Initial management of meningiomas: Analysis of the National Cancer Database

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ABSTRACT

Background: Meningiomas are the most common central nervous system tumor. We describe current trends in treatment and survival using the largest cancer dataset in the United States.

Methods: We analyzed the National Cancer Database from 2004 to 2014, for all patients with diagnosis of meningioma.

Results: 201,765 cases were analyzed. Patients were most commonly White (81.9%) females (73.2%) with a median age of 64 years. Fifty percent of patients were diagnosed by imaging. Patients were reported as grade I (24.9%), grade II (5.0%), grade III (0.7%), or unknown WHO grade (69.4%). Patients diagnosed by imaging were older, received treatment in community facilities, had higher Charlson-Deyo score, and a lower rate of private insurance. Watchful waiting was the most common treatment modality (46.7%), followed by surgery only (40%). Grade II and III patients were more likely to receive therapy. Watchful waiting increased from 35.2% in 2004 to 51.4% in 2014. Younger age, male gender, private insurance, and treatment in academic facilities were determinants for receipt of surgery and/or radiation. Median survival was 12.6 years, higher in histologically confirmed cases (13.1 years). Older patients, Blacks, males, those that received radiation plus surgery, and were treated in community facilities had an increased risk of mortality.

Conclusions: Over half of patients were diagnosed by imaging, suggesting a higher role of clinical determinants over histological confirmation in treatment decisions. Watchful waiting as initial management is increasing. Our survival analysis favored histological confirmation. Patients receiving radiation and surgery had an increased risk of mortality.

1. Introduction

Meningiomas are the most common central nervous system tumor with an incidence rate of 8.14/100,000 population from 2010 to 2014 in the United States [1]. Most meningiomas are benign, slow-growing, but with a consistent pattern of increasing incidence [2]. Meningiomas are classified based on morphologic criteria by the World Health Organization (WHO) into three groups (grade I-III) [3]. Tissue confirmation may be deferred in some patients, as meningiomas can be diagnosed by imaging [4,5], and are frequently diagnosed incidentally. In those cases, magnetic resonance imaging may be used to differentiate benign and atypical meningioma, based on tumor margins, edema, bone destruction, and diffusion coefficient [6,7]. Population-based studies estimate that around 90% are grade I (benign), 10% are grade II (borderline), and less than 3% are grade III (malignant) [1,8].

Treatment approaches for meningiomas include either observation alone, radiation alone, or surgical resection with or without radiation, and rarely, in cases with progression, a trial of systemic treatment, although there are no FDA approved therapies. Patients may be treated conservatively in small, asymptomatic tumors, whereas radiation therapy is reserved to prevent further growth in high grade lesions or in cases where a complete resection cannot be performed [9], with limited level 1 evidence on treatment recommendations.

An early investigation using the National Cancer Database (NCDB) included cases from 1985 to 1988 and 1990 to 1992 [10]. Subsequent analyses of the NCDB focused on discussions of high-grade

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meningiomas [9,11–13] and limited their cohorts to patients with surgical or histological confirmation; these investigations may not be representative of treatment or decision estimates of all patients with diagnosis of meningioma. In addition, a recent NCDB analysis focused on grade I intracranial meningiomas that included cases *without* WHO grade as grade I [14]. Data on the accuracy of imaging alone in determining WHO grade is limited [6,7], and many of the patients without WHO grade reported may have had grade II or III disease, inconclusive pathology reports, contraindications, or refused to undergo biopsy or surgery. We provide an overall estimate on initial treatment decisions along with survival estimates for meningiomas in the United States.

2. Methods

We analyzed the NCDB from 2004 to 2014, for patients with diagnosis of meningioma using International Classification of Disease for Oncology (ICD-O-3) codes 9530–9534 and 9537-9539. The NCDB prospectively collects cancer patient data from over 1500 American College of Surgeons Commission on Cancer (CoC) accredited institutions in the United States [15–18].

Data in our analysis includes age at diagnosis, sex, race, Hispanic origin, comorbidities based on Charlson-Deyo score (CDS) [19], primary payer status, median income, education status (percentage of non-High school graduates), and residency area, as defined by the United States Department of Agriculture Economic Research Service based on the patient's residential zip code. Facility type was included as available, with community facilities defined as centers without graduate medical education.

Patients were divided into grade I, II, III, or unknown using the "cs_site_specific_factor_1" which codes WHO grade as stated in the pathology report. Treatment received was assessed as first course of treatment at any CoC facility. Treatment groups included: 1) surgery, 2) radiation, 3) chemotherapy. 4)radiation and chemotherapy, 5) radiation and surgery, 6) chemotherapy and surgery, 7) radiation, chemotherapy, and surgery, 8) no treatment (watchful waiting), and 9) unknown. No treatment (watchful waiting) was defined as not receiving radiation, chemotherapy, or surgery. Further lines of therapy and recurrence rate are not captured by the database and were therefore not considered for the study. Living region was defined as metropolitan (population of 250,000 or more), urban (2500 to less than 250,000), and rural (less than 2500).

Medians and inter-quartile ranges are presented for continuous variables and compared using Wilcoxon Rank Sum tests. For categorical variables, counts and percentages are presented and compared using chi-square tests. Kaplan Meier was employed to assess survival. Cox proportional hazards models were used to assess risk factors for mortality and receipt of treatment (surgery or radiation). The level of statistical significance was set at 0.05 for all tests conducted, and all analyses were performed with SAS software version 9.4 (SAS Statistical Institute, Cary, North Carolina).

3. Results

A total of 201,765 cases of meningiomas were included in our analysis, with a female gender predominance (73.2%). The median age was 64 (53–76) years, with 10.9% of patients younger than 44 years of age, 39.2% between 45 and 64 years, 21.9% between 65 and 74 years, and 28% older than 75 years of age. The most common race was White (81.9%), followed by Black (12.2%), and Other (4.3%); 6.2% were of Hispanic origin. The racial and ethnic distribution represent a significant variation compared to the United States population, where Whites account for 62%, Blacks for 12.6%, and 17.3% are Hispanic [20]. Tumor location in the spine was reported in 1054 (0.5%) patients.

3.1. Diagnostic confirmation

Fifty percent of the patients were diagnosed by clinical and imaging criteria (n = 101,586), while 49.3% (N = 99,447) were confirmed histologically. Diagnosis confirmation was unknown in 732 patients. Patients diagnosed by clinical and imaging criteria were significantly older (median of 71 years) compared to patients diagnosed histologically (median of 59 years), were more commonly seen in community hospitals (50.4% versus 34.8%), had a slightly higher percentage of ≥ 3 of CDS (3.6% versus 2.4%), had a lower frequency of private insurance (29.5% versus 50.3%), and a higher percentage of patients covered by Medicare (58.8% versus 34.7%). We found no differences in gender, race, Hispanic origin, urban/rural status, education, or median income while comparing patients diagnosed by clinical and imaging criteria to those diagnosed with histological confirmation. In the clinical and imaging group 86.2% received no treatment, 10.5% received radiation, and 0.2% underwent any kind of surgery.

3.2. WHO grade

Overall, WHO grade was reported in 30.6% of the cases. Of these, grade I was reported in 50,282 (81.4%), grade II in 10,183 (16.5%), and grade III in 1337 (2.2%). CDS was found to be zero in 73.3% of the patients, remaining constant among grades. Grade I patients were significantly younger (median age of 58 years) and had a female gender predominance (73.2%). Grade II and III patients were significantly older (age 60 and 64, respectively), and had a higher proportion of males (43.0% and 48.9%, respectively). White race was the most common in all groups, however grade II meningiomas had a higher frequency of Black patients. Hispanic origin remained constant among groups.

3.3. Treatment

Overall, 46.7% received no treatment, 44.8% underwent surgery, 9.6% received radiation, 0.5% received hormone therapy, and 0.2% received chemotherapy. Over 40% of patients were treated with surgery only (Table 1, Fig. 1). In grade III patients, 42.1% received surgery only, as compared to 86.4% of grade I, and 72.7% of grade II. Grade II and III patients were more likely to receive radiation (22.9% and 51.1%, respectively), and chemotherapy (0.3% and 6.2%, respectively) compared to grade I patients.

3.4. Surgery

The extent of surgical resection was reported in 46.8% of patients. Of these, gross total resection was performed in 51.9%. The frequency of gross total resection increased with grade and was highest in patients with anaplastic meningioma (59%). Younger age, male gender, other race, Hispanic origin, private insurance, and treatment in an academic facility were identified as factors for receiving surgery (Supplemental Table 1).

3.5. Radiation

The majority of patients received radiation after surgery (N = 7135; 97.9%). The sequence of radiation and surgery did not vary by WHO grade. The most common type of radiation was stereotactic radiosurgery (SRS), accounting for 55.3% of patients that received radiation, followed by external beam (43.4%). Grade II and III patients were more likely to receive external beam radiation, while in patients without reported grade, SRS was the most common type of radiation. In grade I, external beam radiation was used slightly more than SRS (Table 1). Older age, female gender, Hispanic origin, treatment in a community facility, and not having insurance were identified as factors for receiving radiation (Supplemental Table 2).

Table 1
Demographics and clinical characteristics of meningiomas, NCDB.2004–2014.

		Grade I N = 50282	Grade II N = 10183	Grade III N = 1337	Not Stated N = 139963	All N = 201765
Age in Years (median, range)		58 (48 - 68)	60 (48 - 70)	64 (52 - 74)	67 (55 - 79)	64 (53 - 76)
Gender	Male	13,517 (26.9%)	4375 (43.0%)	654 (48.9%)	35,503 (25.4%)	54,049 (26.8%)
	Female	36,765 (73.1%)	5808 (57.0%)	683 (51.1%)	104,460 (74.6%)	147,716 (73.2%)
Race	Unknown	857 (1.7%)	135 (1.3%)	22 (1.6%)	2091 (1.5%)	3105 (1.5%)
	White	40,908 (81.4%)	7986 (78.4%)	1081 (80.9%)	115,329 (82.4%)	165,304 (81.9%)
	Black	5985 (11.9%)	1536 (15.1%)	173 (12.9%)	16,919 (12.1%)	24,613 (12.2%)
	Other	2532 (5.0%)	526 (5.2%)	61 (4.6%)	5624 (4.0%)	8743 (4.3%)
Hispanic Origin	Unknown	2837 (5.6%)	633 (6.2%)	77 (5.8%)	8146 (5.8%)	11,693 (5.8%)
	No	44,014 (87.5%)	8905 (87.4%)	1169 (87.4%)	123,386 (88.2%)	177,474 (88.0%)
	Yes	3431 (6.8%)	645 (6.3%)	91 (6.8%)	8431 (6.0%)	12,598 (6.2%)
Diagnostic Confirmation	Unknown	32 (0.1%)	1 (0.0%)	1 (0.1%)	698 (0.5%)	732 (0.4%)
	Histology	48,473 (96.4%)	10,128 (99.5%)	1308 (97.8%)	39,538 (28.2%)	99,447 (49.3%)
	Clinical/Imaging	1777 (3.5%)	54 (0.5%)	28 (2.0%)	99,727 (71.2%)	101,586 (50.3%)
Charlson-Deyo Score	0	37,175 (73.9%)	7223 (70.9%)	944 (70.6%)	102,535 (73.3%)	147,877 (73.3%)
	1	9167 (18.2%)	1922 (18.9%)	252 (18.8%)	24,333 (17.4%)	35,674 (17.7%)
	2	2759 (5.5%)	688 (6.8%)	95 (7.1%)	8539 (6.1%)	12,081 (6.0%)
	≥3	1181 (2.3%)	350 (3.4%)	46 (3.4%)	4556 (3.3%)	6133 (3.0%)
Facility Type	Unknown	5095 (10.1%)	1286 (12.6%)	122 (9.1%)	7690 (5.5%)	14,193 (7.0%)
	Community	15,158 (30.1%)	2843 (27.9%)	456 (34.1%)	67,835 (48.5%)	86,292 (42.8%)
	Academic	23,948 (47.6%)	4821 (47.3%)	599 (44.8%)	46,951 (33.5%)	76,319 (37.8%)
	Integrated Network	6081 (12.1%)	1233 (12.1%)	160 (12.0%)	17,487 (12.5%)	24,961 (12.4%)
Type of insurance	Not Insured	2203 (4.4%)	588 (5.8%)	53 (4.0%)	5165 (3.7%)	8009 (4.0%)
	Private Insurance	26,015 (51.7%)	4732 (46.5%)	558 (41.7%)	48,946 (35.0%)	80,251 (39.8%)
	Medicaid	3683 (7.3%)	877 (8.6%)	90 (6.7%)	7575 (5.4%)	12,225 (6.1%)
	Medicare	16,567 (32.9%)	3680 (36.1%)	591 (44.2%)	73,741 (52.7%)	94,579 (46.9%)
	Other Government	716 (1.4%)	152 (1.5%)	24 (1.8%)	1357 (1.0%)	2249 (1.1%)
	Insurance Status Unknown	1098 (2.2%)	154 (1.5%)	21 (1.6%)	3179 (2.3%)	4452 (2.2%)
Median Income Quartiles 2007-2012	Unknown	348 (0.7%)	78 (0.8%)	21 (1.6%)	1473 (1.1%)	1920 (1.0%)
	< $38,000	8318 (16.5%)	1807 (17.7%)	237 (17.7%)	24,146 (17.3%)	34,508 (17.1%)
	$38,000-$47,999	11,254 (22.4%)	2354 (23.1%)	318 (23.8%)	32,146 (23.0%)	46,072 (22.8%)
	$48,000-$62,999	13,434 (26.7%)	2694 (26.5%)	336 (25.1%)	37,729 (27.0%)	54,193 (26.9%)
	≥$68,000	16,928 (33.7%)	3250 (31.9%)	425 (31.8%)	44,469 (31.8%)	65,072 (32.3%)
Percent No High School Degree 2007-2012	Unknown	327 (0.7%)	71 (0.7%)	20 (1.5%)	1412 (1.0%)	1830 (0.9%)
	≥21%	8335 (16.6%)	1769 (17.4%)	231 (17.3%)	24,180 (17.3%)	34,515 (17.1%)
	13.0-20.9%	12,780 (25.4%)	2552 (25.1%)	351 (26.3%)	35,302 (25.2%)	50,985 (25.3%)
	7.0-12.9%	16,058 (31.9%)	3263 (32.0%)	395 (29.5%)	44,553 (31.8%)	64,269 (31.9%)
	< 7.0%	12,782 (25.4%)	2528 (24.8%)	340 (25.4%)	34,516 (24.7%)	50,166 (24.9%)
Living Area	Unknown	1283 (2.6%)	272 (2.7%)	54 (4.0%)	4497 (3.2%)	6106 (3.0%)
	Metro	41,287 (82.1%)	8271 (81.2%)	1064 (79.6%)	116,487 (83.2%)	167,109 (82.8%)
	Urban	5563 (11.1%)	1193 (11.7%)	157 (11.7%)	13,645 (9.7%)	20,558 (10.2%)
	Rural	2149 (4.3%)	447 (4.4%)	62 (4.6%)	5334 (3.8%)	7992 (4.0%)
Surgery	Unknown	917 (1.8%)	241 (2.4%)	27 (2.0%)	1453 (1.0%)	2638 (1.3%)
	None	2908 (5.8%)	236 (2.3%)	64 (4.8%)	105,531 (75.4%)	108,739 (53.9%)
	Yes	46,457 (92.4%)	9706 (95.3%)	1246 (93.2%)	32,979 (23.6%)	90,388 (44.8%)
Radiation	Unknown	555 (1.1%)	95 (0.9%)	16 (1.2%)	1568 (1.1%)	2234 (1.1%)
	No	47,000 (93.5%)	7759 (76.2%)	638 (47.7%)	124,794 (89.2%)	180,191 (89.3%)
	Yes	2727 (5.4%)	2329 (22.9%)	683 (51.1%)	13,601 (9.7%)	19,340 (9.6%)
Chemotherapy	Unknown	1455 (2.9%)	296 (2.9%)	53 (4.0%)	3805 (2.7%)	5609 (2.8%)
	No	48,783 (97.0%)	9852 (96.7%)	1201 (89.8%)	136,004 (97.2%)	195,840 (97.1%)
	Yes	44 (0.1%)	35 (0.3%)	83 (6.2%)	154 (0.1%)	316 (0.2%)
Treatment Summary	Unknown	1729 (3.4%)	343 (3.4%)	58 (4.3%)	4944 (3.5%)	7074 (3.5%)
	None	2432 (4.8%)	162 (1.6%)	44 (3.3%)	91,687 (65.5%)	94,325 (46.7%)
	RT + CT + S	11 (0.0%)	20 (0.2%)	63 (4.7%)	34 (0.0%)	128 (0.1%)
	RT + CT	4 (0.0%)	1 (0.0%)	4 (0.3%)	22 (0.0%)	31 (0.0%)
	RT + S	2232 (4.4%)	2176 (21.4%)	576 (43.1%)	1970 (1.4%)	6954 (3.4%)
	CT + S	27 (0.1%)	12 (0.1%)	14 (1.0%)	26 (0.0%)	79 (0.0%)
	Surgery only	43,433 (86.4%)	7404 (72.7%)	563 (42.1%)	29,989 (21.4%)	81,389 (40.3%)
	RT Only	412 (0.8%)	63 (0.6%)	14 (1.0%)	11,222 (8.0%)	11,711 (5.8%)
	CT Only	2 (0.0%)	2 (0.0%)	1 (0.1%)	69 (0.0%)	74 (0.0%)

RT: Radiation; **CT:** Chemotherapy; **S:** Surgery.

3.6. Year of diagnosis

The type of treatment received varied significantly with each year of diagnosis. Watchful waiting increased significantly during the timeframe, from 35.2% to 51.4% (2004–2014). The use of radiation only and surgery only decreased progressively with more recent years of diagnosis (Supplemental Table 3).

3.7. Socio-economic characteristics

The type of CoC facility was reported in 93% of the cases. Patients were treated in community facilities (42.8%), academic hospitals (37.8%), or integrated network hospitals (12.4%). Grade III meningioma patients were more likely to be treated in community settings (34.1%), compared to 30.1% of grade I, and 27.9% of grade II. Patients living in metropolitan areas accounted for 82.8% of the cohort, and 14.2% lived in urban/rural areas, remaining constant between WHO
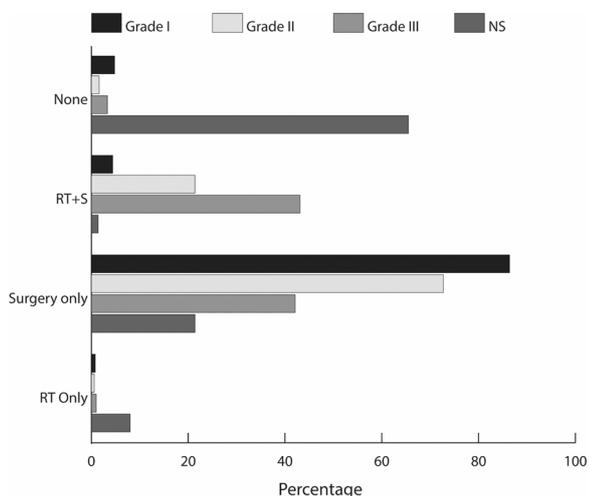
Fig. 1. Summary of treatment receipt overall and by WHO grade. **NS:** Not stated.

grade groups. Fifty-seven percent of patients lived in areas with < 12.9% of non-high school graduates. Overall, the most common type of insurance was Medicare (46.9%), followed by private insurance (39.8%). Medicare was more frequent in patients with anaplastic meningiomas. The majority of patients (60.2%) had an annual income higher than $48,000 per year. Socioeconomic factors did not vary by WHO grade.

3.8. Survival

Median survival was 12.6 years overall. Survival varied significantly by WHO grade; was 11.9 years in grade II, 11.7 years in patients without grade reported, and 4.7 years in grade III (Fig. 2). Median survival could not be assessed in grade I as the survival rates were higher than 50% at the end of the follow-up period. Survival estimates were higher for younger patients, females, and Hispanics (Table 2). Histological diagnostic confirmation was also associated with higher median survival (13.1 years) compared to patients diagnosed by clinical/imaging criteria (9.3 years) (Fig. 3). Patients that received surgery had 5-year survival estimates over 86%, compared to 82.5% for patients that received radiation, 64.9% for patients who did not receive treatment, and 48.2% for patients that received chemotherapy.

Kaplan Meier survival estimates were assessed by type of radiation received; patients that underwent SRS were found to have higher survival estimates compared to external beam radiation in the overall population. Older age, Black race, male gender, receiving surgery plus radiation, and treatment in a community facility were identified as risk factors for mortality (Table 3). Private insurance and overall higher socioeconomic status were protective factors for mortality.
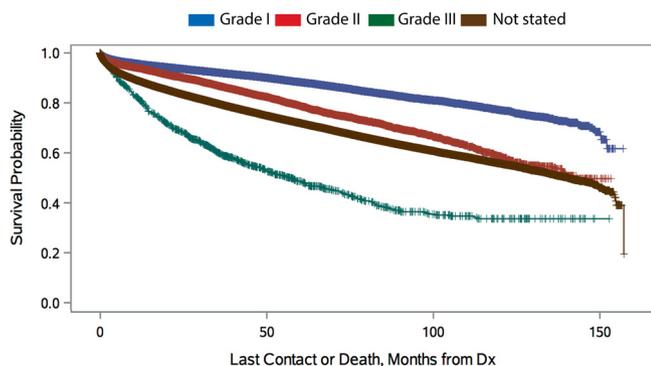

Fig. 2. Survival by WHO grade (p < 0.001).

Table 2
5-year survival estimates by selected characteristics for meningiomas, NCDB.2004–2014.

		# Cases*	5-year Survival (95% CI)
Age Group (years)	0-44	11,072	95.5% (95.2% - 95.9%)
	45-64	42,462	89.8% (89.6% - 90.0%)
	65-74	25,355	77.3% (76.8% - 77.7%)
	≥75	38,462	48.7% (48.2% - 49.2%)
Gender	Female	85,035	78.2% (77.9% - 78.4%)
	Male	32,316	70.3% (69.9% - 70.8%)
Race	Black	14,114	75.2% (74.6% - 75.8%)
	Other	4281	82.4% (81.4% - 83.3%)
	Unknown	1767	84.4% (83.0% - 85.9%)
	White	97,189	75.7% (75.5% - 76.0%)
Hispanic Origin	No	102,931	75.6% (75.3% - 75.8%)
	Unknown	8223	76.7% (75.8% - 77.5%)
	Yes	6197	83.4% (82.6% - 84.1%)
Treatment Summary	None	55,684	64.9% (64.6% - 65.3%)
	RT Only	7099	81.9% (81.2% - 82.7%)
	RT + S	3874	83.7% (82.7% - 84.7%)
	Surgery only	46,254	86.4% (86.1% - 86.7%)

RT: Radiation; **CT:** Chemotherapy; **S:** Surgery.
* Number of patients who were alive 5 years after the diagnosis.

4. Discussion

We provide a comprehensive analysis on patterns of care for meningiomas in the United States. This is important in a disease with an increasing incidence and long-term survival [8]. Over 50% of patients were diagnosed by clinical/imaging modalities alone, and 46.7% did not receive initial therapy. Survival has increased in comparison with previous studies, and our findings emphasize the role of clinical determinants in treatment decisions compared to histological confirmation or WHO grade.

NCDB is a valuable resource for long-term survival estimates, as it is one of the major sources for cancer care improvement [21]. One previous NCDB study presented an overall assessment of meningiomas and was published prior to wide use of modern imaging techniques [10]. Recent descriptions excluded patients without histological confirmation, or focused on specific and uncommon histological subgroups [10–14], limiting their findings to a selective patient population.

In our study, watchful waiting was the most common treatment modality (46.7%), followed by surgery only. The use of watchful waiting increased progressively with each diagnosis year, as previously reported in an NCDB study for grade I intracranial meningioma [14]. Watchful waiting is an option for asymptomatic tumors, generally < 3 cm; deferring surgical treatment until documentation on the pace of tumor growth [22,23]. This correlates with 50% of patients that were diagnosed by imaging, and the large number of patients without reported WHO grade, as meningiomas can be diagnosed incidentally or may be located in surgically challenging areas, such as the posterior fossa [5]. A strength of this study is the inclusion of patients without WHO grade reported along with a separate description of their outcomes and characteristics, reflecting common clinical practice scenario.

Patients without a reported WHO grade may be considered low-risk based on imaging and clinical examination, and over 65% of these patients were followed expectantly. These patients had a similar survival compared to grade II meningiomas in our cohort (Fig. 2). This group was also significantly older compared to grade I, and a had a higher number of patients with a CDS ≥ 3. Previous NCDB investigations grouped these patients as WHO grade I, reporting 50% not receiving initial therapy [14]. Imaging alone is not sufficient to establish grade; other reasons, including non-resectable tumors, inconclusive pathology reports, and contraindications for surgery, may play a role in the decision. From our analysis, 4.8% of grade I patients and 65.5% of patients with unknown grade did not receive initial treatment. Overall, the poorer outcomes of patients diagnosed by imaging only can be
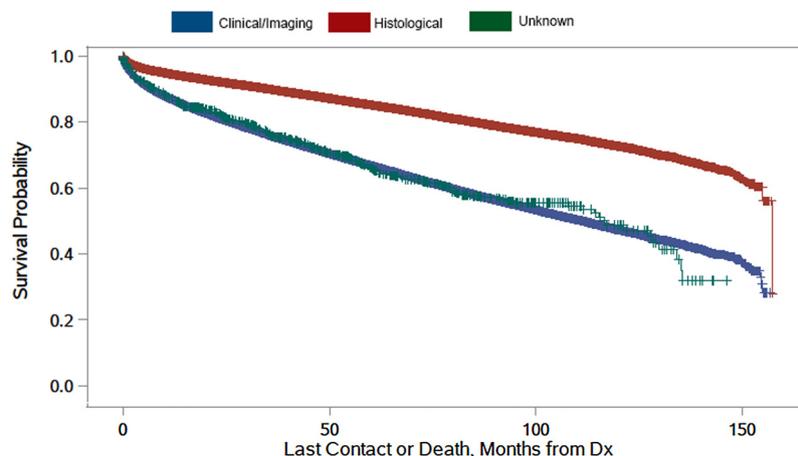
Fig. 3. Survival by type of diagnostic confirmation (p < 0.001).

Table 3
Multivariate analysis for risk factors for mortality in meningiomas, NCDB.2004–2014.

		Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age Group (years)	≥75	8.257	7.482	9.112
	45-64	1.809	1.642	1.993
	65-74	3.403	3.083	3.757
	0-44	ref	–	–
Gender	Male	1.439	1.412	1.468
	Female	ref	–	–
Race	Black	1.419	1.337	1.505
	Unknown	0.962	0.865	1.070
	White	1.193	1.130	1.259
	Other	ref	–	–
Hispanic Origin	Unknown	1.044	1.005	1.084
	Yes	0.829	0.791	0.869
	No	ref	–	–
Insurance	Unknown	0.916	0.834	1.006
	Medicaid	1.241	1.145	1.345
	Medicare	0.998	0.930	1.070
	Other Government	0.973	0.861	1.099
	Private Insurance	0.720	0.672	0.772
	Not insured	ref	–	–
Living Area	Metro	0.965	0.922	1.011
	Urban	1.017	0.965	1.072
	Rural	ref	–	–
Facility Type	Community	1.125	1.102	1.148
	Integrated Network	1.076	1.045	1.108
	Academic	ref	–	–
Treatment Summary	CT Only	3.268	0.447	23.878
	CT + S	1.792	0.241	13.298
	RT Only	0.910	0.724	1.143
	RT + CT	3.970	0.520	30.327
	RT + CT + S	2.770	0.379	20.273
	RT + S	1.365	1.052	1.773
	Surgery only	1.035	0.919	1.165
	Unknown	1.149	0.966	1.366
	None	ref	–	–

RT: Radiation; **CT:** Chemotherapy; **S:** Surgery.

explained by older age, higher number of comorbidities, and possibly having locations or number of lesions preventing tissue confirmation. In addition, dural–based mesenchymal neoplasms, or dural metastases may mimic meningiomas by imaging [24].

The 5-year survival estimates were higher in patients that underwent surgical resection compared to those that did not receive treatment. However, a multivariate analysis did not confirm differences in overall mortality risk while comparing surgical resection alone to watchful waiting. Tumor growth is expected in patients that are

followed expectantly and the decision to undergo surgery is based on degree of extension, proximity to critical central nervous system locations, irresectability or other contraindications for surgery [25], therefore the observed 5-year survival differences may be explained by patient selection alone (for surgery).

The use of radiation plus surgery was associated with mortality, as it is expected that patients who receive this treatment have higher grade lesions or non-resectable tumors. The use of radiation after surgery for grade II and III meningiomas has shown positive results, in a non-randomized clinical trial [26], with results still to be finalized by the European Organization for Research and Treatment of Cancer (EORTC). The majority of data that supports this approach comes from retrospective analyses [27,28], including previous NCDB descriptions of aggressive meningiomas (anaplastic and papillary) [11,12], which may explain the differences in practice patterns with less than 23% of grade II and 51.1% of grade III tumors reporting its use. Interestingly, an NCDB investigation for atypical meningiomas showed an age related benefit of radiation (< 55 years and > 75 years) [9]. Older age was a risk factor for mortality in our analysis, and was also a protective factor for receiving radiation, markedly between 65 and 74 years of age.

Radiation only may be used in non-resectable tumors, particularly in skull base, or optic nerve sheath meningiomas, and in elderly patients where retrospective analyses have demonstrated benefit [9,29,30]. Stereotactic radiosurgery and hypofractionated radiation alone have shown five-year tumor control rates over 84% [31–33]. In our analysis, the most common type of radiation was SRS, and was more common in patients without reported WHO grade. External beam radiation was most common in grade II and III, and survival of these patients was decreased compared to SRS. This could be for many reasons, including patient selection bias for the more technologically advanced SRS, size and number of lesions, limitations in SRS tumor treatment compared to external beam radiation, and possibly as an indicator of higher quality care facility.

Hormone therapy was used in 1094 patients, representing 0.5% of the cohort and was associated with increased mortality. This is at least partially explained because it is offered in patients with limited therapeutic options. The female predominance in benign meningioma and link to breast cancer suggests a possible sex hormone dependency tied to the growth of these tumors [34,35]. However, no therapeutic benefit has been found by targeting sex hormone receptors in clinical trials [36,37]. Somatostatin analogs initially showed benefits in case reports [38], but failed to be verified in clinical trials [39,40].

Median survival was 12.6 years, and 5-year survival rates were 88.3% for grade I, 78.8% for grade II, 48.7% for grade III, and 71.9% for tumors without a reported WHO grade. This demonstrates an increased survival for meningiomas from that reported in previous analyses [10,41]. Interestingly, the survival in grade I and II meningiomas

is higher than reported in previous NCDB analyses excluding imaging based diagnosed cases, but lower for grade III (85.5%, 75.9%, and 55.4%, respectively) [13].

Patients with grade III meningiomas were more likely to receive adjuvant therapy, with 6.2% receiving chemotherapy as first course treatment although there is no Food and Drug Administration (FDA) approved chemotherapy. This is slightly smaller than the 7% previously described [11], and is in keeping with the literature as chemotherapy has not shown survival benefits in meningiomas.

Treatment with chemotherapy only (without surgery or radiation therapy) showed the lowest 5-year survival rates (32.7%). This lower survival is expected as chemotherapy is used in cases of surgically inaccessible tumors and in patients who cannot receive further radiation therapy [42]. Hydroxyurea was dropped from the National Comprehensive Cancer Network (NCCN) guideline for WHO grade II meningiomas starting in 2009, based on the lack of survival benefits [42]. The only systemic therapies that have shown limited efficacy are somatostatin analogues, sunitinib, bevacizumab, everolimus, and interferon-alpha at recurrence [43–45]. Immunotherapy with immune checkpoint inhibitors may have a role in the future as evidence demonstrates PD-L1 expression in anaplastic meningiomas [46].

The main limitations of our study include the inability to evaluate cause of death, recurrence rate, individual patient characteristics, overall performance, further treatment lines, and the reasons behind treatment decisions. Our analysis provides a large-scale evaluation of the treatment and survival patterns of meningiomas in the United States, and highlights the increasing survival of meningiomas and the large number of cases diagnosed by imaging only. We believe our combined assessment provides a real-world picture of treatment and survival patterns of meningiomas, as treatment decisions are made before pathological confirmation. The observed 5-year survival differences between watchful waiting and surgery only, along with the use of chemotherapy in anaplastic lesions, calls for prospective evaluations and the need for development of further systemic treatment approaches in patients with aggressive tumors or contraindications for surgery.

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Declarations

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.02.018.

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