positive adenomas, one patient had a functional growth-hormone (GH) and PRL positive adenoma, and one patient had a null cell adenoma. Three silent ACTH-producing adenomas progressed to become functional at recurrence.

All 14 patients had recurrent disease. Patients experienced a median of 2.0 local recurrences (range 1.0-5.0) prior to metastasis. The median time to pituitary adenoma recurrence was 1.4 years (range 0.7-10.0). Patients initially treated with surgery and radiation had a significantly greater ($p = 0.04$) median time to recurrence of 3.8 years (range 1.0-10.0) compared to a median of 1.3 years (range 0.7-3.0) for patients who underwent TNTS resection alone. Most pituitary adenomas (n = 12, 85.7%) were invasive at local recurrence, with sites of invasion including the cavernous sinus (n = 9, 64.3%), dorsum sellae dura (n = 2, 14.3%), and sphenoid sinus (n = 1, 7.1%). Ten patients underwent a repeat TNTS and seven patients received a craniotomy at recurrence for better visualization of suprasellar tumor extension (n = 3, 21.4%), optic nerve or chiasm compression (n = 2, 14.3%), or carotid artery invasion (n = 1, 7.1%). Nine patients received adjuvant radiotherapy and two patients completed adjuvant chemotherapy after resection of recurrence.

Eight patients had pituitary adenoma recurrences treated solely with radiotherapy including both proton beam stereotactic radiosurgery (n = 5, 35.7%), gamma knife radiosurgery (n = 2, 14.3%) and fractionated

radiotherapy (FRT) (n = 1, 7.1%). One patient had a sellar recurrence treated with TMZ.

Of 12 patients with ACTH-positive adenomas, seven developed uncontrolled hypercortisolism during their disease course. Uncontrolled hypercortisolism had no significant impact on OS or PFS since PC diagnosis. Four patients required bilateral adrenalectomies for refractory Cushing syndrome a median of 7.0 years (range 4.5-20.4) after initial pituitary adenoma diagnosis. All four patients had pituitary adenomas that were ACTH-positive by IHC, of which three were initially functional. The fourth was silent at initial presentation and became functional upon the development of liver metastases. One patient had radiographic evidence of a sellar pituitary adenoma recurrence in the weeks prior to adrenalectomy. Adrenalectomies directly preceded the development of metastatic disease in all four patients by a median of 8.9 months (range 0.0-15.7), with three patients subsequently developing liver metastases and the fourth developing a metastasis to the prepontine cistern. Of note, only a single patient had tumor staging completed prior to adrenalectomy, so the presence of metastases prior to adrenalectomy could not be ruled out.

*Management of metastatic disease*

The mean age at pituitary carcinoma diagnosis was 52.5 years (SD 19.4), with a median latency period of 6.1 years (range 2.2-20.4) between initial diagnosis and metastasis. Half of patients (n = 7, 50.0%) had a recurrent or progressive pituitary adenoma in the pituitary gland at the identification of metastases. The sites of primary and subsequent metastases are summarized in **Table 2**. After the development of metastases, eight patients completed 10 additional metastasis resections, including surgery for brain, orbital, cervical spine, and liver metastases.

All patients for which data was available (n = 12) were initially diagnosed with imaging. Seven patients had intracranial metastases diagnosed via magnetic resonance (MR) brain imaging, one patient had a foramen magnum metastasis initially identified via a computed tomography (CT) scan of the head and ultimately diagnosed by MR brain imaging, and one patient had an iliac metastasis diagnosed by MR lower extremity imaging. Three patients were diagnosed with metastatic disease based on positron emission tomography (PET)-CT scans. Nine patients had the diagnosis of metastases confirmed by tissue biopsy: five patients had tissue samples collected during surgery while four patients underwent dedicated biopsies prior to treatment.

Radiotherapy was used to treat metastases in five patients. FRT was the most frequently employed for metastatic disease (n = 4, 28.6%) with targets including the femur, spinal column, and intracranial metastases.

Stereotactic radiosurgery was employed to treat intracranial metastases in two patients and stereotactic body radiation therapy was used for liver metastases in a single patient.

Half of the patients (n = 7, 50.0%) received chemotherapy for metastases, of which four were treated with TMZ alone. Three patients received TMZ as primary therapy after metastasis while one was given adjuvant TMZ after surgical resection. Of patients treated with TMZ, one experienced a complete response, two a partial response, and one progressive disease. Patients with pituitary carcinomas who were treated with TMZ were followed for a median of 2.3 years (range 0.5-3.2) and experienced a median of 1.9 years (range 0.0-2.1) of stable disease prior to recurrence. One patient treated with combinatorial TMZ and thalidomide recurred after 1.6 years, while a second that received treatment with cisplatin and etoposide died six months later. A single patient with CNS metastases underwent treatment with bevacizumab and pembrolizumab, which failed to halt disease progression. Of note, the protocol (NCT02886585) used to treat this patient did not require quantification of PD-1/PDL-1 expression for inclusion. The patient died five months after completing pembrolizumab treatment from a CNS infection.

| **Site** | **n (%)** |
|---|---|
| *Sites of CNS Metastasis (n = 7)* | |
| Cavernous sinus | 3 (21.4) |
| Frontal lobe | 3 (21.4) |
| Cerebellum | 2 (14.3) |
| Clivus | 2 (14.3) |
| Prepontine cistern | 2 (14.3) |
| Foramen magnum | 1 (7.1) |
| Mesial temporal lobe | 1 (7.1) |
| Midbrain | 1 (7.1) |
| Parafalcine dura | 1 (7.1) |
| Planum sphenoidale | 1 (7.1) |
| Pontomedullary junction | 1 (7.1) |
| *Sites of Extra-CNS Metastasis (n = 8)* | |
| Ilium | 5 (35.7) |
| Liver | 4 (28.6) |

| | |
|---|---|
| Lungs | 2 (14.3) |
| Orbit | 2 (14.3) |
| Vertebral bodies | 2 (14.3) |
| Femoral head | 1 (7.1) |
| Humeral head | 1 (7.1) |
| Nasal cavity | 1 (7.1) |
| Palate | 1 (7.1) |



**Table 2**. Sites of central nervous system (CNS) and extra-CNS metastasis by number of patients.

*Histopathology and Genomics*

Pathological analysis was completed on specimens from all but one patient during their treatment course. There was no significant difference in Ki-67 index between primary and metastatic lesions across specimens from all sites ($p = 0.94$). Staining for p53 expression was completed in 10 patients: 2 were negative, 6 were focally positive, and 2 were diffusely positive. The mitotic counts collected from eight patients were heterogeneous: 1 had no observable mitoses, 4 exhibited scattered mitoses, and 3 had samples with frequent mitoses. O[6]-methylguanine-DNA methyltransferase (MGMT) methylation status was assessed in samples from three patients, all of which were MGMT unmethylated. PD-1/PDL-1 expression was not analyzed for any patient in this cohort.

Molecular testing was performed in three patients using the SNAPSHOT-NGS-V2 Assay®, a PCR-based next generation sequencing panel of 91 genes [11]. The panel identified variants in *DDR2, SDHB, ARID1A, NRAS, PIK3CA, MSH6, APC, MAP3K1, FGFR3, KIT, ABL1, TSC1, STAG2, PTEN, RB1, BRCA2, PTPN11*, and *TSC2* in an intrasellar pituitary adenoma recurrence that developed after metastasis (Case 13); a novel missense variant in *KDR* in a recurrent pituitary adenoma (Case 3); and variants in *ATRX* and *MEN1* in an intracranial metastasis (Case 12). No TP53 mutations were identified in these patients.

*Outcomes*

At pituitary adenoma diagnosis, the median PFS was 1.4 years (range 0.7-10.0) which declined to 0.6 years (range 0.0-2.2) after metastasis **(Fig. 2)**. The median OS from initial pituitary adenoma diagnosis was 8.4 years (range 2.3-24.0) while the median OS from the development of metastasis was 1.5 years (range 0.1-9.6) **(Fig. 3)**. Use of radiation therapy as part of primary treatment and treatment era (first 15 years vs. second 15 years) had no significant impact on median OS since primary pituitary adenoma or carcinoma diagnosis. At last follow-up, 10 patients were deceased, three were under surveillance for recurrence, and one patient's status was unknown. Cause of death included infection in three patients (gas gangrene, pneumonia, and meningitis), of which one each was receiving chemotherapy and immunotherapy, a cerebral infarct in one patient, and was undetermined in six patients.

**Fig. 2.** Treatment timeline of pituitary carcinoma patients from initial pituitary adenoma diagnosis. Treatments (including the use of surgery, radiotherapy, stereotactic radiosurgery [SRS], and chemotherapy), timing of recurrences, and status at last follow-up are summarized. Date of last follow up is provided for all patients. Total radiation dose per treatment is provided, when available, in Gy. All timelines are continuous and to scale save for small adjustments to improve readability.
BVZ, bevacizumab; CAPE, capecitabine; CIS/ET, cisplatin/etoposide; CTX, cyclophosphamide; GEM, gemcitabine; PEM, pembrolizumab; T/P, trametinib/palbociclib; THAL, thalidomide; TMZ, temozolomide.

**Fig. 3.** Cumulative Kaplan-Meier curves depicting overall (OS) and progression-free survival (PFS) for pituitary carcinoma patients since initial pituitary adenoma diagnosis **(a)** and initial pituitary carcinoma diagnosis **(b)**.

*Systematic Review*

The literature review identified 14 case reports and series published since 1999 that describe patients with pituitary carcinomas **(Table 3).** Included studies covered the disease course and treatment of 101 patients with pituitary carcinomas. A pooled survival analysis was conducted across 37 patients from six studies with available survival data, including the 14 patients in this cohort. There was a median PFS of 3.0 years (range 0.7-10.0) after primary pituitary adenoma diagnosis and 0.7 years (range 0.0-2.3) after the discovery of metastases. Pooled median OS since primary pituitary adenoma and carcinoma diagnosis was 12.5 years (range 2.3-31.0) and 3.6 years (range 0.1-13.5) respectively, with a median latency period of 5.9 years (range 0.0-29.0) between diagnoses.

Across all 37 cases, there was no relationship between sex ($p = 0.30$), histologic subtype ($p = 0.80$), or the location of metastases ($p = 0.78$) and survival since metastasis. There was no clinically meaningful association among primary to metastatic disease latency (hazard ratio [HR] 0.94; confidence interval [CI] 0.83-1.04) or age at the development of metastasis (HR 1.02; CI 1.0-1.05) and OS since metastasis. Among the patients with available treatment data, 14 received chemotherapy as their initial treatment for metastases, 8 received radiotherapy, 7 received both chemotherapy and radiotherapy, and 7 received surgery alone or no treatment. The median PFS after metastasis significantly differed between treatment groups ($p = 0.02$): no treatment group (median PFS of 0.5 years [range 0.0-0.7]), radiotherapy group (median PFS of 0.7 years [range 0.1-1.1]), chemotherapy group (median PFS 1.9 years [range 0.0-2.2]), and combination therapy group (median PFS of 1.6 years [range 0.9-2.3]).

However, there was no significant difference (p = 0.14) in median OS between treatment types: no treatment group (median OS of 1.0 years [range 0.4-13.5]), chemotherapy group (median OS of 3.4 years [range 0.8-5.4]), and combination therapy group (median OS of 10.5 years [range 1.0-10.5]). The radiation therapy group had an undefined median OS due to a large proportion of survivors (n = 5/8). PFS and OS by treatment was available for 17 and 35 patients respectively.

| Study | No. PC | Subtype | Site(s) of Metastasis | PC Therapy | Median PFS (years) | Median OS (since PA/ PC) |
|---|---|---|---|---|---|---|
| *Roncaroli et al., 2003[12]* | 2 | 2 PRL | Cranium, dura mater, larynx, nasal sinus, ribs, vertebral bodies | CTX, DTIC, VIN | NR | NR/NR |
| *Losa et al., 2010[13]* | 1 | ACTH | Frontal lobe, prepontine cistern | SRS, TMZ | 2.3 | 8.3/2.3 |
| *Raverot et al., 2010[14]* | 5 | 2 ACTH, 3 PRL | NR | RT, SRS, TMZ | NR | NR |
| *Hirohata et al., 2013[15]* | 12 | 3 ACTH, 4 NC, 2 NR, 3 PRL | NR | TMZ, otherwise NR | NR | NR |
| *Zacharia et al., 2014[16]* | 1 | ACTH | Clivus | CAPE, CIS/ET, RT, TMZ | 0.5 | NR |
| *Bengtsson et al., 2015[17]* | 8 | 3 ACTH, 3 GH, 2 PRL | Bone, brainstem, cerebral, intraspinal, liver, lymph node | CAPE, irinotecan, TMZ, PEM | NR | NR |
| *Bruno et al., 2015[18]* | 1 | PRL | Parietal lobe | Surgery, TMZ | 0.0 | NR |
| *Wang et al., 2015[19]* | 2 | 1 ACTH, 1 GH | Cerebellopontine angle, intraspinal | RT, surgery | NR | NR/NR |
| *Jordan et al., 2018[20]* | 3 | 2 ACTH, 1 PRL | NR | RT, surgery, TMZ | 0.5† | 14.0/NR |
| *McCormack et al., 2018[8]* | 40 | 19 ACTH, 2 FSH/LH, 1 GH, 3 NC, 15 PRL | NR | Adriblastin, BCNU, BVZ, carboplatin, CAPE, CIS/ET, CTX, DOX, erlotinib, everolimus, lapatinib, oxaliplatin, RT, sunitib, surgery, THAL, TMZ, 5-FU | NR | 12.0/NR |
| *Yoo et al., 2018[21]* | 2 | 2 ACTH | Cervical lymph node, liver | Nivolumab, PD-1, RT, TMZ | 0.7# | NR/NR |
| *Santos-Pinheiro et al., 2019[5]* | 17 | 5 ACTH, 2 FSH/LH, 1 GH, 5 NC, 4 PRL | Bone, dura, epidural spine, LMD, lung, liver, lymph node, liver, optic chiasm, orbits | CAPTEM, carboplatin, CIS/ET, CYVADIC, PD-1, RT, surgery, TMZ, 5-FU | 0.8 | 13.0/10.5 |
| *Xu et al., 2020[22]* | 2 | 1 ACTH, 1 NC | Epidural spine, frontal lobe | BVZ, lomustine, RT, surgery, TMZ | 0.7 | 7.3/2.1 |
| *Du Four et al., 2022[23]* | 5 | 3 ACTH, 1 GH/PRL, 1 PRL | Bone, cerebellum, frontal lobe, retroclival | Ipilimumab, nivolumab, RT, surgery, TMZ | NR | NR/NR |
| ***Current Study*** | **14** | **12 ACTH, 1 GH/PRL, 1 NC** | **Cavernous sinus, cerebellum, clivus, foramen magnum, femur, frontal lobe, iliac bone, liver, lung, maxilla, mesial temporal bone, nasal cavity, olfactory groove, parafalcine dura, planum sphenoidale, prepontine cistern, sphenoid sinus** | **BVZ, CAPE, CIS/ET, CTX, GEM, PEM, RT, SRS, surgery, T/P, THAL, TMZ** | **0.7** | **8.4/1.5** |

**Table 3.** Pituitary carcinoma case series published since 1999.
All survivals are since pituitary carcinoma diagnosis and reported in years unless otherwise indicated. Survivals are calculated from complete cases if not explicitly provided.

ACTH, adrenocorticotropic hormone positive tumor; BCNU, carmustine; BVZ, bevacizumab; CAPE, capecitabine; CAPTEM, capecitabine and temozolomide; CIS/ET, cisplatin/etoposide; CTX, cyclophosphamide; CYVADIC, cyclophosphamide, vincristine, and dacarbazine; DOX, doxorubicin; DTIC, dacarbazine; FSH, follicle stimulating hormone positive tumor, GEM, gemcitabine; GH, growth hormone positive tumor; LH, luteinizing hormone positive tumor; LMD, leptomeningeal disease; NC, null cell; NR, not reported; OS, overall survival; PA, pituitary adenoma; PC, pituitary carcinoma; PD-1, programmed cell death protein 1 inhibitor; PEM, pembrolizumab; PFS, progression-free survival; PRL, prolactin hormone positive tumor; RT, radiotherapy; SRS, stereotactic radiosurgery; T/P, trametinib/palbociclib; THAL, thalidomide; TMZ, temozolomide; VIN, vincristine; 5-FU, 5-fluorouracil.

† PFS was calculated since TMZ initiation.

# PFS only provided for a single patient.

## DISCUSSION

Pituitary carcinomas represent a fraction of pituitary tumors with a limited body of published literature [2-5]. Despite multidisciplinary treatment including surgery, radiation, chemotherapy, and immunotherapy, outcomes remain poor. We present a comprehensive case series of 14 patients treated for a pituitary carcinoma over a 30-year period to improve the understanding of this challenging pathology.

We observed a median OS of 8.4 years (range 2.3-24.0) and median latency to metastasis of 6.1 years (range 2.2-20.4) in this cohort compared to 12.5 years (range 2.3-31.0) and 5.9 years (range 0.0-29.0) identified by pooled analysis [5, 13, 16, 21, 22]. Both measures varied widely by individual patient in our series, which underscores the heterogeneity in time to malignant transformation for pituitary carcinomas. The 1.5 year median OS after the development of metastatic disease was similar to prior studies but lower than the aggregated median survival of 3.6 years. Santos-Pinheiro et al. [5] is the most comparable cohort given its recency and size, and they reported a 5-year survival rate after metastasis of 35% with a similarly variable range of individual outcomes. Of note, 10 of 17 of their patients were alive at last follow-up, making measurement of median survival difficult. No clinically meaningful association was identified between patient or tumor characteristics and OS. It remains unclear what clinicopathologic differences exist between subgroups of patients that die soon after pituitary carcinoma diagnosis versus those with years of stable disease.

Although many pituitary carcinomas originally present as invasive pituitary tumors, no reliable method has been determined to definitively identify subpopulations that progress to become pituitary carcinomas. Molecular markers such as Ki-67 proliferative index, MGMT methylation status, and p53 mutation status have been investigated as predictors of pituitary carcinoma behavior, with heterogenous results [24-26]. In a study of the pathobiology of pituitary carcinomas, Scheithauer et al. [27] observed significantly greater MIB-1 labeling indexes and a trend toward a higher

degree of aneuploidy in metastatic lesions when compared to premetastatic. Roncaroli et al. [12] additionally reported an increase in mitoses from 5 to 15 per 10 high-power field between the primary lesion and dural metastasis. Recent work has suggested that a Ki-67 greater than 10%, ATRX mutations, and TP53 mutations may be associated with a greater risk of metastases [28-30]. In this series, both patients for which data was available had initial Ki-67 indices below 10%. Of the three patients with sequencing data available, one was identified to have an ATRX mutation.

Little is known of the potential molecular drivers of metastatic transformation. The most common somatic mutations associated with all pituitary adenomas include those in *AIP*, *BRAF*, *GNAS*, *PIK3CA*, *TP53*, *USP48*, and *USP8* [31]. Of the three patients with genomic analysis in this cohort, a single patient had a variant in *PIK3CA,* with no other observed overlap in mutational burden. Santos-Pinheiro et al. [5] identified variants in 21 targetable genes in one patient and one genetic variant in another patient. The only overlap in gene variants identified between Santos-Pinheiro et al. and this study was in *APC*, a tumor suppressor gene that codes for a protein in the Wnt signaling pathway. For the three patients within this cohort for which the same gene panel was applied, there was no overlap in observed mutations. Larger gene panels across a greater cohort of patients will be needed to further clarify targetable mutations in these patients.

Large cohort studies of patients with Cushing syndrome have observed that 7-18% of patients complete a bilateral adrenalectomy for refractory disease [32, 33]. In comparison, 44.4% of patients with functional ACTH-producing adenomas in this cohort underwent adrenalectomy, all in the 1.5 years preceding the development of metastatic disease. Although the lack of tumor staging prior to adrenalectomy cannot preclude the pre-existence of metastatic disease, the subsequent development of metastasis after bilateral adrenalectomy in three patients raises concern about the presence of a systemic correlate of Nelson-Salassa syndrome (NSS) in these patients, with the removal of negative feedback from adrenal cortisol accelerating the growth of metastases [34]. Although exceedingly rare, NSS has been previously reported in patients with pituitary carcinomas, albeit with a greater latency period than the 8.9 months observed in this cohort [35-37]. While this data is far from conclusive, this phenomenon should be further explored in larger pituitary carcinoma cohorts.

TMZ remains the first-line treatment for pituitary carcinomas [10]. Santos-Pinheiro et al. [5] reported that treatment with TMZ increased the median time to recurrence by 20 months compared to radiation therapy or non-TMZ chemotherapy. In our pooled analysis, the use of chemotherapy as the primary treatment of metastases yielded the greatest median PFS (1.9 years), while failing to significantly prolong OS compared to other

treatments. In a large international cohort of 156 patients with aggressive pituitary adenomas or carcinomas, TMZ yielded a complete or partial regression in 9.6% and 30.1% of patients respectively [38]. In patients with aggressive pituitary adenomas, the literature is mixed on the relationship between MGMT expression and TMZ response [39-42]. However, recent European Society of Endocrinology guidelines recommend that all patients diagnosed with a pituitary carcinoma complete an evaluation of MGMT status by IHC [10]. In this cohort, three patients completed such an evaluation, of which one has responded well to TMZ with 1.3 years of stable disease since starting treatment. Efforts should be made to maximize the clinical uptake of MGMT promoter analysis in this population to further characterize its prognostic value and identify patients who could potentially benefit the most from treatment with TMZ.

Multiple studies have suggested that the combination of radiotherapy and TMZ as primary or salvage therapy for metastases has the potential to further delay disease progression compared to either therapy alone [5, 13, 43, 44]. This analysis found that chemotherapy and combination therapy yielded near-equivalent PFSs (1.9 years vs. 1.6 years). However, treatment with combination therapy yielded a nonsignificant increase in OS compared to chemotherapy alone (3.4 years vs. 10.5 years). Two of three patients under surveillance with stable disease in this cohort had metastases solely treated with radiation therapy. Du Four et al. [23] reported a similar phenomenon in which a pituitary carcinoma patient treated with FRT achieved biochemical regression of disease. Indeed, out of the eight patients treated solely with radiation therapy in the pooled analysis, five were still alive at last follow-up. McCormack et al. [8], however, observed a more mixed picture in which radiotherapy induced stable disease in four patients and failed to halt progression in six patients. The relative benefit of treatment with radiation alone remains poorly understood.

The present study has several limitations that warrant consideration. This analysis was retrospectively conducted on a cohort of 14 patients which introduces bias. While all patients received most of their care at institutional affiliates of Mass General Brigham, records were incomplete for care received elsewhere. One patient (case 2) was recently diagnosed with metastatic disease and therefore lacks treatment or survival data. Pathology data was heterogeneously characterized between patients, making direct comparisons difficult. Future work is needed to improve risk stratification and further characterize the benefits of a combination of TMZ and radiotherapy in these patients. There is little expert consensus on second-line treatment options after patients fail primary therapies such as TMZ or radiotherapy. Isolated case reports have investigated the use of VEGF inhibitors, immune checkpoint inhibitors, and peptide receptor radionuclide therapy with limited success [45-47]. More work is needed to

better define the scope and benefit of these alternative treatments in pituitary carcinoma patients.

## CONCLUSION

Pituitary carcinomas present with variable disease courses accompanied by unpredictable response to treatment. Most patients complete multimodal treatment including surgery, radiation, and chemotherapy. Although some favorable responses have been shown to TMZ-based chemotherapy and radiation therapy, most patients ultimately die of complications related to their disease or treatment. Further investigation is needed to determine the optimal combination of therapies for each individual patient to maximize progression-free and overall survival.

## DECLARATIONS

### Ethical Approval

This study was approved by the Mass General Brigham Institutional Review Board (Protocol #2015P002352).

### Competing interests

JDB has an equity position in Treovir Inc., an oHSV clinical stage company and is a member of the POCKiT Diagnostics, Centile Bioscience and NeuroX1 Boards of Scientific Advisors.

### Authors' contributions

**A.G.Y.:** Conceptualization, Methodology, Software, Writing – Original Drafting, Writing – Review & Editing, Visualization; **E.J.C.**: Conceptualization, Methodology, Software, Writing – Original Drafting, Writing – Review & Editing; **S.G.**: Conceptualization, Methodology, Writing – Review & Editing, Supervision; **J.I.C.**: Conceptualization, Methodology, Writing – Review & Editing, Supervision; **J.D.B.**: Writing – Review & Editing, Supervision; **N.N.**: Methodology, Software, Writing – Review & Editing; **O.A.**: Conceptualization, Resources, Writing – Review & Editing, Supervision; **T.R.S.**: Conceptualization, Resources, Writing – Review & Editing, Supervision; **D.A.R.**: Writing – Review & Editing, Supervision, Methodology; **E.R.L.**: Conceptualization, Resources, Methodology, Writing – Review & Editing, Supervision.

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### Availability of data and materials

Not applicable.

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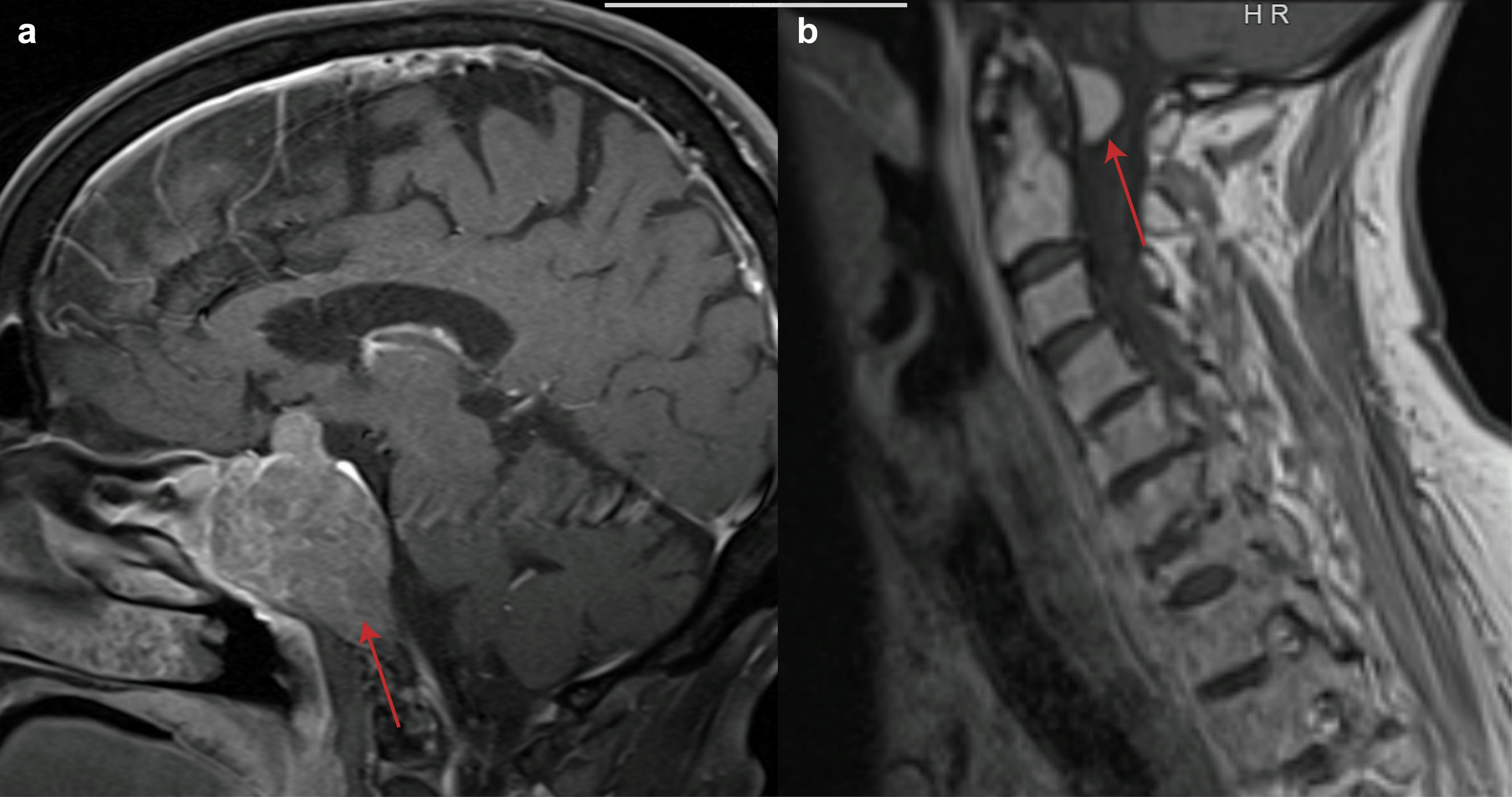
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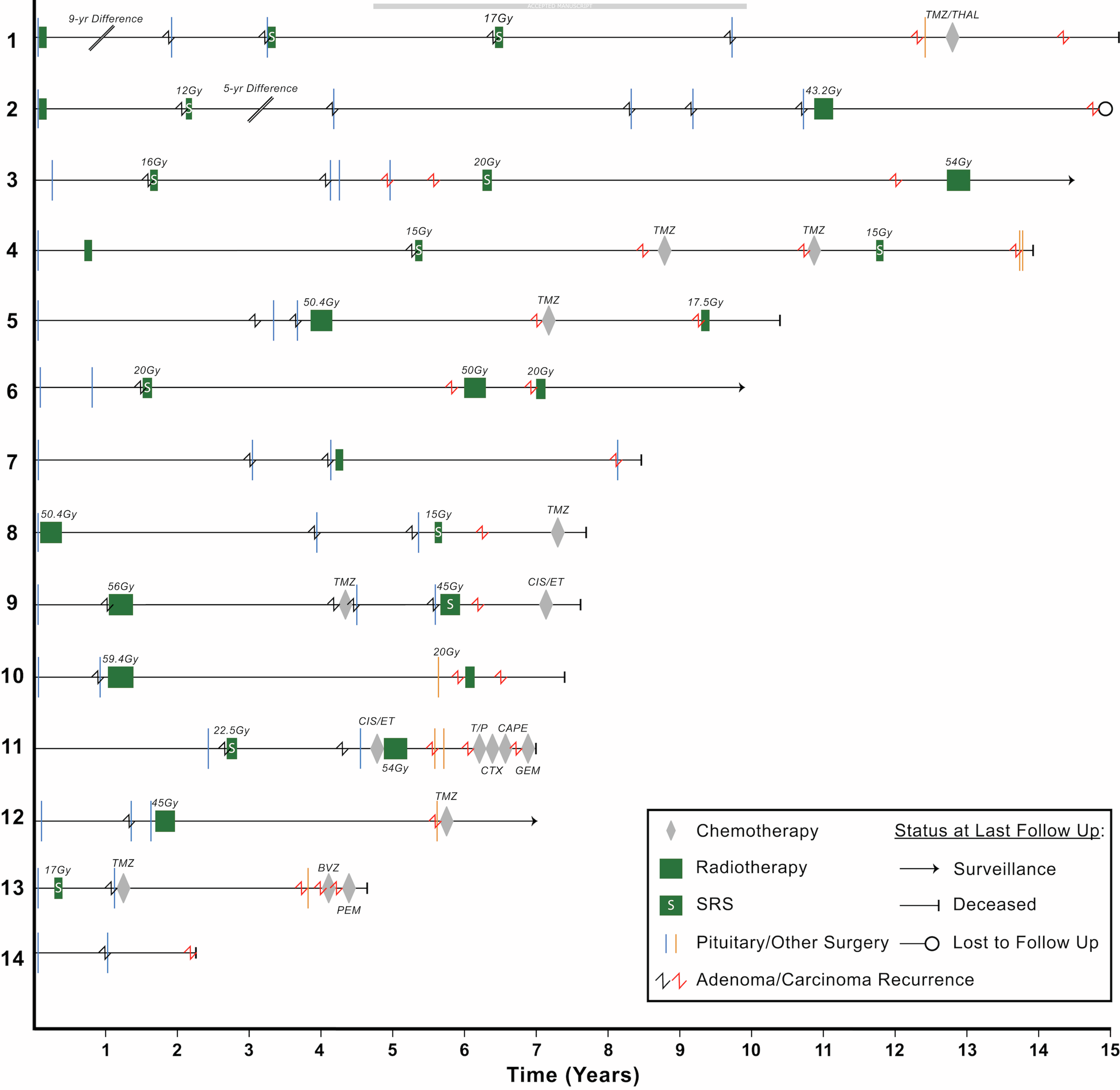

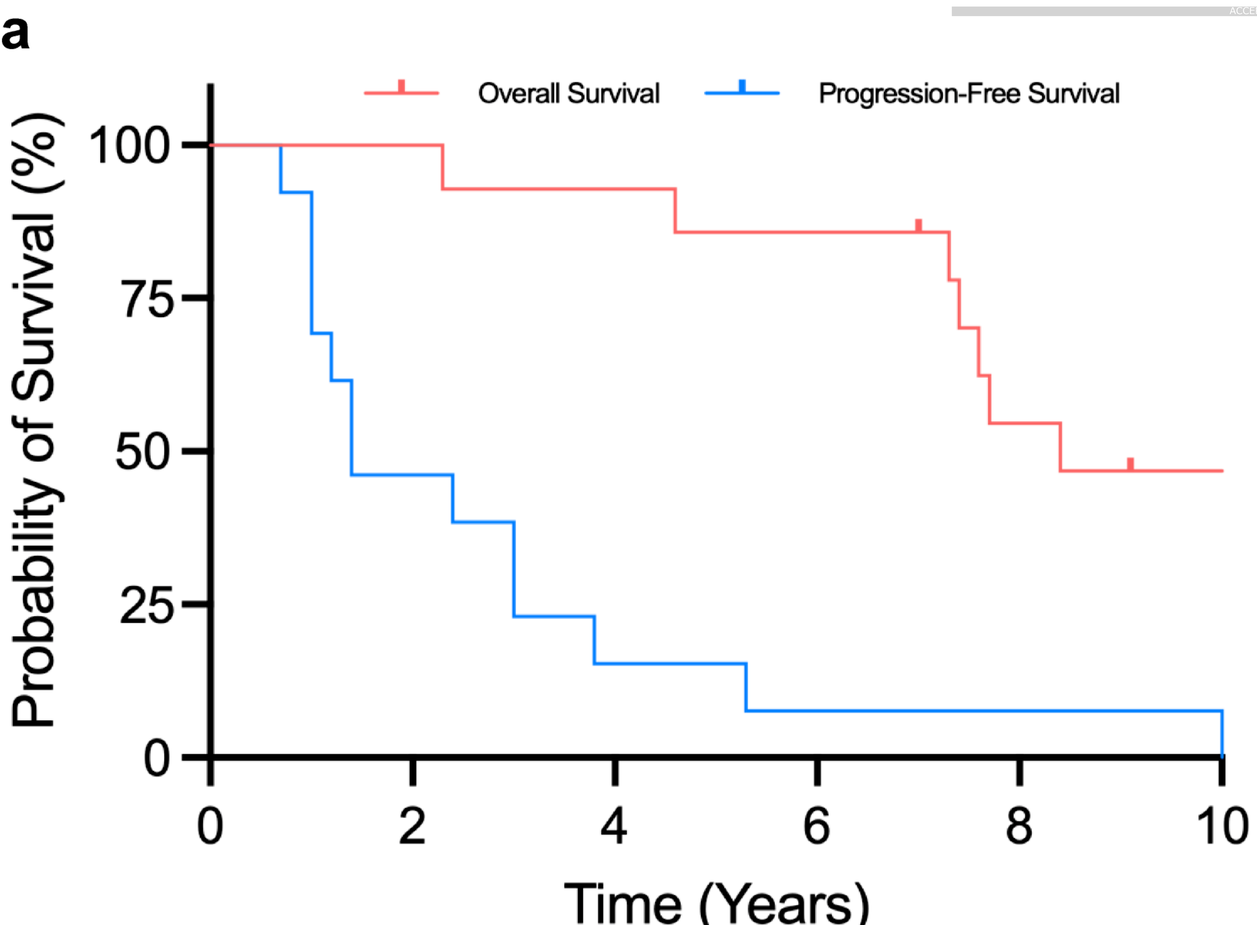


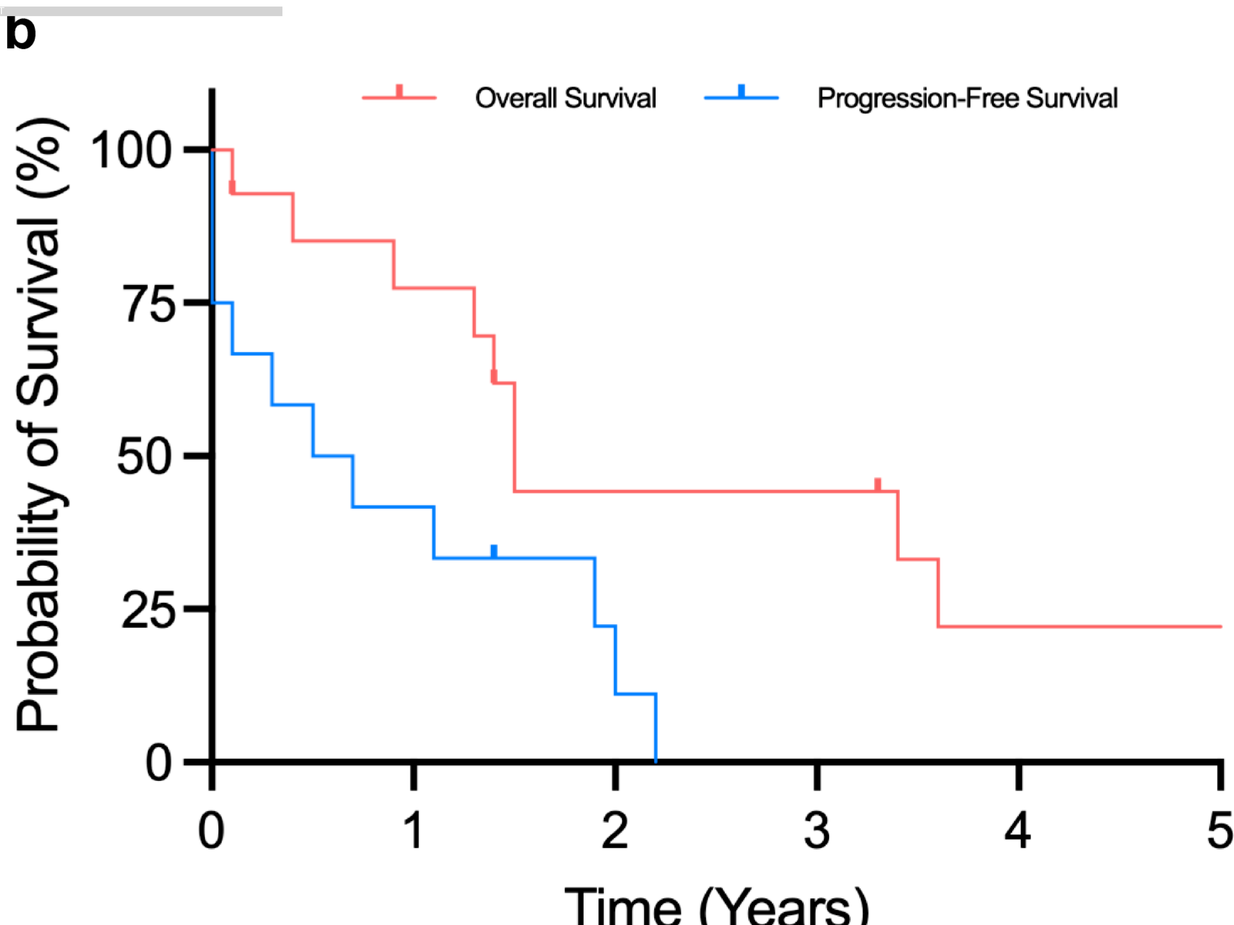

| Case | Age, Gender | Subtype | Initial Ki-67 (%) - PA | Initial Ki-67 (%) - PC | PA to PC Latency (years) | Site of Initial Metastasis | No. PA/ PC Recurrences | PC Therapy at Diagnosis | PC Therapy at Recurrence | Current Status | PFS PA/ PC | OS PA/ PC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *1* | 11F | ACTH | | 27.5 | 20.4 | Femoral head, liver, rib | 4/1 | Surgery, THAL, TMZ | | Deceased | 10.0/ 2.0 | 24.0/3.6 |
| *2* | 61F | ACTH † | | | 19.9 | Frontal lobe, parafalcine dura, planum sphenoidale | 5/0+ | | | Lost to Follow-Up | 2.4/- | 20.0+/0 .1+ |
| *3* | 14F | ACTH † | 4.1 | 10.1 | 4.9 | Clivus, cerebellum | 2/2+ | Surgery | RT, SRS | Surveillance | 1.4/0. 7 | 14.5+/9 .6+ |
| *4* | 53M | ACTH | | | 8.5 | Prepontine cistern | 1/2 | TMZ | SRS, surgery, TMZ | Deceased | 5.3/1. 9 | 13.9/5.4 |
| *5* | 33F | ACTH † | | | 7.0 | Liver, iliac bone | 2/1 | TMZ | RT | Deceased | 3.0/2. 2 | 10.0/3.4 |
| *6* | 18F | ACTH | 8.4 | | 5.8 | Liver | 1/1+ | RT | RT | Surveillance | 1.4/1. 1 | 9.1+/3. 3+ |
| *7* | 49F | Null Cell# | | | 8.0 | Frontal lobe, cerebellum | 2/0 | Surgery | | Deceased | 3.0/0. 0 | 8.4/0.4 |
| *8* | 63F | ACTH # | | | 6.2 | Clivus | 2/0 | TMZ | | Deceased | 3.8/0. 0 | 7.7/1.5 |
| *9* | 49M | ACTH | | 5.9 | 6.2 | Iliac bone, vertebral bodies | 4/0 | CIS/ET | | Deceased | 1.0/- | 7.6/1.4 |
| *10* | 72F | GH, PRL | | | 5.9 | Foramen magnum | 1/1 | RT, surgery | | Deceased | 0.7/0. 1 | 7.4/1.5 |
| *11* | 43M | ACTH # | | | 6.0 | Nasal cavity, maxilla | 2/2 | Surgery | CAPE, CTX, GEM, T/P | Deceased | -/0.5 | 7.0/1.3 |
| *12* | 35F | ACTH | | 5.1 | 5.6 | Frontal lobe, prepontine cistern, olfactory groove | 1/0+ | Surgery, TMZ | | Surveillance | 1.2/1. 4+ | 7.0+/1. 4+ |
| *13* | 57M | ACTH | | >70. 0 | 3.7 | Mesial temporal lobe | 1/2 | Surgery | BVZ, PEM | Deceased | 1.0/0. 3 | 4.6/0.9 |
| *14* | 67M | ACTH # | | | 2.2 | Liver, lung | 1/0 | | | Deceased | 1.0/0. 0 | 2.3/0.1 |

**Table 1.** Overview of Mass General Brigham cohort of patients diagnosed with a pituitary carcinoma between 1992 and 2022. Patients are ordered by overall survival since pituitary adenoma diagnosis.
+ indicates since last follow-up.
† Indicates that the tumor was initially nonfunctioning and became functioning at recurrence.
# Indicates that the tumor was nonfunctioning at last follow-up.
ACTH, adrenocorticotropic hormone positive tumor; BVZ, bevacizumab; CAPE, capecitabine; CIS/ET, cisplatin/etoposide; CTX, cyclophosphamide; GEM, gemcitabine; GH, growth hormone positive tumor; OS, overall survival; PA, pituitary adenoma; PC, pituitary carcinoma; PEM, pembrolizumab; PFS, progression-free survival; PRL, prolactin hormone positive tumor; RT, radiotherapy; SRS, stereotactic radiosurgery; THAL, thalidomide; TMZ, temozolomide; T/P, trametinib/palbociclib.

| Site | n (%) |
|---|---|
| *Sites of CNS Metastasis (n = 7)* | |
| Cavernous sinus | 3 (21.4) |
| Frontal lobe | 3 (21.4) |
| Cerebellum | 2 (14.3) |
| Clivus | 2 (14.3) |
| Prepontine cistern | 2 (14.3) |
| Foramen magnum | 1 (7.1) |
| Mesial temporal lobe | 1 (7.1) |
| Midbrain | 1 (7.1) |
| Parafalcine dura | 1 (7.1) |
| Planum sphenoidale | 1 (7.1) |
| Pontomedullary junction | 1 (7.1) |
| *Sites of Extra-CNS Metastasis (n = 8)* | |
| Ilium | 5 (35.7) |
| Liver | 4 (28.6) |
| Lungs | 2 (14.3) |
| Orbit | 2 (14.3) |
| Vertebral bodies | 2 (14.3) |
| Femoral head | 1 (7.1) |
| Humeral head | 1 (7.1) |
| Nasal cavity | 1 (7.1) |
| Palate | 1 (7.1) |

**Table 2**. Sites of central nervous system (CNS) and extra-CNS metastasis by number of patients.

| Study | No. PC | Subtype | Site(s) of Metastasis | PC Therapy | Median PFS (years) | Median OS (since PA/ PC) |
|---|---|---|---|---|---|---|
| *Roncaroli et al., 2003[11]* | 2 | 2 PRL | Cranium, dura mater, larynx, nasal sinus, ribs, vertebral bodies | CTX, DTIC, VIN | NR | NR/NR |
| *Losa et al., 2010[12]* | 1 | ACTH | Frontal lobe, prepontine cistern | SRS, TMZ | 2.3 | 8.3/2.3 |
| *Raverot et al., 2010[13]* | 5 | 2 ACTH, 3 PRL | NR | RT, SRS, TMZ | NR | NR |
| *Hirohata et al., 2013[14]* | 12 | 3 ACTH, 4 NC, 2 NR, 3 PRL | NR | TMZ, otherwise NR | NR | NR |
| *Zacharia et al., 2014[15]* | 1 | ACTH | Clivus | CAPE, CIS/ET, RT, TMZ | 0.5 | NR |
| *Bengtsson et al., 2015[16]* | 8 | 3 ACTH, 3 GH, 2 PRL | Bone, brainstem, cerebral, intraspinal, liver, lymph node | CAPE, irinotecan, TMZ, PEM | NR | NR |
| *Bruno et al., 2015[17]* | 1 | PRL | Parietal lobe | Surgery, TMZ | 0.0 | NR |
| *Wang et al., 2015[18]* | 2 | 1 ACTH, 1 GH | Cerebellopontine angle, intraspinal | RT, surgery | NR | NR/NR |
| *Jordan et al., 2018[19]* | 3 | 2 ACTH, 1 PRL | NR | RT, surgery, TMZ | 0.5† | 14.0/NR |
| *McCormack et al., 2018[7]* | 40 | 19 ACTH, 2 FSH/LH, 1 GH, 3 NC, 15 PRL | NR | Adriblastin, BCNU, BVZ, carboplatin, CAPE, CIS/ET, CTX, DOX, erlotinib, everolimus, lapatinib, oxaliplatin, RT, sunitib, surgery, THAL, TMZ, 5-FU | NR | 12.0/NR |
| *Yoo et al., 2018[20]* | 2 | 2 ACTH | Cervical lymph node, liver | Nivolumab, PD-1, RT, TMZ | 0.7# | NR/NR |
| *Santos-Pinheiro et al., 2019[4]* | 17 | 5 ACTH, 2 FSH/LH, 1 GH, 5 NC, 4 PRL | Bone, dura, epidural spine, LMD, lung, liver, lymph node, liver, optic chiasm, orbits | CAPTEM, carboplatin, CIS/ET, CYVADIC, PD-1, RT, surgery, TMZ, 5-FU | 0.8 | 13.0/10.5 |
| *Xu et al., 2020[21]* | 2 | 1 ACTH, 1 NC | Epidural spine, frontal lobe | BVZ, lomustine, RT, surgery, TMZ | 0.7 | 7.3/2.1 |
| *Du Four et al., 2022[22]* | 5 | 3 ACTH, 1 GH/PRL, 1 PRL | Bone, cerebellum, frontal lobe, retroclival | Ipililumab, nivolumab, RT, surgery, TMZ | NR | NR/NR |
| ***Current Study*** | **14** | **12 ACTH, 1 GH/PRL, 1 NC** | **Cavernous sinus, cerebellum, clivus, foramen magnum, femur, frontal lobe, iliac bone, liver, lung, maxilla, mesial temporal bone, nasal cavity, olfactory groove, parafalcine dura, planum sphenoidale, prepontine cistern, sphenoid sinus** | **BVZ, CAPE, CIS/ET, CTX, GEM, PEM, RT, SRS, surgery, T/P, THAL, TMZ** | **0.7** | **8.4/1.5** |

**Table 3.** Pituitary carcinoma case series published since 1999.
All survivals are since pituitary carcinoma diagnosis and reported in years unless otherwise indicated. Survivals are calculated from complete cases if not explicitly provided.
ACTH, adrenocorticotropic hormone positive tumor; BCNU, carmustine; BVZ, bevacizumab; CAPE, capecitabine; CAPTEM, capecitabine and temozolomide; CIS/ET, cisplatin/etoposide; CTX, cyclophosphamide; CYVADIC, cyclophosphamide, vincristine, and dacarbazine; DOX, doxorubicin; DTIC, dacarbazine; FSH, follicle stimulating hormone positive tumor, GEM, gemcitabine; GH, growth hormone positive tumor; LH, luteinizing hormone positive tumor; LMD, leptomeningeal disease; NC, null cell; NR, not reported; OS, overall survival; PA, pituitary adenoma; PC, pituitary carcinoma; PD-1, programmed cell death protein 1 inhibitor; PEM, pembrolizumab; PFS, progression-free survival; PRL, prolactin hormone positive tumor; RT, radiotherapy; SRS, stereotactic radiosurgery; T/P,

trametinib/palbociclib; THAL, thalidomide; TMZ, temozolomide; VIN, vincristine; 5-FU, 5-fluorouracil.
† PFS was calculated since TMZ initiation.
# PFS only provided for a single patient.