Determining the role of adjuvant radiotherapy in the management of meningioma: a Surveillance, Epidemiology, and End Results analysis

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OBJECTIVE The aim of this study was to illustrate the demographic characteristics of meningioma patients and observe the effect of adjuvant radiation therapy on survival by using the Surveillance, Epidemiology, and End Results (SEER) database. More specifically, the authors aimed to answer the question of whether adjuvant radiotherapy following resection of atypical meningioma confers a cause-specific survival benefit. Additionally, they attempted to add to previous characterizations of the epidemiology of primary meningiomas and assess the effectiveness of the standard of care for benign and anaplastic meningiomas. They also sought to characterize the efficacy of various treatment options in atypical and anaplastic meningiomas separately since nearly all other analyses have grouped these two together despite varying treatment regimens for these behavior categories.

METHODS SEER data from 1973 to 2015 were queried using appropriate ICD-O-3 codes for benign, atypical, and anaplastic meningiomas. Patient demographics, tumor characteristics, and treatment choices were analyzed. The effects of treatment were examined using a multivariate Cox proportional hazards model and Kaplan-Meier survival analysis.

RESULTS A total of 57,998 patients were included in the analysis of demographic, meningioma, and treatment characteristics. Among this population, cases of unspecified WHO tumor grade were excluded in the multivariate analysis, leaving a total of 12,931 patients to examine outcomes among treatment paradigms. In benign meningiomas, gross-total resection (HR 0.289, p = 0.013) imparted a significant cause-specific survival benefit over no treatment. In anaplastic meningioma cases, adjuvant radiotherapy imparted a significant survival benefit following both subtotal (HR 0.089, p = 0.018) and gross-total (HR 0.162, p = 0.002) resection as compared to gross-total resection alone. In atypical tumors, gross-total resection plus radiotherapy did not significantly change the hazard risk (HR 1.353, p = 0.628) compared to gross-total resection alone. Similarly, it was found that adjuvant radiation did not significantly benefit survival after a subtotal resection (HR 1.440, p = 0.644).

CONCLUSIONS The results of this study demonstrate that the role of adjuvant radiotherapy, especially after the resection of atypical meningioma, remains somewhat unclear. Thus, given these results, prospective randomized clinical studies are warranted to provide clear information on the effects of adjuvant radiation in meningioma treatment.

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KEYWORDS meningioma; radiotherapy; survival; tumor management; SEER; surgery

MENINGIOMAS are one of the most prevalent forms of tumor seen in the central nervous system (CNS), accounting for about a third of all primary brain and CNS tumors. They typically arise from arachnoid cap cells in the meninges surrounding the brain and spine, can be readily diagnosed with imaging, and are often found incidentally during imaging for other medical purposes. An increase in cranial imaging for a variety of medical indications has led to a greater reported incidence of primary meningioma in patients who were not originally being assessed for meningioma. The majority of meningiomas are benign, slow-growing tumors (ICD-O-3 behavior 0); however, some forms are more aggressive and are categorized as either atypical (ICD-O-3 behavior 1) or anaplastic (ICD-O-3 behavior 3) meningiomas. Previous epidemiological studies have shown that be-
nign meningiomas represent approximately 94% of all meningioma cases, whereas atypical and anaplastic meningiomas account for about 4% and 1%, respectively. These tumors are most common in older individuals, with an average age of approximately 64 years at onset and an increasing incidence with age. There is also a well-documented increased incidence of these tumors in women (73% in women overall and 80% of spinal cord meningiomas in women). Some evidence suggests that this trend is not seen in pediatric patients, in whom these tumor types are rare and likely associated with neurofibromatosis type 2 (NF2) or therapeutic radiation for other malignancies. Overall, death from benign meningiomas is very low with exceptions for tumors in locations such as the skull base where the risk from tumor growth is greater. Atypical and anaplastic meningiomas have lower survival rates and are often associated with recurrence.

Given that benign meningiomas are a slow-growing malignancy, the usual treatment course involves observation after diagnosis through imaging. For most patients, the meningioma will be asymptomatic, and as long as the tumor size does not drastically increase, there is no urgency to treat surgically. However, an exception to this stance relates to pediatric patients, in whom there is the concern that future surgery will be required and the decision to perform gross-total resection (GTR) early may be made. For most benign meningiomas for which GTR is successfully completed, adjuvant radiotherapy is not indicated. For atypical meningiomas, which have a higher rate of recurrence, standard practice is to perform GTR when possible; however, there is ongoing debate over whether adjuvant radiotherapy should be provided in cases in which GTR is successful, with studies showing various effects on survival. The advent of newer, more focused radiotherapy options has added to the question of whether to radiate in these cases and whether that radiation will improve outcomes. For anaplastic meningiomas, which are highly aggressive and come with a poor prognosis, GTR and subsequent radiotherapy are both indicated.

In the present study, in which we conducted the largest-to-date Surveillance, Epidemiology, and End Results (SEER) analysis of primary meningiomas, we aimed to answer the question of whether adjuvant radiotherapy following resection of atypical meningioma confers a cause-specific survival benefit. Additionally, we attempted to add to previous characterizations of the epidemiology of primary meningiomas and assess the effectiveness of the standard of care for benign and anaplastic meningiomas. We also sought to characterize the efficacy of various treatment options in atypical and anaplastic meningiomas separately since nearly all other analyses have grouped these two together despite varying treatment regimens for these behavior categories.

**Methods**

**Study Sample**

A retrospective analysis was performed using the SEER Program database collected by the National Cancer Institute from 1973 to 2015. The data set entitled “Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov2017 Sub (1973–2015 varying) - Linked To County Attributes - Total U.S., 1969–2016 Counties” was used, and SEER*STAT version 8.1.2 was used to extract case-level data. SEER contains de-identified individual-level data from 13 cancer registries across the United States. The ICD-O-3 codes were used to identify 89,525 cases of CNS meningioma for the years 1973–2015. Those cases with data collected from autopsy or death certificate and records with incomplete cause-specific survival data were excluded from our study. ICD-O-3 codes with more than 30 patients and records with only one tumor recorded were included in the study, which resulted in a total of 57,998 cases.

**Baseline Characteristics**

Analyzed patient demographics included age group (0–19, 20–39, 40–59, 60–79, and 80+ years), sex (female, male), race (black, white, other), and marital status (married/domestic partner, divorced/separated, single, widowed). Studied tumor characteristics included primary tumor site (cerebral meninges C700, spinal meninges C701, meninges not otherwise specified [NOS] C709, brain C710–C719, spinal cord C720, cauda equina C721, olfactory nerve C722, optic nerve C723, acoustic nerve C724, cranial nerve NOS C725, overlapping lesion of brain and CNS C728, nervous system NOS C729, pituitary gland C751, craniofacial C752, pineal gland C753) and histology (9530/0: meningioma; 9531/0: meningothelial meningioma; 9532/0: fibrous meningioma; 9533/0: psammomatous meningioma; 9534/0: angiomatous meningioma; 9537/0: transitional meningioma; 9538/1: meningiomatosis, NOS; 9539/1: clear cell meningioma; 9539/1: atypical meningioma; 9539/3: meningioma, anaplastic; 9539/3: psammomatous meningioma, anaplastic). Treatment characteristics included biopsy, resection (subtotal resection [STR]; GTR, NOS), radiation (yes, no), and chemotherapy (yes, no).

**Statistical Analysis**

CNS meningiomas were grouped according to behavior category (0, benign; 1, atypical; 3, anaplastic). Patient demographics, tumor characteristics, and treatment regimens for the records identified are summarized in Tables 1 and 2. The effect of treatment regimen on patient survival was evaluated using a Cox proportional hazards model including age, race, sex, marital status, tumor size, histological type, anatomical location, and WHO grade (Tables 3–6). A Firth bias correction was applied to account for the small sample sizes seen in some subgroups. Mortality was defined as cause-specific mortality from a CNS cancer and did not count individuals who died of noncancerous causes, with the follow-up from date of diagnosis until 2015. Additionally, graphic analysis using the Kaplan-Meier method was fitted to evaluate the association between treatment sequence and survival, stratified by anatomical location. Multiple comparisons for the log-rank test with Sidak correction were then performed to compare the different treatment regimens. Multivariate logistic regression models adjusted for sex, age groups,
## TABLE 1. Demographic, tumor, and treatment characteristics of sampled individuals with benign meningioma, grouped according to histological classification

| Variable                  | Total | Meningioma, NOS | Meningothelial Meningioma | Fibrous Meningioma | Psammomatous Meningioma | Angiomatous Meningioma | Transitional Meningioma |
|---------------------------|-------|-----------------|---------------------------|--------------------|--------------------------|------------------------|------------------------|
|                           | No.   | %               | No. %                     | No. %              | No. %                    | No. %                  | No. %                  |
| Age group (yrs)           |       |                 |                           |                    |                          |                        |                        |
| 0–19                      | 201   | 0.4             | 147 0.3                   | 24 0.7             | 7 0.6                    | 4 0.4                  | 8 2.3                  | 11 0.7                |
| 20–39                     | 3,873 | 7.0             | 3,036 6.4                 | 419 11.6           | 133 12.1                 | 69 6.0                 | 39 11.0                | 177 10.6              |
| 40–59                     | 18,821| 34.0            | 15,272 32.2               | 1,651 45.6         | 527 47.7                 | 442 38.3               | 150 42.4               | 779 46.6              |
| 60–79                     | 22,314| 40.3            | 19,293 40.6               | 1,338 37.0         | 382 34.6                 | 531 46.0               | 145 41.0               | 625 37.4              |
| 80+                       | 10,182| 18.4            | 9,741 20.5                | 187 5.2            | 55 5.0                   | 108 9.4                | 12 3.4                 | 79 4.7                |
| Race                      |       |                 |                           |                    |                          |                        |                        |
| Black                     | 6,809 | 12.3            | 5,925 12.5                | 494 13.7           | 119 10.8                 | 95 8.2                 | 31 8.8                 | 145 8.7               |
| Other*                    | 4,800 | 8.7             | 4,122 8.7                 | 310 8.6            | 87 7.9                   | 101 8.8                | 35 9.9                 | 145 8.7               |
| Unknown                   | 741   | 1.3             | 643 1.4                   | 44 1.2             | 8 0.7                    | 14 1.2                 | 4 1.1                  | 28 1.7                |
| Race                      |       |                 |                           |                    |                          |                        |                        |
| White                     | 43,041| 77.7            | 36,799 77.5               | 2,771 76.6         | 890 80.6                 | 944 81.8               | 284 80.2               | 1,353 81.0            |
| Sex                       |       |                 |                           |                    |                          |                        |                        |
| Female                    | 42,025| 75.9            | 36,250 76.3               | 2,503 69.2         | 873 79.1                 | 1,012 87.7             | 184 52.0               | 1,203 72.0            |
| Male                      | 13,366| 24.1            | 11,239 23.7               | 1,116 30.8         | 231 20.9                 | 142 12.3               | 170 48.0               | 468 28.0              |
| Region                    |       |                 |                           |                    |                          |                        |                        |
| Midwest                   | 5,019 | 9.1             | 4,348 9.2                 | 327 9.0            | 97 8.8                   | 93 8.1                 | 31 8.8                 | 123 7.4               |
| North                     | 7,465 | 13.5            | 6,484 13.7                | 421 11.6           | 129 11.7                 | 140 12.1               | 41 11.6                | 250 15.0              |
| South                     | 13,004| 23.5            | 11,372 24.0               | 804 22.2           | 267 24.2                 | 220 19.1               | 57 16.1                | 284 17.0              |
| West                      | 29,903| 54.0            | 25,285 53.2               | 2,067 57.1         | 611 55.3                 | 701 60.8               | 225 63.6               | 1,014 60.7            |
| Marital status            |       |                 |                           |                    |                          |                        |                        |
| Divorced, separated, or widowed | 14,905 | 26.9         | 13,355 28.1               | 686 19.0           | 225 20.4                 | 283 24.5               | 51 14.4                | 305 18.3              |
| Married or domestic partner | 27,826 | 50.2         | 23,335 49.1               | 2,054 56.8         | 630 57.1                 | 629 54.5               | 200 56.5               | 978 58.5              |
| Single                    | 8,460 | 16.0            | 7,326 15.4                | 745 20.6           | 204 18.5                 | 179 15.5               | 77 21.8                | 309 18.5              |
| Unknown                   | 3,820 | 6.9             | 3,473 7.3                 | 134 3.7            | 45 4.1                   | 63 5.5                 | 26 7.3                 | 79 4.7                |
| Anatomical location       |       |                 |                           |                    |                          |                        |                        |
| Cerebral meninges         | 46,307| 83.6            | 40,138 84.5               | 2,987 82.5         | 947 85.8                 | 557 48.3               | 301 85.0               | 1,377 82.4            |
| Meninges (NOS)            | 6,109 | 11.0            | 5,357 11.3                | 353 9.8            | 110 10.0                 | 93 8.1                 | 34 9.6                 | 162 9.7               |
| Nonmeningeal              | 550  | 1.0             | 400 0.8                   | 59 1.6            | 20 1.8                   | 29 2.5                 | 12 3.4                 | 30 1.8                |
| Spine meninges            | 2,425 | 4.4             | 1,594 3.4                 | 220 6.1           | 27 2.4                   | 475 41.2               | 7 2.0                  | 102 6.1               |
| Tumor size                |       |                 |                           |                    |                          |                        |                        |
| <20 mm                    | 18,802| 33.9            | 17,882 37.7               | 356 9.8            | 121 11.0                 | 263 22.8               | 17 4.8                 | 163 9.8               |
| 20–40 mm                  | 16,721| 30.2            | 14,125 29.7               | 1,144 31.6         | 393 35.6                 | 360 31.2               | 131 37.0               | 568 34.0              |
| >40 mm                    | 10,230| 18.5            | 7,577 16.0                | 1,357 37.5         | 388 35.1                 | 183 15.9               | 137 38.7               | 588 35.2              |
| Unknown                   | 9,638 | 17.4            | 7,905 16.6                | 762 21.1           | 202 18.3                 | 348 30.2               | 69 19.5                | 352 21.1              |

CONTINUED ON PAGE 4
### TABLE 1. Demographic, tumor, and treatment characteristics of sampled individuals with benign meningioma, grouped according to histological classification

| Variable                      | Total | Meningioma, NOS | Meningothelial Meningioma | Fibrous Meningioma | Psammomatous Meningioma | Angiomatous Meningioma | Transitional Meningioma |
|-------------------------------|-------|----------------|---------------------------|-------------------|-------------------------|------------------------|------------------------|
|                               | No.   | %              | No.           | %                  | No.           | %                  | No.           | %                  | No.           | %                | No.           | %                |
| **WHO grade**                 |       |                |               |                    |               |                    |               |                    |               |                  |               |                  |
| Unknown                       | 40,075| 72.3           | 37,039        | 78.0              | 1,379         | 38.1              | 482           | 43.7              | 477           | 41.3             | 134           | 37.9             | 564           | 33.8             |
| I                             | 14,434| 26.1           | 9,782         | 20.6              | 2,124         | 58.7              | 594           | 53.8              | 669           | 58.0             | 212           | 59.9             | 1,053         | 63.0             |
| II                            | 855   | 1.5            | 647           | 1.4               | 112           | 3.1               | 28            | 2.5               | 8             | 0.7              | 8             | 2.3              | 52            | 3.1              |
| III                           | 19    | 0.0            | 17            | 0.0               | 1             | 0.0               | —             | —                 | —             | —                | —             | —                | 1             | 0.1              |
| IV                            | 8     | 0.0            | 4             | 0.0               | 3             | 0.1               | —             | —                 | —             | —                | —             | —                | 1             | 0.1              |
| **RT**                        |       |                |               |                    |               |                    |               |                    |               |                  |               |                  |
| No                             | 51,261| 92.5           | 43,767        | 92.2              | 3,391         | 93.7              | 1,058         | 95.8              | 1,123         | 97.3             | 332           | 93.8             | 1,590         | 95.2             |
| Yes                           | 4,130 | 7.5            | 3,722         | 7.8               | 228           | 6.3               | 46            | 4.2               | 31            | 2.7              | 22            | 6.2              | 81            | 4.8              |
| **No chemotherapy**           |       |                |               |                    |               |                    |               |                    |               |                  |               |                  |
| No                             | 55,391| 100            | 47,489        | 100               | 3,619         | 100               | 1,104         | 100               | 1,154         | 100              | 354           | 100              | 1,671         | 100              |
| **Surgery type**              |       |                |               |                    |               |                    |               |                    |               |                  |               |                  |
| None                          | 33,068| 59.7           | 32,696        | 68.8              | 161           | 4.4               | 44            | 4                 | 57            | 4.9              | 15            | 4.2              | 95            | 5.7              |
| Biopsy                        | 5,536 | 10             | 3,702         | 7.8               | 872           | 24.1              | 256           | 23.2              | 258           | 22.4             | 89            | 25.1             | 359           | 21.5             |
| STR                           | 2,311 | 4.2            | 1,621         | 3.4               | 336           | 9.3               | 116           | 10.5              | 74            | 6.4              | 33            | 9.3              | 131           | 7.8              |
| GTR                           | 14,476| 26.1           | 9,470         | 19.9              | 2,250         | 62.2              | 688           | 62.3              | 765           | 66.3             | 217           | 61.3             | 1,086         | 65               |
| **Treatment sequence**        |       |                |               |                    |               |                    |               |                    |               |                  |               |                  |
| No treatment                  | 30,291| 54.7           | 29,937        | 63                 | 151           | 4.2               | 38            | 3.4               | 56            | 4.9              | 15            | 4.2              | 94            | 5.6              |
| Biopsy                        | 5,243 | 9.5            | 3,488         | 7.3               | 822           | 22.7              | 248           | 22.5              | 253           | 21.9             | 84            | 23.7             | 348           | 20.8             |
| STR                           | 1,914 | 3.5            | 1,321         | 2.8               | 279           | 7.7               | 105           | 9.5               | 64            | 5.5              | 30            | 8.5              | 115           | 6.9              |
| GTR                           | 13,813| 24.9           | 9,021         | 19                 | 2,139         | 59.1              | 667           | 60.4              | 750           | 65               | 203           | 57.3             | 1,033         | 61.8             |
| RT                            | 2,777 | 5              | 2,759         | 5.8               | 10            | 0.3               | 6             | 0.5               | 1             | 0.1              | —             | —                | 1             | 0.1              |
| RT + biopsy                   | 293   | 0.5            | 214           | 0.5               | 50            | 1.4               | 8             | 0.7               | 5             | 0.4              | 5             | 1.4              | 11            | 0.7              |
| RT + STR                      | 397   | 0.7            | 300           | 0.6               | 57            | 1.6               | 11            | 1                 | 10            | 0.9              | 3             | 0.8              | 16            | 1                |
| RT + GTR                      | 663   | 1.2            | 449           | 0.9               | 111           | 3.1               | 21            | 1.9               | 15            | 1.3              | 14            | 4                | 53            | 3.2              |

RT = radiotherapy.

* American Indian, Alaska Native, Asian/Pacific Islander.
| Variable                        | Atypical/Borderline Meningioma | Anaplastic Meningioma | Total | Meningiomatosis, NOS | Clear Cell Meningioma | Atypical Meningioma | Total | Meningiomatosis, Malignant | Papillary Meningioma |
|--------------------------------|--------------------------------|-----------------------|-------|----------------------|-----------------------|---------------------|-------|-----------------------------|----------------------|
|                                | No. %                          | No. %                 |       | No. %                | No. %                 | No. %               |       | No. %                       | No. %               |
| Total                          | 1,838 100                      | 133 100               | 173 100 | 1,532 100           | 769 100              | 691 100             | 78 100 |                             |                      |
| Age group (yrs)                |                                |                       |       |                      |                       |                     |       |                             |                      |
| 0–19                           | 45 2.5                         | 7 5.3                 | 12 6.9 | 26 1.7              | 19 2.5               | 14 2.0              | 5 6.4  |                             |                      |
| 20–39                          | 252 13.7                       | 14 10.5               | 35 20.2 | 203 13.3           | 100 13.0             | 80 11.6             | 20 25.6 |                             |                      |
| 40–59                          | 753 41.0                       | 51 38.4               | 79 45.7 | 623 40.7           | 308 40.1             | 281 40.7            | 27 34.6 |                             |                      |
| 60–79                          | 713 38.8                       | 49 36.8               | 41 23.7 | 623 40.7           | 286 37.2             | 264 38.2            | 22 28.2 |                             |                      |
| 80+                            | 75 4.1                         | 12 9.0                | 6 3.5  | 57 3.7             | 56 7.3               | 52 7.5              | 4 5.1   |                             |                      |
| Race                           |                                |                       |       |                     |                       |                     |       |                             |                      |
| Black                          | 244 13.3                       | 21 15.8               | 21 12.1 | 202 13.2           | 118 15.3             | 109 15.8            | 9 11.5  |                             |                      |
| Other*                         | 209 11.4                       | 14 10.5               | 15 8.7  | 180 11.8           | 80 10.4              | 68 9.8              | 12 15.4 |                             |                      |
| Unknown                        | 23 1.3                         | 2 1.5                 | 2 1.2  | 19 1.2             | 2 0.3                | 2 0.3               | — —     |                             |                      |
| White                          | 1,362 74.1                     | 96 72.2               | 135 78.0 | 1,131 73.8     | 569 74.0             | 512 74.1            | 57 73.1 |                             |                      |
| Sex                            |                                |                       |       |                     |                       |                     |       |                             |                      |
| Female                         | 1,086 59.1                     | 99 74.4               | 103 59.5 | 884 57.7          | 461 60.0             | 432 62.5            | 29 37.2 |                             |                      |
| Male                           | 752 40.9                       | 34 25.6               | 70 40.5 | 648 42.3           | 308 40.1             | 259 37.5            | 49 62.8 |                             |                      |
| Region                         |                                |                       |       |                     |                       |                     |       |                             |                      |
| Midwest                        | 212 11.5                       | 24 18.1               | 12 6.9  | 176 11.5           | 70 9.1               | 61 8.8              | 9 11.5  |                             |                      |
| North                          | 253 13.8                       | 19 14.3               | 22 12.7 | 212 13.8           | 180 23.4             | 168 24.3            | 12 15.4 |                             |                      |
| South                          | 405 22.0                       | 37 27.8               | 42 24.3 | 326 21.3           | 151 19.6             | 135 19.5            | 16 20.5 |                             |                      |
| West                           | 968 52.7                       | 53 39.9               | 97 56.1 | 818 53.4           | 368 47.9             | 327 47.3            | 41 52.6 |                             |                      |
| Marital status                 |                                |                       |       |                     |                       |                     |       |                             |                      |
| Divorced, separated, or widowed| 294 16.0                       | 25 18.8               | 25 14.5 | 244 15.9           | 141 18.3             | 127 18.4            | 14 18.0 |                             |                      |
| Married or domestic partner    | 1,039 56.5                     | 68 51.1               | 88 50.9 | 883 57.6           | 414 53.8             | 373 54.0            | 41 52.6 |                             |                      |
| Single                         | 411 22.4                       | 28 21.1               | 51 29.5 | 332 21.7           | 173 22.5             | 152 22.0            | 21 26.9 |                             |                      |
| Unknown                        | 94 5.1                         | 12 9.0                | 9 5.2  | 73 4.8            | 41 5.3               | 39 5.6              | 2 2.6   |                             |                      |
| Anatomical location            |                                |                       |       |                     |                       |                     |       |                             |                      |
| Cerebral meninges              | 1,615 87.9                     | 112 84.2              | 137 79.2 | 1,366 89.2     | 602 78.3             | 535 77.4            | 67 85.9 |                             |                      |
| Meninges (NOS)                 | 151 8.2                        | 12 9.0                | 12 6.9  | 127 8.3           | 105 13.7             | 99 14.3             | 6 7.7   |                             |                      |
| Nonmeningeal                   | 22 1.2                         | 6 4.5                 | . .     | 16 1              | 39 5.1               | 35 5.1              | 4 5.1   |                             |                      |
| Spine meninges                 | 50 2.7                         | 3 2.3                 | 24 13.9 | 23 1.5            | 23 3                 | 22 3.2             | 1 1.3   |                             |                      |
| Tumor size                     |                                |                       |       |                     |                       |                     |       |                             |                      |
| <20 mm                         | 90 4.9                         | 29 21.8               | 7 4     | 54 3.5            | 30 3.9               | 30 4.3              | — —     |                             |                      |
| 20–40 mm                       | 415 22.6                       | 34 25.6               | 44 25.4 | 337 22            | 110 14.3             | 100 14.5            | 10 12.8 |                             |                      |
| >40 mm                         | 1,020 55.5                     | 41 30.8               | 88 50.9 | 891 58.2          | 221 28.7             | 179 25.9            | 42 53.8 |                             |                      |
| Unknown                        | 313 17                         | 29 21.8               | 34 19.7 | 250 16.3          | 408 53.1             | 382 55.3            | 26 33.3 |                             |                      |

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### TABLE 2. Demographic, tumor, and treatment characteristics of sampled individuals with atypical or anaplastic meningioma, grouped according to histological classification

| Variable                        | Atypical/Borderline Meningioma | Anaplastic Meningioma | Meningiomatosis, NOS | Clear Cell Meningioma | Atypical Meningioma | Total | Meningioma, Malignant | Papillary Meningioma |
|--------------------------------|--------------------------------|-----------------------|----------------------|-----------------------|---------------------|-------|----------------------|----------------------|
|                                | No. %                          | No. %                 | No. %                | No. %                 | No. %               | No. % | No. %                | No. %                |
| WHO grade                      |                                |                       |                      |                       |                     |       |                      |                      |
| Unknown                        | 427                            | 23.2                  | 94                   | 70.7                  | 33                  | 19.1  | 300                  | 19.6                 |
| I                              | 73                             | 4                     | 21                   | 15.8                  | 6                   | 3.5   | 46                   | 3.5                  |
| II                             | 1,324                          | 72                    | 18                   | 13.5                  | 131                 | 75.7  | 1,175                | 76.7                 |
| III                            | 14                             | 0.8                   | —                    | —                     | 3                   | 1.7   | 11                   | 0.7                  |
| IV                             | —                              | —                     | —                    | —                     | —                   | —     | —                   | —                    |
| RT                             |                                |                       |                      |                       |                     |       |                      |                      |
| No                             | 1,303                          | 70.9                  | 111                  | 83.5                  | 111                 | 64.2  | 1,081                | 70.6                 |
| Yes                            | 535                            | 29.1                  | 22                   | 16.5                  | 62                  | 35.8  | 451                  | 29.4                 |
| No chemotherapy                | 1,838                          | 100                   | 133                  | 100                   | 173                 | 100   | 1,532                | 100                  |
| Surgery type                   |                                |                       |                      |                       |                     |       |                      |                      |
| None                           | 194                            | 10.6                  | 73                   | 54.9                  | 9                   | 5.2   | 112                  | 7.3                  |
| Biopsy                         | 87                             | 4.7                   | 2                    | 1.5                   | 10                  | 5.8   | 75                   | 4.9                  |
| STR                            | 295                            | 16.1                  | 10                   | 7.5                   | 35                  | 20.2  | 250                  | 16.3                 |
| GTR                            | 1,262                          | 68.7                  | 48                   | 36.1                  | 119                 | 68.8  | 1,095                | 71.5                 |
| Treatment sequence             |                                |                       |                      |                       |                     |       |                      |                      |
| No treatment                   | 173                            | 9.4                   | 58                   | 43.6                  | 7                   | 4     | 108                  | 7                   |
| Biopsy                         | —                              | —                     | —                    | —                     | —                   | —     | —                   | —                    |
| STR                            | 174                            | 9.5                   | 10                   | 7.5                   | 18                  | 10.4  | 146                  | 9.5                  |
| GTR                            | 956                            | 52                    | 43                   | 32.3                  | 86                  | 49.7  | 827                  | 54                  |
| RT                             | 21                             | 1.1                   | 15                   | 11.3                  | 2                   | 1.2   | 4                    | 0.3                  |
| RT + biopsy                    | 87                             | 4.7                   | 2                    | 1.5                   | 10                  | 5.8   | 75                   | 4.9                  |
| RT + STR                       | 121                            | 6.6                   | —                    | —                     | 17                  | 9.8   | 104                  | 6.8                  |
| RT + GTR                       | 306                            | 16.6                  | 5                    | 3.8                   | 33                  | 19.1  | 268                  | 17.5                 |

* American Indian, Alaska Native, Asian/Pacific Islander.
race, marital status, histological type, anatomical location, tumor size, WHO grade, radiation, and surgical intervention were fitted to evaluate the association between treatment sequence and cause-specific survival (Fig. 1). Only variables with more than 80% completion rates were included in the multivariate model. For the survival analyses mentioned above, only samples for which the WHO grade was recorded were included in the analysis. Additionally, since the WHO only recognizes grades I, II, and III as options in the grading of meningiomas, patients with a reported WHO grade IV tumor were removed from all survival analyses. The significance level was set at alpha = 0.05. Odds ratios, hazard ratios, 95% confidence intervals, and p values were calculated. SAS software version 9.4 M3 for Linux was used to perform all data analysis (SAS Institute). This study complies with STROBE guidelines.\textsuperscript{22}

**Results**

**Sample Characteristics**

A total of 57,998 patients in the SEER database met the study criteria and were considered for analysis. Patients were further divided according to tumor behavior and histological classification. Analyses of patient and tumor characteristics were performed within each behavioral group and are represented in Tables 1 and 2.

Ninety-six percent of the patients (55,391) were diagnosed with benign meningiomas. Patients in this category were predominantly 60–79 years old at diagnosis (22,314 [40.3%]), female (42,025 [75.9%]), and white (43,041 [77.7%]). Tumors were mostly < 20 mm (18,802 [33.9%]) or 20–40 mm (16,721 [30.2%]) in size and were predominantly located in the cerebral meninges (46,307 [83.6%]). One lesion subtype, psammomatous meningioma, had a greater tendency to be located in the spinal meninges (2425 [4.4%]) compared to benign meningiomas in general (2245 [4.4%]).

Atypical meningiomas were found in 1838 (3.2%) patients. They mostly occurred in the patients who were female (1086 [59.1%]), white (1362 [74.1%]), and ages 40–59 years (753 [41.0%]) or 60–79 years (713 [38.8%]). The tumors mostly arose in the cerebral meninges (1615 [87.7%]) and presented with sizes > 40 mm (1020 [55.5%]). However, meningiomatosis (NOS) had a more even distribution among the tumor size categories of < 20 mm (29 [21.8%]), 20–40 mm (34 [25.6%]), and > 40 mm (41 [30.8%]).

Seven hundred sixty-nine (1.3%) cases were identified as anaplastic meningiomas. Much like the other two groups of tumors, the pattern of white (569 [74.0%]), married (414 [53.8%]), female (461 [60.0%]) patients was seen in the anaplastic type. However, the papillary meningioma subtype specifically showed a male predominance (49 [62.8%]). The age group most affected was 40–59 years old (308 [40.1%]), followed by 60–79 years old (286 [37.2%]). Tumors were generally located in the cerebral meninges (602 [78.3%]). Although most cases had tumors measuring > 40 mm in size (221 [28.7%]), a majority of cases in this behavior category had unknown sizes (408 [53.1%]).

**Trends in Treatment Paradigms**

Tables 1 and 2 outline the trends in the treatment para-

| Variable | p Value | HR | 95% CI |
|----------|---------|----|--------|
| No treatment | Reference | | |
| Biopsy | 0.0795 | 0.101–1.053 |
| STR | 0.697 | 0.291–2.175 |
| GTR | 0.0129\* | 0.289 | 0.109–0.769 |
| RT | 0.676 | 0.186 | 0.727 |
| RT + biopsy | 0.3826 | 0.253 | 0.012–5.529 |
| RT + STR | 0.6553 | 1.395 | 0.329–5.917 |
| RT + GTR | 0.5371 | 0.608 | 0.125–2.956 |

* Statistically significant.
digms for each type of meningioma. Of the three behavior categories, benign meningiomas were least likely to be treated (30,291 [54.7%]). When they were treated, however, resection was preferred, with GTR being achieved in 13,813 (24.9%) patients. Generally, no radiotherapy (51,261 [92.5%]) was administered. Cases of atypical meningioma were managed mostly by GTR alone (956 [52.0%]), followed by GTR and radiation (306 [16.6%]). A total of 535 (29.1%) patients did receive radiotherapy. Anaplastic tumors were managed similarly to atypical tumors, with most treated via GTR alone (258 [33.6%]) or GTR followed by radiation (151 [19.6%]). A higher proportion of patients with anaplastic tumors received radiotherapy (267 [34.7%]) compared to the other groups.

| TABLE 4. Results of Cox proportional hazards models for atypical meningioma |
| --- |
| Variable | p Value | HR       | 95% CI       |
| **Treatment sequence** |         |          |              |
| GTR | Reference |          |              |
| No treatment | 0.2437 | 3.107 | 0.462–20.898 |
| STR | 0.0735 | 2.973 | 0.902–9.801 |
| RT + biopsy | 0.6189 | 1.600 | 0.251–10.204 |
| RT + STR | 0.0334* | 4.282 | 1.121–16.354 |
| RT + GTR | 0.6284 | 1.353 | 0.398–4.603 |
| **Histology** |         |          |              |
| Atypical meningioma | 0.3755 | 0.192 | 0.005–7.370 |
| Meningiomatosis, NOS | 0.3055 | 0.413 | 0.076–2.242 |
| Clear cell meningioma | 0.0001* | 45.524 | 11.83–175.178 |
| **Age (yrs)** |         |          |              |
| 0–19 | 0.8308 | 0.705 | 0.029–17.373 |
| 20–39 | 0.7527 | 1.247 | 0.316–4.914 |
| 40–59 | Reference |          |              |
| 60–79 | 0.2766 | 1.784 | 0.626–5.085 |
| 80+ | <0.0001* | 45.524 | 11.83–175.178 |
| **Race** |         |          |              |
| White | Reference |          |              |
| Black | 0.6821 | 1.269 | 0.406–3.965 |
| Other | 0.5389 | 0.572 | 0.096–3.398 |
| **Sex** |         |          |              |
| Male | Reference |          |              |
| Female | 0.9341 | 1.035 | 0.457–2.344 |
| **Marital status** |         |          |              |
| Single | Reference |          |              |
| Divorced, separated, or widowed | 0.7523 | 0.817 | 0.234–2.858 |
| Married or domestic partner | 0.2414 | 0.542 | 0.195–1.509 |
| **Anatomical location** |         |          |              |
| Brain meninges | Reference |          |              |
| Meninges (NOS) | 0.8688 | 0.859 | 0.141–5.217 |
| Nonmeningeal | 0.9959 | 1.009 | 0.031–33.056 |
| Spine meninges | 0.5941 | 2.289 | 0.109–48.141 |
| **Tumor size** |         |          |              |
| <20 mm | Reference |          |              |
| 20–40 mm | 0.5415 | 0.378 | 0.017–8.567 |
| >40 mm | 0.9252 | 1.149 | 0.063–20.945 |
| **WHO grade** |         |          |              |
| II | Reference |          |              |
| III | 0.0777 | 5.034 | 0.836–30.313 |

| TABLE 5. Results of Cox proportional hazards models for anaplastic meningioma |
| --- |
| Variable | p Value | HR       | 95% CI       |
| **Treatment sequence** |         |          |              |
| GTR | Reference |          |              |
| No treatment | 0.7305 | 1.81 | 0.062–52.894 |
| Biopsy | 0.0851 | 0.144 | 0.016–1.308 |
| STR | 0.2441 | 0.259 | 0.027–2.515 |
| RT + biopsy | 0.0593 | 0.261 | 0.065–1.054 |
| RT + STR | 0.0184* | 0.089 | 0.012–0.665 |
| RT + GTR | 0.0019* | 0.162 | 0.052–0.511 |
| **Histology** |         |          |              |
| Meningioma, malignant | Reference |          |              |
| Papillary meningioma | 0.0880 | 0.273 | 0.061–1.213 |
| **Age (yrs)** |         |          |              |
| 0–19 | 0.3120 | 6.486 | 0.173–243.224 |
| 20–39 | 0.7937 | 0.659 | 0.029–15.063 |
| 40–59 | Reference |          |              |
| 60–79 | 0.0113* | 4.395 | 1.399–13.808 |
| 80+ | 0.0640 | 4.570 | 0.915–22.822 |
| **Race** |         |          |              |
| White | Reference |          |              |
| Black | 0.4161 | 1.650 | 0.494–5.514 |
| Other | 0.9532 | 1.034 | 0.337–3.175 |
| **Sex** |         |          |              |
| Male | Reference |          |              |
| Female | 0.5479 | 1.295 | 0.557–3.014 |
| **Marital status** |         |          |              |
| Single | Reference |          |              |
| Divorced, separated, or widowed | 0.0484* | 8.001 | 1.014–63.108 |
| Married or domestic partner | 0.0498* | 7.463 | 1.002–55.603 |
| **Anatomical location** |         |          |              |
| Brain meninges | Reference |          |              |
| Meninges (NOS) | 0.6773 | 1.343 | 0.335–5.38 |
| Nonmeningeal | 0.9859 | 1.033 | 0.027–39.155 |
| Spine meninges | 0.9797 | 0.957 | 0.031–29.142 |
| **Tumor size** |         |          |              |
| <20 mm | Reference |          |              |
| 20–40 mm | 0.5001 | 0.448 | 0.043–4.629 |
| >40 mm | 0.8490 | 1.213 | 0.167–8.819 |
| **WHO grade** |         |          |              |
| II | Reference |          |              |
| III | 0.0050* | 8.625 | 1.914–38.862 |

* Statistically significant.
Multivariate Results

The outcomes of different treatment sequences were examined using multivariate analysis with the Cox proportional hazards model, controlling for histological characteristics, demographic factors, anatomical location and size of the tumor, and WHO grade. Tumors without a known WHO grade were excluded from this analysis. In the benign meningioma group (11,673 cases; Table 3), GTR, as compared to no treatment, yielded a significant decrease in the cause-specific mortality risk (HR 0.289, 95% CI 0.109–0.769, p = 0.0129). In the analysis of atypical and anaplastic meningiomas, the reference group was set as GTR in order to better examine the effects of radiotherapy on the risk of death since all standard of care in these treatments involved attempts at GTR. In doing this, we observed that for anaplastic tumors (166 cases; Table 5), adjuvant radiation led to a significant decrease in mortality for the patients who had undergone either GTR (HR 0.162, 95% CI 0.052–0.511, p = 0.0019) or STR (HR 0.089, 95% CI 0.012–0.665, p = 0.0184). However, for atypical tumors (1092 cases; Table 4), adjuvant radiotherapy with STR increased the mortality risk compared to GTR alone (HR 4.282, 95% CI 1.121–16.354, p = 0.0334). Moreover, we saw that the addition of adjuvant radiotherapy had no statistically significant effect in patients with GTR (HR 1.353, 95% CI 0.398–4.603, p = 0.6284).

Across all behavior types of meningioma, an increase in mortality risk was seen in the patient populations ages 60–79 and above 80 compared to patients 40–59 years old (HR 4.396, p = 0.0006 and HR 19.123, p < 0.0001 for benign; HR 1.784, p = 0.2786 and HR 45.523, p < 0.0001 for atypical; HR 4.395, p = 0.0113 and HR 4.570, p = 0.0640 for anaplastic). In benign meningiomas, significantly increased mortality was associated with an increased tumor size and WHO grade II tumors (HR 4.430, 95% CI 1.084–18.114, p = 0.0383; HR 2.963, 95% CI 1.373–6.392, p = 0.0056, respectively). A similar trend was seen for anaplastic tumors, in which WHO grade III meningiomas had unfavorable outcomes compared to WHO grade II tumors (HR 8.625, 95% CI 1.914–38.862, p = 0.005).

In order to more closely examine the increased mortality risk associated with both STR and RT in atypical meningiomas, we performed a breakaway analysis comparing all treatment groups, with STR as the reference group (Table 6). We found that adjuvant radiation did not significantly lower risks in the setting of performing STR (HR 1.440, 95% CI 0.307–6.766, p = 0.6438).

Graphic analysis using the Kaplan-Meier curve was performed to evaluate the association between treatment sequences involving resection or radiation and survival outcomes in atypical meningiomas (Fig. 1). Using a log-rank test with Sidak correction, we found no significant differences between any of the four treatment groups tested.

| Treatment Sequence | p Value | HR  | 95% CI        |
|--------------------|---------|-----|---------------|
| STR Reference      |         |     |               |
| No treatment       | 0.9671  | 1.045 | 0.128–8.562 |
| GTR                | 0.0735  | 0.336 | 0.102–1.109 |
| RT + biopsy        | 0.5530  | 0.538 | 0.070–4.165 |
| RT + STR           | 0.6438  | 1.440 | 0.307–6.766 |
| RT + GTR           | 0.3012  | 0.455 | 0.102–2.024 |

* All other findings for histology, age, sex, etc. from Table 4 are unchanged in this analysis.
Discussion

This largest-to-date SEER-based assessment of the epidemiology of primary meningiomas included a total of 57,998 patients. Our study confirmed previously reported information suggesting a predisposition for benign meningiomas in older, female, white populations with the tumors predominantly smaller than 40 mm and located in the cerebral meninges. Similar distributions of patient demographics were seen in the atypical and anaplastic cases with the only difference in lesion characteristics being a larger proportion of cases with tumors larger than 40 mm, which is consistent with the literature.

The Cox proportional hazards model allowed us to assess the relative hazard of various treatment paradigms on the cause-specific mortality of patients with various levels of primary meningioma. For benign meningiomas, standard of care is a “wait and watch” approach for most of the nonaggressively growing tumors. Performing resection only in those cases in which size may create a mass effect or growth rates increase. This is reflected in our analysis, which showed that the majority of patients received no treatment and that even when resection was performed, radiotherapy was uncommon. Our analysis also showed a significantly lower HR for patients who underwent GTR but no significant HRs for the other treatments. This suggests that in patients with symptoms associated with their benign tumor, resection without the use of adjuvant radiotherapy is beneficial, which is consistent with the literature.

In atypical meningioma, the standard of care is GTR when possible, although there is no consistency regarding the role of radiotherapy. Our analysis showed that more than a quarter of all atypical meningiomas were treated with adjuvant radiotherapy. In cases in which STR was performed with adjuvant radiotherapy, there was a significantly increased hazard as compared to GTR alone. This finding confirms that GTR should always be attempted. However, our data showed that after GTR, radiation did not impart a significant survival benefit despite the trend of using adjuvant radiotherapy for these tumors. Additionally, our findings showed that, compared to a baseline of performing STR only, radiotherapy following STR was not associated with a lower HR. Therefore, even in cases in which surgeons are unable to resect the entirety of an atypical meningioma, our data do not support the use of concomitant radiotherapy.

The standard of care for anaplastic meningioma is to perform GTR if possible and to provide adjuvant radiotherapy. Our data revealed that only about a third of all atypical meningiomas were treated with adjuvant radiotherapy. In the absence of a similarly large-scale database that includes these other factors, this analysis represents the largest available baseline from which to work, with acknowledgment of its limitations, and makes valuable suggestions about the treatment choices that physicians make. Moreover, given the limitations of using this type of registry data, we strongly suggest that further work be done in a prospective manner (while documenting a wide variety of clinically relevant cofactors) to assess the effectiveness of adjuvant radiotherapy use (while noting the specific type
and dosing regimen) after resection of an atypical meningioma.

Conclusions

The results of this retrospective population-based study provide some insight into the role of adjuvant radiotherapy in the management of meningiomas. We demonstrated that the use of radiation after an attempt at GTR did not impart a mortality risk reduction in cases of benign or atypical meningiomas. Notably, adjuvant radiation did not significantly reduce the hazard risk in the STR of atypical meningiomas, suggesting that radiotherapy may not be beneficial despite residual tumor. On the other hand, anaplastic meningiomas did see significant risk reduction with radiotherapy following both GTR and STR. Given the inherent limitations of the SEER database and retrospective analysis, our results are insufficient to redefine the standard management of these tumors; however, they do provide a direction for prospective randomized clinical trials to measure the outcomes of radiation therapy after meningioma resection and define which populations may benefit from adjuvant radiotherapy.

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Disclosures

Dr. Mehta has been a consultant for Depuy Synthes and Globus Medical.

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Conception and design: Mehta, Reddy, Ryoo, Denyer. Acquisition of data: Mehta. Analysis and interpretation of data: Reddy, Ryoo, Denyer, McGuire. Drafting the article: Reddy, Ryoo, Denyer. Critically revising the article: Ryoo, McGuire. Reviewed submitted version of manuscript: all authors. Statistical analysis: Reddy, Denyer. Study supervision: Mehta.

Supplemental Information

Videos

Video Abstract. https://vimeo.com/334430572.

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