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A Population-Level Analysis of Pituitary Carcinoma from the National Cancer Database

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Abstract

Objectives Pituitary carcinoma is a rare entity with fewer than 200 total cases reported in the English literature. Analysis of the population-level data from the National Cancer Database (NCDB) affords the opportunity to study this poorly understood tumor type.

Methods The NCDB was queried for site, histology, and metastasis codes corresponding to pituitary carcinoma. Statistical analyses were performed to determine factors associated with overall survival (OS).

Results A total of 92 patients with pituitary carcinoma met inclusion criteria. The 1 and 5 years of OS for all patients was 93.3% (95% confidence interval [CI]: 88.2–98.6%) and 80.0% (95% CI: 71.6–89.4%), respectively. Patients with invasive primary tumor behavior had 1 and 5 years of OS of 69.2% (95% CI: 48.2–99.5%) and 52.7% (95% CI: 31.2–89.2%), respectively. Multivariate analysis demonstrated that compared with benign primary behavior, invasive behavior had increased all-cause mortality (hazard ratio [HR], 1,296, 95% CI: 15.1– > 2,000). Surgery without adjuvant radiation or chemotherapy was the most common therapy (48.9%), followed by no treatment (40.2%). Compared with surgery alone, no treatment had worse OS (HR, 11.83, 95% CI: 1.41–99.56). Increasing age and female sex were both associated with increased mortality.

Conclusions The most common treatment for pituitary carcinoma is surgery alone followed by no surgery. Surgery alone has significantly better OS compared with no treatment. The efficacy of radiation, chemotherapy, and neurohormonal treatments needs to be examined with prospective studies.

Keywords
- pituitary carcinoma
- National Cancer Database
- overall survival
- pituitary
- skull base
- outcomes

Introduction

Pituitary carcinoma is a rare primary malignancy of the pituitary gland characterized by distant metastases or noncontiguous spread from the primary sellar site, an important distinction from invasive pituitary adenomas which can invade the surrounding sellar structures.[1,2] The specific biology of pituitary carcinomas is poorly understood but most appear to originate from functional pituitary adenomas.[3] Pituitary carcinomas are exceedingly uncommon, representing just 0.1% of all pituitary tumors with a prevalence estimated at approximately 4,616 cases globally.[2,4] Due to the low prevalence, studies on pituitary carcinoma are mostly limited to case series and literature reviews,[2,5] with fewer than 200 total cases reported in the English literature.[2]

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The prognosis of pituitary carcinoma is poor yet variable. The reported median survival ranges from 1 year for patients with systemic metastases versus 2.6 years for patients with metastases confined to the central nervous system.[2,5–8] There has been at least one report of a patient surviving 20 years with the disease.[9] Currently, there is no definitive consensus on the optimal treatment approach for pituitary carcinomas.[8,10] However, in 2017, the European Society of Endocrinology (ESE) published clinical practice guidelines for the management of pituitary carcinoma which suggested roles for surgery, radiation, and chemotherapy, namely, temozolomide, in specific disease contexts.[11]

Utilization of the National Cancer Database (NCDB) represents a unique opportunity to analyze population-level data for this rare tumor. Our results provide important descriptive information on demographics, treatment, and survival for this rare entity. Additionally, we describe overall survival (OS) as it relates to tumor behavior and treatment type, with the intention to improve selection of therapies, impact long-term survival, and better counsel patients.

Methods

Data were obtained from the NCDB for patients with tumors of the central nervous system diagnosed between 2004 and 2014. The NCDB is a hospital-based clinical oncology database sponsored by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It includes data from more than 1,500 commission accredited cancer programs and captures data from approximately 70% of newly diagnosed cancer cases in the United States (www.facs.org/quality%20programs/cancer/ncdb). The CoC's NCDB and the hospitals participating in the CoC, NCDB is the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. This study was determined to be exempt by the Institutional Review Board of the primary institution of the senior author.

The NCDB was queried for the primary site code for pituitary tumors (C751) and histology codes for adenoma or adenocarcinoma (8140, 8146, 8246, 8260, 8270, 8271, 8272, 8280, 8281, 8290, 8300, and 8323). To select cases of pituitary carcinoma, only patients with metastasis at the time of diagnosis were included in the study. To avoid confounding of different surgical procedures and ensure that the surgeries were on the primary site, cases were excluded if there was evidence of oncologic surgery at a distant site. The variables investigated included age, sex, race, Charlson's/Deyo's score, tumor size, margin status, primary site behavior code (0, "benign"–benign behavior or growing in place without potential for spread; or 3, "invasive"–invasion of surrounding tissues), and treatment modality. The Charlson's/Deyo's score was an abbreviated version of the Charlson's comorbidity score obtained from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) secondary diagnosis codes (0 corresponds to a Charleson's score of 0 or none of the conditions from the scoring map, 1 corresponds to a score of 1, and 2 corresponds to a score of 2 or greater). In the NCDB, margin status is obtained from the pathology report. "Negative margins" are when "all margins are grossly and microscopically negative." In this study, positive margins included "residual tumor, not otherwise specified (NOS)" (when "involvement is indicated but NOS"), "microscopic residual tumor" (when margins "cannot be seen by the naked eye"), and "macroscopic residual tumor" (when there is "gross tumor of the primary site which is visible to the naked eye").

The primary outcome of interest was OS (time from initial diagnosis to death from any cause). Descriptive statistics were calculated. Univariate analysis was performed using the Kaplan–Meier method and statistical significance evaluated using the log rank test. Cox's proportional hazard models were generated for multivariate comparison of OS outcomes using hazard ratios with corresponding 95% confidence intervals (CI). Covariates were selected a priori. Statistical analyses were performed with R v.3.4.1 (https://cran.r-project.org) via RStudio v. 1.1.23 (RStudio, Boston, MA, U.S.A.). A significance level of 0.05 was used for all tests.

Results

A total of 92 patients were identified in the NCDB as having a diagnosis of pituitary carcinoma. ►**Tables 1** and **2** detail the

Table 1 Demographics

Variable	No., %[a] ($n = 92$)
Age (y)	
≤54	46 (50.0)
55–64	20 (21.7)
65–74	15 (16.3)
≥74	11 (12.0)
Sex	
Male	56 (60.9)
Female	36 (39.1)
Race	
White	67 (72.8)
Black	15 (16.3)
Other	8 (8.7)
Asian	2 (2.2)
Ethnicity	
Non-Hispanic	81 (88.0)
Hispanic	8 (8.7)
Unknown	3 (3.3)
Charlson/Deyo score	
0	77 (83.7)
1	12 (13.0)
2	3 (3.3)

[a]Percentages may not be equal to 100% due to rounding.

Table 2 Disease and treatment characteristics

Variable	No., %[a] ($n = 92$)
Histology	
Pituitary adenoma/carcinoma, NOS (8272)	72 (78.3)
Adenoma/adenocarcinoma, NOS (8140)	13 (14.1)
Prolactinoma (8271)	4 (4.3)
Neuroendocrine adenoma/ carcinoma (8246)	2 (2.2)
Chromophobe adenoma/ carcinoma (8270)	1 (1.1)
Tumor behavior	
Benign (0)	79 (85.9)
Invasive (3)	13 (14.1)
Tumor margins	
Negative	21 (22.8)
Positive	9 (9.8)
No surgery or unknown	62 (67.4)
Tumor size (cm)	
< 1	13 (14.1)
1–2	13 (14.1)
2–3	19 (20.7)
3–4	12 (13.0)
4–5	7 (7.6)
5–6	2 (2.2)
> 6	1 (1.1)
Unknown	25 (27.2)
Treatment sequence	
Surgery alone	45 (48.9)
Surgery then radiation	5 (5.4)
Radiation alone	1 (1.1)
Other	4 (4.3)
No treatment	37 (40.2)

Abbreviation: NOS, not otherwise specified.
[a]Percentages may not be equal to 100% due to rounding.

various demographic, disease, and treatment variables included in this study. The average length of follow-up (from diagnosis to last contact or death) was 52.53 +/− 36.40 months. The mean time from diagnosis to treatment was 49.4 +/− 103.9 days. The majority of cases ($n = 79$, 85.9%) had benign behavior; the remaining 14.1% of patients ($n = 13$) had invasive behavior.

The 1-, 2-, and 5-year OS for all patients and those with behavior codes 0 (benign) and 3 (invasive) are displayed in ►**Fig. 1**. On univariate analysis, invasive behavior was associated with increased all-cause mortality (hazard ratio [HR], 4.58; 95% CI: 1.69–12.45). Multivariate analysis controlling for factors, such as age, tumor size, margins, and treatment, again demonstrated that invasive behavior was associated with worse OS compared with benign behavior (HR, 1,296; 95% CI: 15.1– > 2,000; ►**Table 3**).

The two most common primary treatments were surgery alone (48.9%) and no treatment (40.2%). The majority of patients did not receive radiation (90.2%) or chemotherapy (92.4%), either as an adjuvant therapy or alone. Compared with surgery alone, univariate analysis showed that 'other' treatment was associated with worse OS (HR, 7.11; 95% CI: 1.40–36.28; ►**Fig. 2**). On multivariate analysis, "other" treatment was not significantly associated with OS; however, "no treatment" demonstrated worse OS compared with surgery alone (HR, 11.83; 95% CI: 1.41–99.56; ►**Table 3)**. The numbers of patients for each treatment separated by tumor size are displayed in ►**Table 4**.

The types of radiation administered included external beam ($n = 1$), gamma knife ($n = 1$), intensity-modulated radiation therapy (IMRT; $n = 3$), and photon radiation ($n = 1$). There was no difference in OS for radiation type on univariate or multivariate analyses.

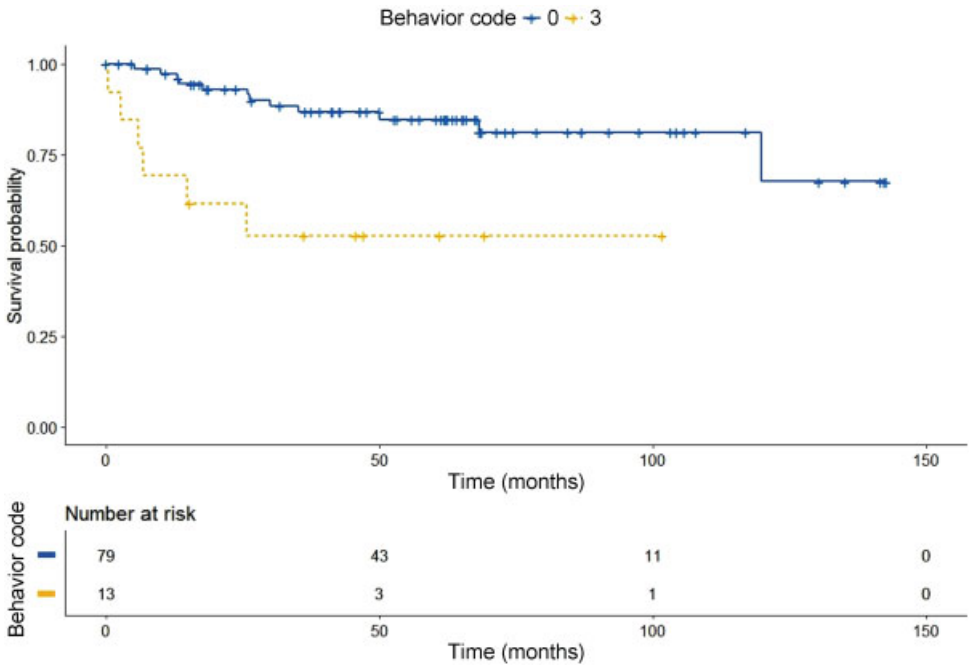
Tumor size and margins were not associated with OS on univariate or multivariate analyses. Although not significant on univariate analyses, increasing age and female sex were both associated with worse OS on multivariate analysis (HR, 1.07; 95% CI: 1.02, 1.31 and HR, 8.41; 95% CI: 1.60, 44.26; respectively).

Discussion

Existing literature suggests that pituitary carcinomas most often present in patients with pre-existing secretory pituitary macroadenomas,[2,3,12] the majority of which are of the prolactin and adrenocorticotrophic hormone (ACTH) subtypes.[3,13,14] The distinction between carcinoma and adenoma is not made pathologically[5]; instead, pituitary carcinoma is often suspected when an "adenoma" has multiple recurrences and is ultimately diagnosed clinically when there are metastases present, either to other locations within the central nervous system or outside the skull base and brain.[5,8,15] The average latency period from the diagnosis of a pituitary tumor to the presence of metastasis is 9 years.[14]

To our knowledge, the current study is the largest single study of pituitary carcinomas to date. The previous largest reported series included 15 pituitary carcinoma cases and demonstrated a poor 1-year OS of 34% and mean survival of 2 years.[5] A prior Surveillance, Epidemiology, and End Results (SEER) database analysis comparing invasive adenomas to pituitary carcinomas identified just seven patients with pituitary carcinoma with OS of 57.1, 28.6, and 28.6% at 1, 2, and 5 years, respectively[16]; however, the SEER study only included patients with behavior code 3 corresponding to the presence of invasive features. Here we demonstrate a higher OS for all patients and for the subset with invasive features (behavior code 3) with 1-, 2-, and 5-year OS's of 93.3, 88.5, and 80.0% and 69.2, 61.5, and 52.7%, respectively (►**Fig. 1**).

The current study included both benign and malignant pathology designations, corresponding to behavior codes 0



Percentage overall survival (OS) at 1, 2, and 5 y			
	1 y OS	2 y OS	5 y OS
All patients	93.3 (88.2–98.6)	88.5 (82.0–95.5)	80.0 (71.6–89.4)
Benign behavior	97.3 (93.8–100.0)	93.1 (87.5–99.1)	84.8 (76.4–94.1)
Invasive behavior	69.2 (48.2–99.5)	61.5 (40.0–94.6)	52.7 (31.2–89.2)

Fig. 1 Unadjusted Kaplan–Meier chart for overall survival of patients with pituitary carcinoma based on tumor behavior. OS, overall survival.

and 3, respectively. The worse OS associated with invasive behavior, though not surprising, reinforces the fact that tumors with the ability to infiltrate bone, dura mater, and critical neurovascular structures portend a worse prognosis, whether it be due to local destruction or damage at the metastatic site. At least one study demonstrated that for prolactinomas, extent of invasion and pathological classification was associated with tumor recurrence or progression as evidenced by persistently elevated prolactin levels after surgery.[17]

Although worsening of specific histologic features may be seen with the progression of adenoma to carcinoma, grading is not a reliable indicator of the malignant nature of pituitary carcinomas.[18] For this reason, grade was not included in our analysis of the NCDB, nor was it available in almost all cases (unknown in 91 of 92 cases). Ultimately, there is a need for better radiographic or cellular and molecular methods for determining which pituitary lesions possess the ability to metastasize, effectively allowing pituitary "carcinomas" to be identified, and successfully treated in their sellar phase.

Surgery, typically via a transsphenoidal approach, is the most common treatment for pituitary carcinomas. When there is extensive invasion and presence of metastases, surgery is often performed for palliative purposes and/or in conjunction with additional therapies.[6,8,16] Our results demonstrate that surgery alone was the most common treatment, followed by no treatment. It is not surprising that no treatment was associated with worse OS compared with surgery alone, as patients that do not undergo treatment may have more advanced disease deemed unresectable or have worse prognosis due to other comorbidities. The relative success of surgery suggested by the multivariate should therefore be interpreted with caution. Importantly, it is not possible to determine when surgery was performed without curative intent for palliation only. Furthermore, the database does not include comprehensive data on surgical techniques.

Radiation, usually employed for local control following subtotal resection, to slow growth, or for treatment of metastasis, has an unclear benefit in pituitary carcinoma treatment according to available literature.[5,8,13,15] For patients with metastasis at the time of diagnosis, we found that only a minority received surgery followed by radiation ($n = 5$) or radiation alone ($n = 1$). Interestingly, the one patient that received radiation alone had the highest OS. Additionally, the current study showed a HR for OS of 0.06 (< 0.01–1.91) for patients receiving surgery with radiation

Table 3 Predictors of all-cause mortality

Variable	Hazard ratio (95% confidence interval)	*p*-Value
Age (y)		
≤40	1	
> 40	1.07 (1.02–1.31)	0.01
Sex		
Male	1	
Female	8.41 (1.60–44.26)	0.01
Race		
White	1	
Black	2.26 (0.45–11.08)	0.33
Other/Unknown	0.67 (0.02–27.01)	0.83
Asian	–	–
Charlson's/ Deyo's score		
0	1	
1	2.62 (0.52–13.08)	0.24
2	–	–
Behavior		
Benign (0)	1	
Invasive (3)	1,296 (15.1– > 2,000)	< 0.01
Tumor margins		
Negative	1	–
Positive	0.03 (< 0.01–4)	0.17
No surgery or unknown	0.20 (0.01–3.38)	0.26
Treatment sequence		
Surgery alone	1	
Surgery then radiation	0.06 (< 0.01–1.91)	0.11
Radiation alone	–	–
Other	2.42 (0.13–46.92)	0.56
No treatment	11.83 (1.41–99.56)	0.02

compared with surgery alone. It is plausible that a study with higher power would demonstrated greater efficacy with radiation treatment alone or as an adjunct to surgery. Furthermore, differences between radiation types could not be elucidated due to the small number of patients who received radiation. Similarly, the use of chemotherapy, reported in some studies to have limited efficacy for pituitary carcinoma,[6,15] was only utilized in three cases in this study. Recent work investigating the use of temozolomide, an alkylating chemotherapeutic drug, has demonstrated complete tumor regression in at least five patients[11,19]; therefore, temozolomide monotherapy is now recommended by the ESE as the first-line chemotherapy for pituitary carcinomas with tumor growth.[11]

The majority of cases in this study were pituitary adenoma/carcinoma, NOS (8272, $n = 72$) and adenoma/adenocarcinoma, NOS (8140, $n = 13$); there were four cases of prolactinoma (8271; ►**Table 2**). The NCDB does not include comprehensive data regarding hormone secretion which is important because there is reported variation in survival between the different tumor subtypes.[5,9] Additionally, medical treatment of secretory pituitary carcinomas with neurohormonal agents, such as dopamine agonists and somatostatin analogues, is often recommended for reduction of tumor burden and disease control.[8,11,20] The NCDB does not explicitly report the use of such agents and it is uncertain if neurohormonal treatment is categorized as "other" treatment in the NCDB.

No definitive gender predominance or difference in survival has been reported for pituitary carcinomas.[16,21] The SEER study reported improved OS for females compared with males for invasive pituitary adenomas but did not have enough patients to perform statistical analysis of OS for carcinomas as it relates to gender.[16] One analysis of prolactinomas demonstrated that males had lower expression of estrogen receptor α and worse OS, possibly due to resistance to medical treatment.[22] In the current study, we demonstrate an 8-fold increase in mortality for female gender, suggesting that the impact of gender on carcinoma biology and treatment response may be distinctly different from that seen with adenomas.

The current study included the subset of pituitary carcinoma patients that presented with metastases and intended to exclude patients that may have later been diagnosed with pituitary carcinoma after metastases were identified. A patient with a tumor initially diagnosed as a pituitary adenoma which later underwent malignant degeneration and metastasized to become a pituitary carcinoma should have been excluded from our analysis, as the NCDB captures tumor data at the time of initial presentation. Importantly, the NCDB also does not report data regarding tumor recurrences and only includes the first course of treatment administered.[23] For this reason, repeated surgery or use of additional modalities for recurrences would likely not be included in the treatment data but could impact OS in the NCDB cohort.

The results presented in this study are valuable for improving our understanding of pituitary carcinoma and providing more accurate prognostic information to our patients. There are several limitations to the current study and thus, caution must be exercised when using the results for clinical decision-making and selection of treatment. The NCDB does not include all clinically relevant variables, some of which are important for determining if patients are candidates for specific types of therapy. Furthermore, there is no disease-specific survival reported, making it impossible to determine if patients died from the tumor or other causes.

Conclusions

Pituitary carcinoma is an extremely rare tumor type and there is limited data for advising patients and selecting

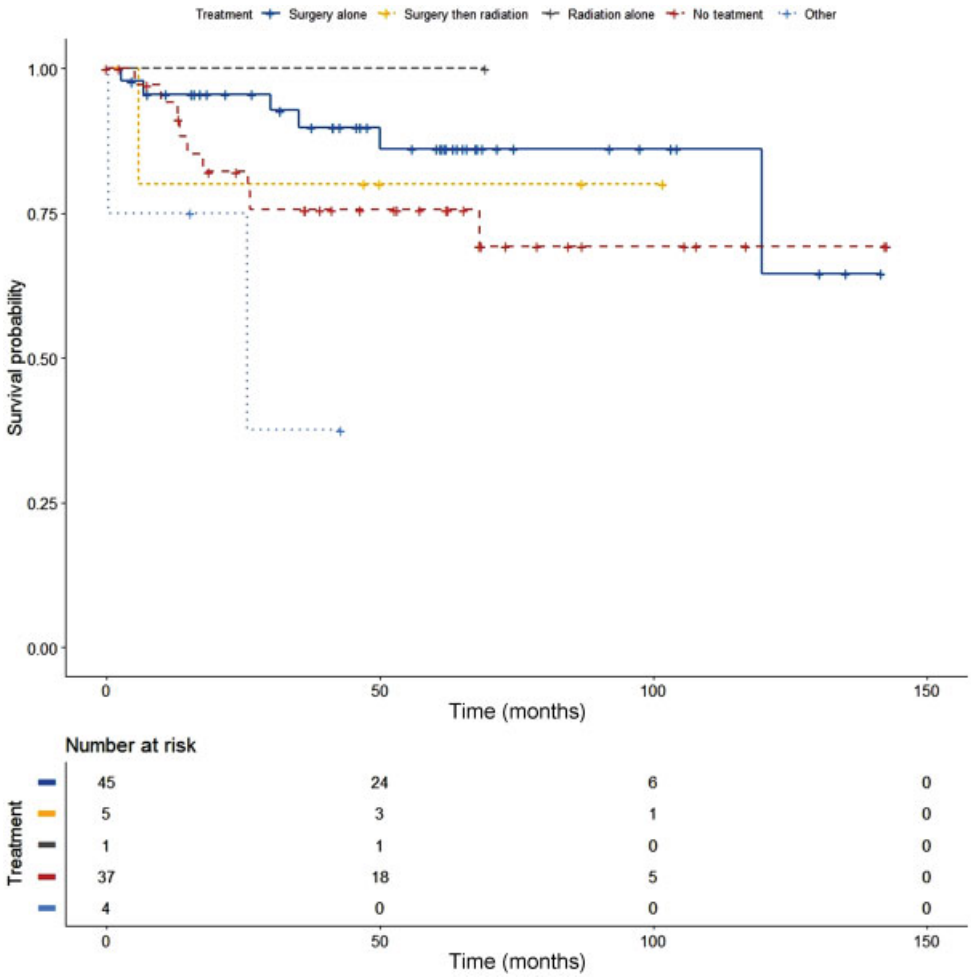


Fig. 2 Unadjusted Kaplan–Meier chart for overall survival of patients with pituitary carcinoma based on treatment received.

Table 4 Treatment by tumor size (No., %)

	< 1 cm (%)	1–2 cm (%)	2–3 cm (%)	3–4 cm (%)	4–5 cm (%)	5–6 cm (%)	> 6 cm (%)	Unknown
Surgery alone	1 (7.7)	7 (53.8)	11 (57.9)	8 (66.7)	5 (71.4)	–	–	13 (52.0)
Surgery then radiation	–	–	1 (5.3)	–	1 (14.3)	1 (50.0)	–	2 (8.0)
Radiation alone	–	–	–	–	–	–	–	1 (4.0)
Other	–	–	–	1 (8.3)	–	–	–	3 (12.0)
No treatment	12 (92.3)	6 (46.2)	7 (36.8)	3 (25.0)	1 (14.3)	1 (50.0)	1 (100.0)	6 (24.0)

therapies. This study utilized the population-level data of the NCDB to improve our understanding of pituitary carcinoma prognosis. We demonstrated that no treatment and invasive behavior are both associated with worse OS. Ultimately, prospective, multi-institutional studies are necessary to determine the ideal strategy for treating this elusive tumor. Improved diagnostic techniques for distinguishing pituitary carcinoma from adenomas and predicting malignant transformation prior to metastasis would improve local control and survival.

Financial Disclosure
None.

Conflicts of Interest
None.

References

1 Scheithauer BW, Kovacs KT, Laws ER Jr, Randall RV. Pathology of invasive pituitary tumors with special reference to functional classification. J Neurosurg 1986;65(06):733–744
2 Heaney AP. Clinical review: pituitary carcinoma: difficult diagnosis and treatment. J Clin Endocrinol Metab 2011;96(12):3649–3660
3 Kontogeorgos G. Classification and pathology of pituitary tumors. Endocrine 2005;28(01):27–35
4 Daly AF, Tichomirowa MA, Beckers A. The epidemiology and genetics of pituitary adenomas. Best Pract Res Clin Endocrinol Metab 2009;23(05):543–554
5 Pernicone PJ, Scheithauer BW, SeboTJ, et al. Pituitary carcinoma: a clinicopathologic study of 15 cases. Cancer 1997;79(04):804–812
6 Kaltsas GA, Grossman AB. Malignant pituitary tumours. Pituitary 1998;1(01):69–81
7 Scheithauer BW, Kurtkaya-Yapicier O, Kovacs KT, Young WF Jr, Lloyd RV. Pituitary carcinoma: a clinicopathological review. Neurosurgery 2005;56(05):1066–1074, discussion 1066–1074
8 Kaltsas GA, Nomikos P, Kontogeorgos G, Buchfelder M, Grossman AB. Clinical review: diagnosis and management of pituitary carcinomas. J Clin Endocrinol Metab 2005;90(05):3089–3099
9 Landman RE, Horwith M, Peterson RE, Khandji AG, Wardlaw SL. Long-term survival with ACTH-secreting carcinoma of the pituitary: a case report and review of the literature. J Clin Endocrinol Metab 2002;87(07):3084–3089
10 Touma W, Hoostal S, Peterson RA, Wiernik A, SantaCruz KS, Lou E. Successful treatment of pituitary carcinoma with concurrent radiation, temozolomide, and bevacizumab after resection. J Clin Neurosci 2017;41:75–77
11 Raverot G, Burman P, McCormack A, et al; European Society of Endocrinology. European Society of Endocrinology clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas. Eur J Endocrinol 2018;178(01):G1–G24
12 Roncaroli F, Scheithauer BW, Young WF, et al. Silent corticotroph carcinoma of the adenohypophysis: a report of five cases. Am J Surg Pathol 2003;27(04):477–486
13 Ragel BT, Couldwell WT. Pituitary carcinoma: a review of the literature. Neurosurg Focus 2004;16(04):E7
14 Yoo F, Kuan EC, Heaney AP, Bergsneider M, Wang MB. Corticotrophic pituitary carcinoma with cervical metastases: case series and literature review. Pituitary 2018;21(03):290–301
15 Kaltsas GA, Mukherjee JJ, Plowman PN, Monson JP, Grossman AB, Besser GM. The role of cytotoxic chemotherapy in the management of aggressive and malignant pituitary tumors. J Clin Endocrinol Metab 1998;83(12):4233–4238
16 Hansen TM, Batra S, Lim M, et al. Invasive adenoma and pituitary carcinoma: a SEER database analysis. Neurosurg Rev 2014;37(02):279–285, discussion 285–286
17 Raverot G, Wierinckx A, Dantony E, et al; HYPOPRONOS. Prognostic factors in prolactin pituitary tumors: clinical, histological, and molecular data from a series of 94 patients with a long postoperative follow-up. J Clin Endocrinol Metab 2010;95(04):1708–1716
18 Scheithauer BW, Fereidooni F, Horvath E, et al. Pituitary carcinoma: an ultrastructural study of eleven cases. Ultrastruct Pathol 2001;25(03):227–242
19 Bengtsson D, Schrøder HD, Andersen M, et al. Long-term outcome and MGMT as a predictive marker in 24 patients with atypical pituitary adenomas and pituitary carcinomas given treatment with temozolomide. J Clin Endocrinol Metab 2015;100(04):1689–1698
20 Bode H, Seiz M, Lammert A, et al. SOM230 (pasireotide) and temozolomide achieve sustained control of tumour progression and ACTH secretion in pituitary carcinoma with widespread metastases. Exp Clin Endocrinol Diabetes 2010;118(10):760–763
21 Lenders N, McCormack A. Malignant transformation in nonfunctioning pituitary adenomas (pituitary carcinoma). Pituitary 2018;21(02):217–229
22 Delgrange E, Vasiljevic A, Wierinckx A, et al. Expression of estrogen receptor alpha is associated with prolactin pituitary tumor prognosis and supports the sex-related difference in tumor growth. Eur J Endocrinol 2015;172(06):791–801
23 In H, Bilimoria KY, Stewart AK, et al. Cancer recurrence: an important but missing variable in national cancer registries. Ann Surg Oncol 2014;21(05):1520–1529