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Factors Associated with and Temporal Trends in the Use of Radiation Therapy for the Treatment of Pituitary Adenoma in the National Cancer Database

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Abstract

Objective Radiation therapy represents an uncommon but important component of treatment plans for some pituitary adenomas (PAs). Although radiation therapy has been used to treat pituitary adenomas for over a century, general trends in the usage of radiation therapy for this purpose have not been reviewed. Additionally, there are few large studies evaluating how radiation therapy is used for the treatment of these benign tumors. Investigating these trends and identifying any variations in radiation therapy utilization would help to better inform treatment decisions and improve patient outcomes.
Design Present study is a retrospective analysis of cases using the National Cancer Database.
Setting The research was organized at a tertiary academic medical center.
Participants Patients were diagnosed with pituitary adenoma between 2004 and 2014 within the National Cancer Database (NCDB).
Methods Temporal trends in the usage of radiation therapy to treat pituitary adenoma were analyzed through a retrospective analysis of 77,142 pituitary adenoma cases from the NCDB between 2004 and 2014. Univariate and multivariate analyses were to examine the relationship between patient, tumor, and treatment factors, and the incorporation of radiation therapy into the treatment of pituitary adenomas. We adjusted for potential confounders such as age, sex, race, comorbidity score, facility type, and year of diagnosis.

Keywords
- radiation therapy
- pituitary adenoma
- national cancer database
- temporal trends
- radiation
- watchful waiting
- skull base
- anterior skull base

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Results A total of 77,142 patients met inclusion criteria. Inclusion of radiation therapy in pituitary adenoma treatment was 8.0% in 2004 and steadily declined to a low of 3.1% in 2014. Overall, patients were less likely to receive radiation for their pituitary adenoma over time ($p < 0.001$). Similarly, patients were found to be less likely to receive any type of treatment for PA over time ($p < 0.001$). Multivariable evaluation found patients who were female, between 54 and 64 years of age, or treated at either a Comprehensive Community Cancer Program or an Integrated Network Cancer Program were more likely to receive radiation as part of their pituitary adenoma treatment ($p < 0.001$, odds ratio [OR] = 2.01, confidence interval [CI]: 1.54–2.63; $p < 0.001$, OR = 1.84, CI: 1.38–2.44, respectively). Patients were less likely to receive radiation for their PA if they were African American ($p < 0.001$, OR = 0.81, CI: 0.72–0.91). Logistic regression also identified a progressive increase in the likelihood of receiving radiation after a PA diagnosis with increasing tumor size starting with microscopic tumors, peaking at 4 to 5 cm ($p < 0.001$; OR = 15.57; CI: 12.20–19.87).

Conclusion In this sample of pituitary adenoma patients treated at NCDB institutions between 2004 and 2014, we found a steady decline in the incorporation of radiation therapy in treatment, as well as in the use of any type of intervention for PA treatment, suggesting a rise in noninterventional observation of PA.

Introduction

Pituitary adenomas (PAs) are benign tumors that arise from the anterior pituitary gland. They represent between 10 and 20% of all primary brain tumors.[1,2] These tumors can present in a variety of fashions; they may be discovered due to oversecretion of pituitary hormones or due to nonspecific symptoms arising due to a mass effect. Increasingly, they are incidentally identified in imaging studies, in which case they are commonly referred to as "incidentalomas."

Radiation therapy has played a central role in the treatment of PA for over a century, with Dr. Harvey Cushing outlining his then-revolutionary approach to treatment in his 1912 *The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*.[3] Because of their size and location, pituitary adenomas are often difficult to resect surgically, and radiation therapy continues to be a common component of treatment plans for PA today.

Specifically, the standard primary treatment for all pituitary adenomas except for prolactinoma is surgery, with radiation being used for recurrent tumors or in cases where surgery may be risky (e.g., carotid or optic nerve encasement). Radiation treatment can be delivered via stereotactic radiosurgery (SRS) or fractionated radiation therapy (FRT). Furthermore, radiation offers local control rates between 90 and 100% for all types of PA, as well as biochemical complete response rates of approximately 50%, which is augmented by the addition of medical therapies.[4]

With increased use and quality of imaging technologies, the diagnosis of PA has been increasing, and recent studies have reported its prevalence to be higher than previously believed. Unfortunately, due to a lack of mandatory reporting, prior studies using cancer registries, such as the Swedish National Cancer Registry, the Brain Tumor Registry of Japan, and the Central Brain Tumor Registry of the United States have been limited by under-reporting and consequently, unreliable or unrepresentative data.[5–9] Due to this paucity of reliable, high-quality, large-volume studies, we are limited in our epidemiological understanding of PA, as well as our knowledge of trends in the use of radiation therapy to treat PA.[10,11]

Estimates from a 2004 meta-analysis of radiologic and autopsy studies predict that pituitary adenomas are present in approximately 16.7% of the general population.[10] Studies on macroadenomas have estimated a prevalence between 0.16 to 0.3%.[12–15]

Although ionizing radiation is commonly used in medical treatment of pituitary adenomas and indications for its integration into a treatment regimen have been outlined,[4] utilization of the treatment modality remains highly influenced by physician preference, and trends of radiation treatment for pituitary adenomas remain poorly characterized. Here, we analyze the NCDB database to identify temporal trends in the utilization of radiation therapy in the treatment of pituitary adenomas.

Methods

Data Source

Data were obtained from the NCDB on November 7, 2017 for patients with tumors of the head and neck diagnosed between 2004 and 2012. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, and data are collected from over 1,500 commission-accredited cancer programs representing approximately 30% of all hospitals in the United States and more than 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 are the source of the deidentified data used herein; however, 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 Hospital of the University of Pennsylvania.

Study Population

Using the ICD-O-3 (International Classification of Diseases for Oncology, third ed.), the NCDB was queried for tumors of the pituitary gland (location code: C75.1) with histology codes corresponding to pituitary adenomas (8140, 8146, 8260, 8270, 8271, 8272, 8280, 8281, 8290, 8300, and 8323). Cases that lacked values for either follow-up or vital status or that had a record of surgery at a distant site were excluded.

Variables Analyzed

The demographic and tumor variables analyzed included patient age at diagnosis, race, sex, medical comorbidities (Charlson–Deyo score, outlined in ►**Table 1**), treatment facility type and tumor size. Race was categorized into White, Black, Asian, or other. Ethnicity was categorized as Hispanic or non-Hispanic. Treatment facility type was categorized as follows: facility type was classified using the following method: community cancer program (100–500 newly diagnosed cancer cases per year), comprehensive community cancer program (>500 newly diagnosed cancer cases per year), academic cancer program (>500 newly diagnosed cancer cases per year and at least four postgraduate medical education programs), or integrated network cancer program (owns, operates, leases, or is part of a joint venture with multiple facilities providing integrated cancer care and offers comprehensive services).

Statistical Analysis

The primary outcome of interest for this study was the incorporation of radiation therapy of any type into treatment for pituitary adenoma, with a secondary endpoint being the type of radiation therapy used. Pearson's Chi-square tests were utilized for categorical variables and Mann–Whitney tests were used for continuous variables. Excluding cases lacking complete information, a multiple logistic regression model was performed to determine the independent factors associated with receipt of radiation for the treatment of pituitary adenoma. Variables included in the final multivariable Cox's proportional hazard model were age, sex, race, comorbidity score, facility location, tumor size, and year of diagnosis. The results were expressed as an odds ratio (OR) and a 95% confidence interval (CI). All data processing and analysis were performed with Microsoft Open R v. 3.3.2 (*https://mran.microsoft.com/open/*) via RStudio v.1.1.23 (RStudio, Boston, Massachusetts, United States).

Table 1 Charlson–Deyo comorbidity score

Score	Condition
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Dementia Cerebrovascular disease Chronic lung disease Connective tissue disease Peptic ulcer disease Chronic liver disease Diabetes
2	Diabetes with chronic complications Hemiplegia or paraplegia Renal disease
3	Moderate or severe liver disease

Note: scores are summed for each patient and categorized by a value of 0, 1, 2, or 3 or more. A zero score means that a patient did not have any of the conditions listed in the table.

Results

Demographics of Pituitary Adenoma in the United States

A total of 80,287 cases of pituitary adenoma were identified in the NCDB, with 77,142 meeting the inclusion criteria. The number of cases of PA diagnosed per year increased from 4,410 in 2004 to 8,574 in 2014. ►**Table 2** outlines the demographic distribution of patients. The mean age at diagnosis was 50.88 years (standard deviation [SD] = 18.06), and 53.9% of patients were female. Notably, the average age of men at diagnosis was older than that of women (54.9 vs. 47.5, $p < 0.001$). The most commonly reported race was White (73.7%). 36.6% of the patients received care in an academic program and the majority had a Charlson–Deyo comorbidity score of 0 (80.5%).

Trends in Radiation Therapy for Pituitary Adenomas

Over the 10-year study period, 3,457 of the 77,142 patients (4.48%) underwent radiation for their pituitary adenoma. While the proportion of patients receiving radiation peaked at 8.0% in 2004, this proportion declined to 3.1% in 2014 ($p < 0.001$). This decline was still significant after controlling for patient, tumor, and treatment attributes. There was also a significant decrease in the overall treatment of pituitary adenoma during this time period, with 64.8% of patients receiving some sort of treatment in 2004 and 53.5% undergoing treatment for their pituitary adenoma in 2014 ($p < 0.001$; ►**Fig. 1** and ►**Table 3**).

The second primary endpoint of this study was the radiation modality employed to treat pituitary adenoma. Information regarding the type of radiation administered to patients was available for 3,439 cases, constituting 99.5% of the patients who received radiation for PA. Overall, the most commonly used radiation modality during the study period was External Beam Radiation Therapy (EBRT) which was utilized for 63.1% of these. Similar to the proportion of patients receiving radiation, the distribution in types of radiation used also shifted over the 10 years analyzed in this study (►**Fig. 2** and ►**Table 4**). In 2004, EBRT was used for 69.4% of cases, significantly declining to 60.5% of cases in 2014 ($p = 0.027$). Stereotactic radiosurgery, on the other

Table 2 Patient and tumor characteristics of 77,142 cases of PA in the NCDB

	n	%
Age (y)		
< 54	43,356	56.2
54–64	14,187	18.4
64–74	11,543	15.0
74–100	8,046	10.4
Gender		
Male	35,577	46.1
Female	41,565	53.9
Race		
White/Caucasian	56,855	73.7
African American	14,678	19
Asian	2,638	3.4
Other/unknown	2,970	3.9
Ethnicity		
Hispanic	8,194	10.6
Non-Hispanic	64,990	84.2
Unknown	3,958	5.1
Facility type		
Academic/research	28,213	36.6
CCC	17,185	22.3
Integrated network	7,011	9.1
Community	2,454	3.2
Charlson–Deyo		
0	62,101	80.5
1	11,542	15.0
2	2,532	3.3
3	967	1.3
Tumor size		
< 1 cm	16,935	22.0
1–2 cm	16,815	21.8
2–3 cm	15,715	20.4
3–4 cm	7,080	9.2
4–5 cm	2,472	3.2
5–6 cm	884	1.1
> 6 cm	1,324	1.7

Abbreviations: CCC, community cancer center; NCBD, national cancer database; PA, pituitary adenoma.

hand, was used for 30.0% of cases in 2004 but was employed for 39.5% of cases in 2014 ($p = 0.018$).

Factors Associated with Radiation Therapy for Pituitary Adenoma

Overall, 3,457 patients (4.5%) received radiation therapy as part of their initial treatment for their PA. Mean time from diagnosis to the initiation of radiation was 154 days with a standard deviation of 192 days. Median time from diagnosis to radiation was 119 days with interquartile range of 117 days.

A multivariable logistic regression model for the factors associated with receiving radiation was conducted for the 61,225 patients with complete data and is shown in ►**Table 5** and ►**Fig. 3**. Over time, patients were significantly less likely to receive radiation for their PA ($p < 0.001$). Additionally, females were more likely to receive radiation than males ($p < 0.001$, OR = 1.24, CI: 1.14–1.37). Compared with patients under 54 years of age, patients between 54 and 64 years old were more likely to receive radiation ($p < 0.001$, OR = 1.19, CI: 1.06–1.33).

Relative to White patients, African American patients were less likely to receive radiation ($p < 0.001$, OR = 0.81, CI: 0.72-.91). Patients with macroadenomas (>1 cm in size) were significantly more likely to receive radiation than patients with microadenomas ($p < 0.001$).

Patients who were treated at a Comprehensive Community Cancer Program or an Integrated Network Cancer Program were more likely to receive radiation for their PA than patients treated at a Community Cancer Program ($p < 0.001$, OR = 2.01, CI: 1.54–2.63; $p < 0.001$, OR = 1.84, CI: 1.38–2.44, respectively).

With regard to tumor size, the logistic regression identified a progressive increase in the likelihood of receiving radiation after a PA diagnosis with increasing tumor size starting with microscopic tumors, peaking at 4 to 5 cm ($p < 0.001$; OR = 15.57; CI: 12.20–19.87), and then progressively decreasing with tumors beyond that size. Extending the multivariable model to consider factors associated with receiving any type of treatment for PA identified a similar pattern, with a slightly shifted peak corresponding to tumor sizes between 3 and 4 cm ($p < 0.001$; OR = 5.12; CI: 4.72–5.56; ►**Table 6**).

Discussion

Pituitary adenoma is a relatively common, benign tumor of the anterior pituitary gland, and it has an extensive history of advances in its treatment and outcomes. It is also among the first benign tumor types to be treated primarily with radiation, and as more PA patients are treated with radiation, there is a growing population of individuals with prior pituitary irradiation who may suffer from potential late toxicities of such radiation. However, despite the longstanding relationship between PA and radiation, we lack a comprehensive understanding of actual rates of radiation utilization for PA treatment, as well as the factors that influence this relationship. This is largely due to limitations of prior studies on the subject, which include under-reporting, short-study periods, or relatively small sample sizes.[8] Greater information on these management patterns could inform the development of more standardized and reliable national treatment guidelines which would prevent potentially detrimental variation in the quality or intensity of treatment plans across the country.

This study represents the largest review of trends in the management of PA in the United States, to date and to our knowledge, the first to use the NCDB to do so, as well as the first to describe temporal patterns, in the use of radiation therapy for all types of PA. Using the NCDB, we were able to

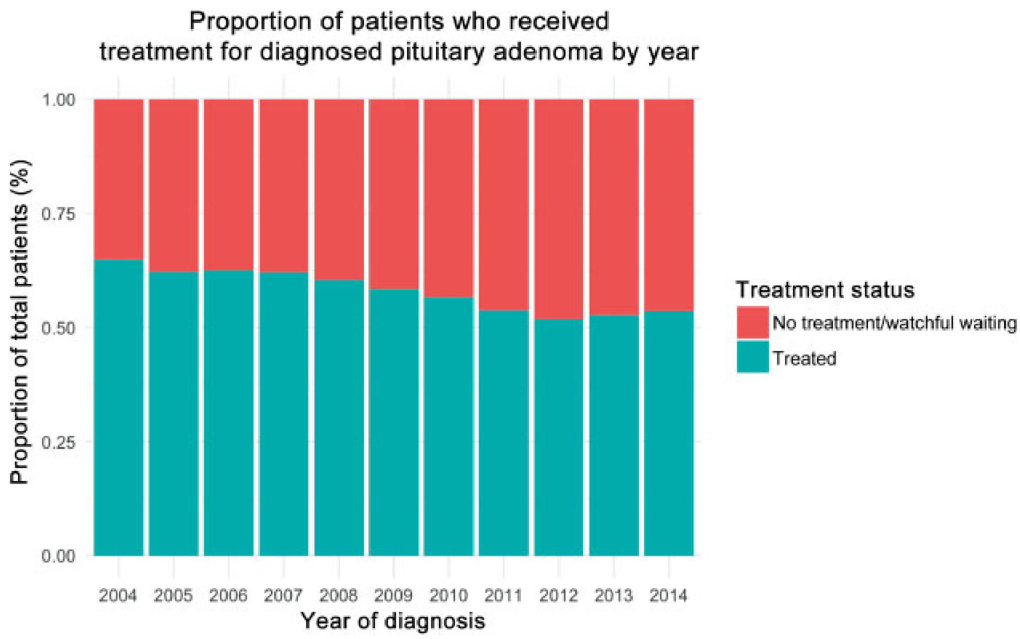

Fig. 1 Distribution of pituitary adenoma patients who were treated with medical, surgical, or radiation therapy or watchful waiting between 2004 and 2014.

Table 3 Distribution of pituitary adenoma patients who were treated with medical, surgical, or radiation therapy or watchful waiting between 2004 and 2014

	level	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
n		4,294	5,036	5,550	6,109	6,623	7,426	7,540	7,942	8,600	8,605	8,537
Treated status (%)	No treatment/ watchful waiting	1,510 (35.2)	1,899 (37.7)	2,082 (37.5)	2,314 (37.9)	2,622 (39.6)	3,096 (41.7)	3,276 (43.4)	3,671 (46.2)	4,141 (48.2)	4,075 (47.4)	3,966 (46.5)
n (%)	Treated	2,784 (64.8)	3,137 (62.3)	3,468 (62.5)	3,795 (62.1)	4,001 (60.4)	4,330 (58.3)	4,264 (56.6)	4,271 (53.8)	4,459 (51.8)	4,530 (52.6)	4,571 (53.5)

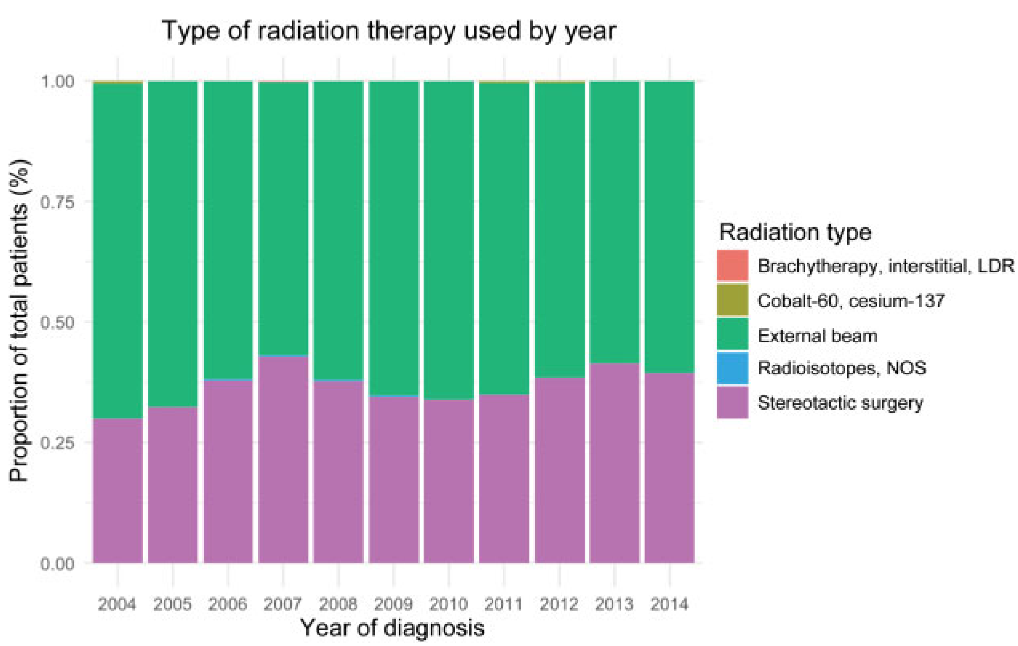

Fig. 2 Distribution of radiation therapy modality utilized for 3,439 cases of pituitary adenoma between 2004 and 2014. NOS, not otherwise specified.

Table 4 Radiation therapy modality usage over time for 3,439 cases with available data in the NCDB

		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
n		350	313	330	360	368	339	281	283	283	266	266
Radiation type (%)	Brachytherapy, interstitial, LDR	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cobalt-60, cesium-137	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
	External beam	243 (69.4)	212 (67.7)	204 (61.8)	204 (56.7)	228 (62.0)	221 (65.2)	186 (66.2)	183 (64.7)	173 (61.1)	156 (58.6)	161 (60.5)
	Radioisotopes, NOS	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stereotactic surgery	105 (30.0)	101 (32.3)	125 (37.9)	154 (42.8)	139 (37.8)	117 (34.5)	95 (33.8)	99 (35.0)	109 (38.5)	110 (41.4)	105 (39.5)

Abbreviations: LDR, low dose rate; NCBD, national cancer database.

Table 5 Factors associated with likelihood of receiving radiation after PA diagnosis

	OR	95%CI	p-Value
Year of diagnosis			
2004	1	Reference	–
2005	**0.84**	**0.68–1.05**	**0.13**
2006	**0.80**	**0.64–0.99**	**0.039**
2007	**0.78**	**0.62–0.97**	**0.023**
2008	**0.76**	**0.62–0.94**	**0.010**
2009	**0.66**	**0.54–0.82**	**<0.001**
2010	**0.51**	**0.41–0.63**	**<0.001**
2011	**0.48**	**0.39–0.60**	**<0.001**
2012	**0.43**	**0.35–0.53**	**<0.001**
2013	**0.40**	**0.32–0.49**	**<0.001**
2014	**0.40**	**0.32–0 0.50**	**<0.001**
Age (y)			
< 4	1	Reference	–
54–64	**1.19**	**1.06–1.33**	**0.002**
64–74	1.11	0.98–1.26	0.089
74–100	0.92	0.79–1.06	0.25
Gender			
Male	1	Reference	–
Female	**1.24**	**1.14–1.37**	**<0.001**
Tumor Size (cm)			
< 1	1	Reference	–
1–2	**3.14**	**2.5–3.94**	**<0.001**
2–3	**5.22**	**4.2–6.50**	**<0.001**
3–4	**9.31**	**7.45–11.66**	**<0.001**
4–5	**15.57**	**12.20–19.87**	**<0.001**
5–6	**13.63**	**9.97–18.66**	**<0.001**
> 6	**7.41**	**5.36–10.27**	**<0.001**
Race			
White/Caucasian	1	Reference	–
African American	**0.81**	**0.72–0.91**	**<0.001**
Asian	0.97	0.76–1.23	0.80
Other/unknown	0.81	0.61–1.06	0.12
Facility type			
Community	1	Reference	–
CCC	**2.01**	**1.54–2.63**	**<0.001**
Integrated network	**1.84**	**1.38–2.44**	**<0.001**
Academic/research	1.23	0.94–1.61	0.13
Charlson–Deyo			
0	1	Reference	–
1	0.93	0.83–1.05	0.23
2	0.80	0.63–1.01	0.06
3	**0.49**	**0.30–0.78**	**0.003**

Abbreviations: CCC, comprehensive community cancer program; CI, confidence interval; OR, odds ratio.
Note: Bold rows represent a significant difference the $p < 0.05$ level.

identify several factors that predict the use of radiation therapy for PA treatment, as well as general trends, in the utilization of radiation therapy for PA.

We observed an increasing incidence of PA during the time period. This finding is in line with similar observations reported in other studies.[5] As suggested by others, this increase is likely due to improvements in imaging modalities and diagnostic techniques, which would result in a higher rate of incidentally identified PAs, or "incidentalomas." With additional institutions reporting to the NCDB over time, this could also account for increased numbers of documented PA cases each year. The increase in the reported number of PAs is also likely a result of additional reporting centers joining the

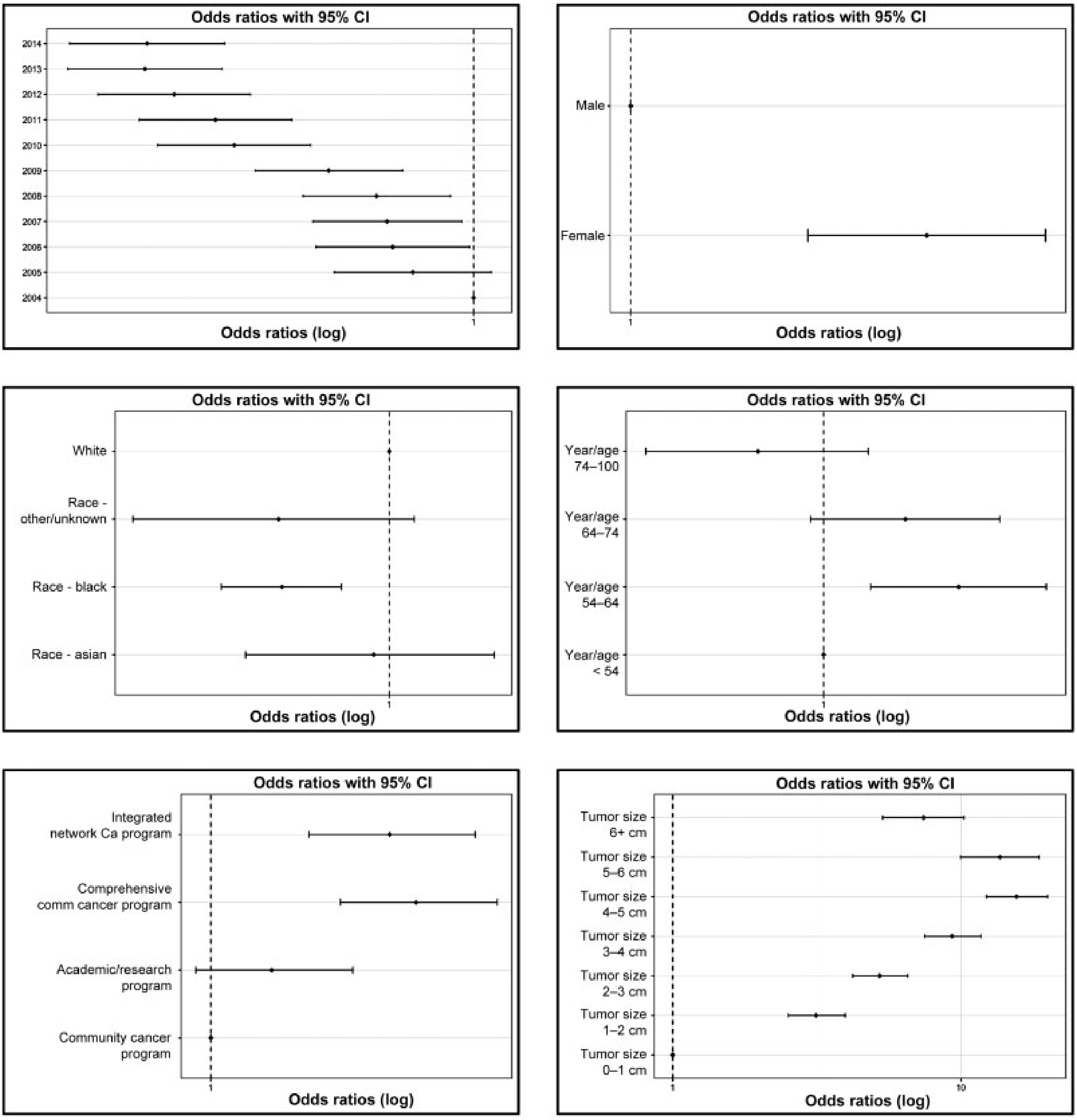

Fig. 3 Probability of receiving radiation therapy for pituitary adenoma in a multivariable model. CI, confidence interval.

NCDB each year. With more sites participating in the database, more cases could be captured and reported each year, resulting in an apparent increase in the number of overall cases per year over time.

With regard to its utilization for PA treatment, radiation therapy experienced a significant decline between 2004 and 2014. More generally, patients with PA were also found to be increasingly less likely to receive any type of treatment over time. These findings may be the result of several potential mechanisms. First, as diagnostic modalities improve and a greater number of adenomas are identified incidentally, without any associated symptoms or potentially harmful hormone release, a rise in the number of unsymptomatic PAs that are managed conservatively may underlie the overall lower rate of PAs that receive some sort of treatment.[5] Alternatively, as the natural history of PAs is better understood over time, there may be a rise in "watchful waiting," or noninterventional monitoring of PAs, which may not progress in a clinically significant fashion or may be in a location that poses a high perioperative risk.[16] A recent study on the natural history of clinically nonfunctioning pituitary incidentalomas reported a tumor growth rate of only 4% in the year following the incidental diagnosis, supporting the practice of noninterventional monitoring of such tumors.[17] Similarly, because of the potential long-term effects of radiation and the strong association of hypopituitarism following

Table 6 Factors associated with likelihood of receiving any type of treatment (medical, surgical, and radiation) after PA diagnosis

	OR	95% CI	*p*-Value
Year of diagnosis			
2004	1	Reference	–
2005	0.93	0.81–1.07	0.328
2006	0.92	0.91–1.06	0.251
2007	0.99	0.87–1.13	0.889
2008	0.96	0.84–1.09	0.541
2009	0.93	0.82–1.05	0.258
2010	0.84	0.74–0.95	0.006
2011	0.83	0.74–0.94	0.004
2012	0.83	0.74–0.94	0.003
2013	0.87	0.77–0.98	0.022
2014	0.93	0.82–1.05	0.23
Age (y)			
< 54	1	Reference	–
54–64	0.86	0.81–0.91	<0.001
64–74	0.63	0.59–0.67	<0.001
74–100	0.25	0.24–0.27	<0.001
Gender			
Male	1	Reference	–
Female	0.93	0.89–0.97	0.001
Tumor size (cm)			
< 1	1	Reference	–
1–2	3.51	3.29–3.74	<0.001
2–3	9.36	8.74–10.02	<0.001
3–4	16.28	14.87–17.82	<0.001
4–5	16.98	14.74–19.56	<0.001
5–6	8.47	6.96–10.30	<0.001
> 6	4.30	3.69–5.02	<0.001
Race			
White/Caucasian	1	Reference	–
African American	0.68	0.64–0.72	<0.001
Asian	0.97	0.86–1.11	0.732
Other/unknown	0.79	0.69–0.89	<0.001
Facility type			
Community	1	Reference	–
CCC	2.95	2.63–3.31	<0.001
Integrated network	4.44	3.92–5.03	<0.001
Academic/research	5.82	5.20–6.51	<0.001
Charlson–Deyo			
0	1	Reference	–
1	1.41	1.33–1.50	<0.001
2	0.99	0.88–1.10	0.785
3	0.48	0.40–0.57	<0.001

Abbreviations: CCC, comprehensive community cancer program; CI, confidence interval; OR, odds ratio; PA, pituitary adenoma.

pituitary radiation, there has been a call for more conservative management of PA with endocrinological surveillance.[4]

With regards to the type of radiation used, there was a decline in the use of EBRT over time, with a simultaneous rise in the rates of use of SRS for PA treatment. As SRS only requires a single-radiation session, it is a more convenient option for patients. Furthermore, it has been found to have equivalent efficacy and safety when compared with EBRT.[4,18–20] However, prior studies have identified a substantially lower risk of damage to the optic pathway with EBRT relative to SRS.[21,22] Further studies have demonstrated that these detrimental effects are the result of doses above 8 to 10 Gy delivered in a single dose to optic pathway structures,[23,24] suggesting that EBRT should be utilized in place of SRS in cases where an adenoma is proximal to the optic pathway, thereby increasing the risk of damage. Together, these features support the use of SRS in place of EBRT for the treatment of PA when the tumor is not in a location that would involve a risk of high doses of radiation to the optic pathway.

Overall, this analysis identifies several factors that are associated with the use of radiation therapy as part of treatment for PA. Patients with microadenomas were less likely to receive radiation therapy, likely due to higher rates of successful surgical resection or a "watchful waiting" approach to smaller and thus potentially less symptomatic adenomas. Radiation therapy use peaked for adenomas 4 to 5 cm in size. We hypothesize that this may be because patients with tumors larger than 5 cm are less likely to receive treatment of any kind due to an increased risk of morbidity or mortality associated with the intensive interventions that would be required, including a significantly higher risk of developing a new anterior pituitary deficit and a higher likelihood of recurrence.[25,26] Our analysis identified a similar pattern in the treatment of PA using any type of intervention, with a peak likelihood of intervention found in tumors between 3 and 4 cm in size.

Females were found to more commonly receive radiation for PAs than their male counterparts. Females were also found to be younger at diagnosis than males, a finding that is consistent with other reports.[17]

Our analysis revealed that African Americans are less likely to undergo radiation for PA than White patients, a finding that is echoed in prior works on disparities in radiation therapy for head and neck cancers.[27] Similar studies that consider additional cancer types suggest potential mechanisms for this disparity, including lower referral rates to radiation oncologists for African American patients,[28,29] differences in socioeconomic status, lack of adequate health insurance, or lack of access to health care resources.[30,31] A recent meta-analysis of studies on the disparities in access to radiation therapy found this racial disparity to be prevalent across multiple cancer types.[32]

Patients between 54 and 64 were more likely to receive radiation than those under 54. This could be due to avoidance of radiation in younger patients due to the potential for late toxicities that it entails, having been associated with cerebrovascular disease, secondary brain tumors, and cognitive deficits.[21,33,34] This finding may also be related to the use of radiation therapy for pituitary adenomas that have recurred, an event that is more likely in older patients.

Limitations

Limitations of this study are inherent to a retrospective analysis. As with any cross-institutional database, the NCDB may be limited by inconsistencies in data collection and reporting across participating hospitals. While the NCDB provides a wide array of tumor and patient data, it does not collect or report on patient symptoms at presentation or whether PAs were identified incidentally, precluding a comparison between symptomatic adenomas and "incidentalomas." Similarly, because the NCDB does not collect data on the secretory status of PAs, we were not able to stratify our analysis by functional tumor status.

Conclusion

This study identified increasing rates of pituitary adenoma diagnosis between 2004 and 2014. Additionally, we observed a progressive decline in the rate of radiation therapy in pituitary adenoma treatment in this time period, as well as an overall decrease, in the use of any treatment as initial therapy for pituitary adenoma. These findings can inform treatment decisions and guide the use of radiation therapy for pituitary adenomas moving forward.

Conflict of Interest
None declared.

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