Cancer Epidemiology 62 (2019) 101562

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Incidence, mortality and outcome of meningiomas: A population-based study from Germany

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ARTICLE INFO

Keywords:
Meningioma
Etiology
Epidemiology
Outcome

ABSTRACT

Background: Meningiomas are mostly benign tumors that originate from the coverings of the brain and spinal cord. Compared to malignant glial tumors, meningiomas are relatively understudied with regard to their risk factors and epidemiology. In particular, population-based data on cancer burden and patient outcomes are scant.
Methods: Population-based data from Saarland, a federal state in South-Western Germany, were used; the data included 992 patients diagnosed with a first meningioma between 2000 and 2015. Incidence and mortality rates—as well as estimates of observed and relative survival and cumulative incidence of tumor recurrence up to 10 years after diagnosis—were derived by sex, age, WHO grade, and whether or not the patient had undergone surgery.
Results: This population-based study not only included patients treated in the regional university hospital but also those treated elsewhere or patients without any surgical treatment. The mean age of the patients at diagnosis was 63 years, and 70%, 28% and 3% had WHO grade I, II and III meningiomas, respectively. Ten-year observed and relative survival of all patients combined was 72% and 91% respectively. Tumor-related mortality varied by sex and increased with age at diagnosis and the WHO grade of the tumor. The overall 10-year cumulative incidence of meningioma recurrence was 9%.
Conclusion: This analysis represents the first modern population-based analysis of meningioma incidence and mortality and outcomes of patients with such neoplasms in Germany. Derived from an unselected sample of patients, this study may fill a hitherto existing gap in the literature on meningiomas.

1. Introduction

Meningiomas are derived from the arachnoidal cap cells of the leptomeninges, the soft coverings of the brain and spinal cord. Although the matrix tissue constitutes less than 5 g of the intracranial and intraspinal mass, meningiomas are estimated to constitute between 26% and 34% of the primary tumors of these tissues. Most meningiomas are sporadic, slowly growing benign tumors. However, certain histological subtypes, and also a minority of common-type meningiomas, show a more aggressive biological behavior and are associated with an increased risk of recurrence and an unfavorable prognosis. Therefore, the current WHO classification of brain tumors [1] distinguishes three grades of meningiomas: the common type (WHO grade I), the atypical or intermediate type (grade II) and the anaplastic or malignant type (grade III).

Currently, meningiomas are among the most common intracranial tumors, with an estimated incidence of eight cases per 100,000 persons per year [1,2]. It is well known that adult females are affected by meningiomas far more frequently than adult males [3–6]. The majority (˜90%) of meningiomas are located intracranially, but 10% are found in the spinal meninges [7–10]. Meningiomas primarily occur in elderly patients, with increased incidence in individuals > 65 years of age [2]. These tumors are exceedingly rare in children (representing 0.4–4.1% of all pediatric tumors) [11]. The meningioma is one of the cytogenetically best-studied solid tumors. The characteristic and most frequent chromosomal aberration in meningiomas is monosomy 22 [5], which, however, has been shown to be an isolated anomaly not relevant for prognosis [6,9,10].

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https://doi.org/10.1016/j.canep.2019.07.001
Received 26 April 2019; Received in revised form 28 June 2019; Accepted 3 July 2019
Available online 17 July 2019

Compared to the malignant glial tumors, meningiomas are relatively understudied. The literature on the burden of meningioma is limited: e.g. the most recent volume of Cancer Incidence in Five Continents does not include any data on the incidence of meningiomas [12]. Several available studies reported results from the US but these were often restricted with regard to the types of meningiomas included. A recently published study included incidence of meningiomas of WHO grades II and III in the US only [13]. Up-to-date and detailed population-based data on the burden of meningiomas from other regions and on the outcomes of meningioma patients are sparse, as most published studies are based on hospital cohorts or used otherwise selected samples of patients (e. g [14–17].).

2. Materials and methods

For this study, population-based cancer registry (CR) data from Saarland were used; these data included records of 992 patients diagnosed between 2000 and 2015 with a first meningioma: code of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) D32, D42, C70, topography and morphology codes of the International Classification of Diseases for Oncology (first revision of the third edition, ICD-O 3) [18] C70 and 9530/0-9539/3. Saarland is a federal state in South-Western Germany with a population of 1.0 million residents in 2011. The CR has been in operation since 1967 and its case ascertainment is regularly estimated as almost complete ($\geq$95%) [19,20]. The CR regularly contributes data to descriptive and analytical studies on cancer etiology, burden of malignant diseases, and outcomes of cancer patients (e.g [12,21,22]).

In Saarland, cancer reporting is mandatory by law. The CR obtains notifications from hospitals, pathology laboratories, outpatient clinics, radiotherapy departments, doctors in private practice, screening programs and other regional CRs. To ascertain complete mortality follow-up of the registered patients, the CR obtains death certificates of all deaths in the covered population from local health authorities and records of outmigration and deaths from registration offices. In addition to notifications of newly diagnosed cancers, the CR obtains notifications of recurrent cancers from the above-listed sources on the occasion of their detection and repeat treatment.

The following patient and tumor characteristics and classifications were available and used: sex (male, female), cancer diagnosis according to ICD-10 and site and morphology according to ICD-O3, date of and age at diagnosis, WHO grade (I, II, III, missing) [1], end of follow-up, vital status at end of follow-up (alive, dead), surgical treatment (yes, no, unknown), date of first occurrence of tumor recurrence, and reporting source. The date of the first pathology report was used as date of diagnosis for patients with histologically proved tumors. Of patients without histologically confirmed tumors, the reported date of the first admission to a hospital or outpatient clinic was used. Survival observations were right censored if no event was observed until end of follow-up (31 December 2017 at the latest) and survival times between diagnosis and first occurrence of meningioma recurrence, death and end of follow-up were derived.

Descriptive analyses of the included patients were derived according to sociodemographic and tumor characteristics. We calculated age-standardized rates of incidence and mortality—including all deaths with meningioma recorded as the (underlying) cause of death—per 100,000 persons per year, using the European Standard Population [23]. Kaplan–Meier estimates of observed survival (OS) up to 10 years after diagnosis were derived overall and by sex, age, WHO grade and provision of surgery. The logrank test was applied to test for differences between the estimated OS curves (H0: no differences in the probability of death between different patient populations at any point during follow-up) [24]. Cox proportional regression modeling was used to estimate hazard ratios (HRs) of the effect of sex, age and WHO grade of the meningioma and provision of surgery on the OS (while adjusting for covariables). Plots of observed versus modeled survival showed no systematic departures from the proportional hazards assumption and are provided as Supplementary material. To quantify tumor-related excess mortality, estimates of relative survival (RS) up to 10 years after diagnosis were derived overall and by sex, age, WHO grade and provision of surgery. RS is derived as the ratio of OS of the patients and expected survival of a sex-, age- and calendar-time-matched group of persons of the underlying population with average risk of death (thus, an RS estimate of 100% results if the observed mortality of the patients is equal to their expected mortality) [25]. We used the Ederer II method [26] to calculate RS after a meningioma diagnosis, using life tables provided by the Statistical Office of Saarland to estimate the expected survival of the general population. Regression modelling of RS was used to test for differences in the relative excess risk of death according to sex, age, WHO grade, and provision of surgery, respectively. The used models of RS assumed the excess number of deaths to follow a Poisson distribution and included the follow-up year along with each of the aforementioned items as categorical explanatory variables [27,28]. The survival experience of all patients with available follow-up were used for the estimation of OS and RS.

Estimates of the cumulative incidence of meningioma recurrence in patients who had received surgery up to 10 years after diagnosis were derived overall and stratified by sex, age and WHO grade, respectively, taking into account mortality from any cause as a competing risk. The used estimator of the cumulative incidence is based on a generalization of the Kaplan–Meier estimator and quantifies the risk that the event under study will occur before any specified time in the presence of competing risks [29,30]. Three patients with a recorded recurrence within 90 days after surgery were excluded from the analyses.

Standard errors of the point estimates of OS, RS and cumulative incidence of recurrence are based on the Greenwood approach [31,32]. The R Language and Environment for Statistical Computing (release 3.1.3) [33] along with the extension packages survival, periodR [34] and cmprsk [35] were used for data preparation, statistical analyses and visualization. P-values of chi-squared goodness-of-fit tests, two-sided logrank tests, Wald chi-squared tests and tests on the equality of cumulative incidence curves across subsamples [35] were derived and considered as a statistically significant result if < 0.05.

3. Results

Overall, data of 992 patients who were diagnosed between 2000 and 2015 were included; among these almost three out of four (72%) were women, resulting in a female:male ratio of 2.53 ($p < 0.001$; Table 1). Overall, 28%, 49% and 23% of the patients were aged $\leq$54, 55–74, and 75+ years, respectively. Mean age at diagnosis was 63 years. WHO grade was available for 80% of the patients, of whom 70% had a benign meningioma (WHO grade I), 28% had an atypical meningioma (grade II), and 3% had an anaplastic meningioma (grade III). Higher proportions of atypical and anaplastic meningiomas occurred in men (39%) than in women (27%), respectively ($p = 0.003$). The proportion of meningiomas with a death certificate as the only source of information was 6%. Follow-up information was available for 94% of the patients. In total 26 meningiomas arose from the spinal meninges (2.6%).

Information on tumor resection was available for 922 patients (93%), of whom 847 (92%) underwent surgery. The proportion of patients with surgery decreased from 93% among patients aged $\leq$74 years to 86% among older patients ($p = 0.001$). Of the patients with information on surgical treatment, 678 (74%) were treated at the state university hospital. The proportion of WHO grade II and III meningiomas was about double (31%) in patients who were treated at the university hospital compared to patients who received surgery somewhere else (14%; data not shown). The recorded morphological types of the resected meningiomas according to the ICD-O 3 were as follows: 614 (73%) ‘meningioma, not otherwise specified (NOS)’ (morphological code: 9530/0), 126 (15%) ‘meningiomatosis, NOS’ (9530/1), 32

Table 1
Characteristics of the included patients diagnosed with a first meningioma (ICD-10: D32, D42, C70) between 2000 and 2015.

		Overall		Male		Female		P-value
		N	%	N	%	N	%	
Overall		992	100.0					
Sex	male	281	28.3					
	female	711	71.6					< 0.001
Age	< = 54	276	27.8	74	26.3	202	28.4	
	55-74	485	48.9	144	51.2	341	48.0	
	75+	231	23.3	63	22.4	168	23.6	0.643
WHO grade	available	789	79.5	226	80.4	563	79.2	
	I [a]	550	69.7	138	61.1	412	73.2	
	II [a]	217	27.5	81	35.8	136	24.2	
	III [a]	22	2.8	7	3.1	15	2.7	0.003
Source of information	death certificate only	62	6.3	21	7.5	41	5.8	–
Follow-up available		931	93.9	260	92.5	671	94.4	–
Surgery	Available	922	92.9	259	92.2	663	93.2	
	no [a]	75	8.1	17	6.6	58	8.7	
	yes [a]	847	91.9	242	93.4	605	91.3	0.334
	< = 54 [b]	256	30.2	68	28.1	188	31.1	
	55-74 [b]	434	51.2	131	54.1	303	50.1	
	75+ [b]	157	18.5	43	17.8	114	18.8	0.558
Recurrence [c]		61	6.1	21	7.5	40	5.6	–
Death [c]		315	31.8	96	34.1	219	30.8	–

Annotations: [a] percentages among patients/cases with available information, [b] among patients with surgery, [c] among patients with available follow-up. The Chi-squared test was used to test for an unequal sex ratio of the patients and for differences in the distribution of age, WHO grade of the meningiomas and provision of surgery treatment overall and by age between male and female patients. ICD-O 3 topography and morphology codes of the selected cases were C70 and 9530–9539, respectively.

(4%) 'fibrous meningioma' (9532/0), 25 (3%) 'meningothelial meningioma' (9531/0), 21 (3%) 'meningioma, malignant' (9530/3), 16 (2%) 'transitional meningioma' (9537/0), and 13 (1%) other specified forms of meningiomas.

During follow-up, meningioma recurrence was observed in 61 patients (6%) with surgery, and 315 (32%) of all included patients died. Overall mean follow-up time was 9.0 years.

During the study period, the age-standardized incidence rate of meningiomas was 2.5 and 5.8 cases per 100,000 men and women per year, respectively. Between 2000 and 2015, incidence remained constant in both male and female populations (Fig. 1A). Age-standardized mortality rate was 0.3 deaths from meningioma per 100,000 men and women per year, respectively, which remained constant over time (Fig. 1C). Whereas age-specific incidence increased continuously from age 20–24 years onwards, deaths from meningiomas were essentially observed in patients aged 75+ years only (Fig. 1B, C).

Five- and 10-year OSs of all meningioma patients combined were 85% and 72% respectively (Table 2). Ten-year OS was 69% among male and 73% among female patients ($p = 0.281$). Survival (statistically) significantly decreased with WHO grade. Patients with benign, atypical and malignant meningiomas had 5-year OSs of 88%, 86% and 50% and 10-year OSs of 77%, 71% (HR 1.10, $p = 0.529$) and 23% (HR 5.54, $p \leq 0.001$), respectively. Median survival of patients with a malignant meningioma was 4 years and 1 month.

Five- and 10-year RSs of all patients combined were 94% and 91% respectively (Table 2). Tumor-related excess mortality varied with regard to sex and increased by age of the patients and WHO grade of the meningioma. Overall 10-year RS was 95% among male and 90% among female patients ($p = 0.243$). Of patients aged ≤54 years, 10-year RS was 95% compared to 90% in older patients ($p < 0.001$). Patients with benign meningiomas had a 5- and 10-year RS of 97% and thus suffered from little tumor-related excess mortality. Five- and 10-year RSs for patients with atypical meningiomas were 96% and 90% respectively. Patients with malignant meningiomas had a limited prognosis as their 5- and 10-year RSs were 61% and 30% respectively ($p < 0.001$).

Overall 5- and 10-year cumulative incidence of meningioma recurrence was 5% and 9% respectively (Table 2). Ten-year cumulative incidence of recurrence varied between 12% among males and 8% among females ($p = 0.212$). The risk of recurrence decreased with age. The 10-year cumulative incidence of meningioma recurrence was 13%, 8% and 5% among patients aged ≤54, 55–74 and 75+ years respectively ($p = 0.072$). The risk of recurrence further increased with WHO grade. Patients with benign, atypical and malignant meningiomas had a 5-year cumulative incidence of recurrence of 4%, 9% and 23%, which increased to 6%, 17% and 30% 10 years after diagnosis, respectively ($p < 0.001$).

Figs. 2 and 3 depict the curves of observed OSs and cumulative incidences of meningioma recurrence up to 10 years after diagnosis.

4. Discussion

Meningiomas, as well as other tumors of the brain, are relatively uncommon, and most of the evidence of potential risk factors comes from case–control studies, as there are insufficient cases for reliable estimations in most cohort studies. In addition, as meningiomas are typically benign, most population-based CRs do not collect data on these neoplasms. Thus, many available studies are based on hospital cohorts or have used otherwise selected samples of patients (e.g. [14–17]).

For this study, population-based data from Saarland were used; these data included the records of 992 patients diagnosed with a first meningioma between 2000 and 2015. The use of these data allowed derivation of unselected estimates of cancer burden and detailed and clinically relevant data on the outcome of meningioma patients in terms of OS, RS, and risk of meningioma recurrence by major socio-demographic factors, tumor characteristics, and whether or not the patient had received surgery.

Of the patients included in this study, the mean age at diagnosis was 63 years. Whereas incidence increased continuously from age 20–24 years onwards, deaths from meningiomas were essentially observed only in patients aged 75+ years. Age-standardized mortality rate of meningiomas was 0.3 deaths per 100,000 men and women per year. Overall, these results are in line with data reported by Dudeley et al. who used data of the Surveillance, Epidemiology, and End Results (SEER) program from the US and reported a median age at diagnosis of 65 years when comparing pediatric and adult patients with meningiomas [36].

There are several notable findings in this study. First, 85% of the patients in our study had surgery with histologial confirmation of the diagnosis. Second, in our study the proportions of meningiomas of WHO grades I, II and III were 70%, 28% and 3% and the observed 10-year survival of the patients with these tumors was 77%, 71% and 23% respectively ($p < 0.001$). The median survival of patients with a malignant meningioma was 4.1 years. The 10-year RSs of patients with WHO grade I, II and III meningiomas were 97%, 90% and 30% respectively, which demonstrates the significant increase in tumor-related excess mortality by WHO grade ($p < 0.001$).

Grading of meningiomas has always been controversial. Obviously, the biological behavior of meningiomas cannot be accounted for by histological parameters alone [3,4,8,9,11,37–41]. In 1956, Zülch stated that it is not the histological grading which is most crucial for the rate of recurrence of meningiomas, but primarily the completeness of extirpation [42]. There is agreement in the literature that radical surgical extirpation is correlated with a good prognosis [3,8,9,17,42,43].

A recent analysis of the SEER data revealed that 55% of meningioma patients from the US treated during 2004–2007 had a histological confirmation of their tumor, and 43% received initial surgery [44]. In this study, the proportion of patients who underwent surgery was 92%.

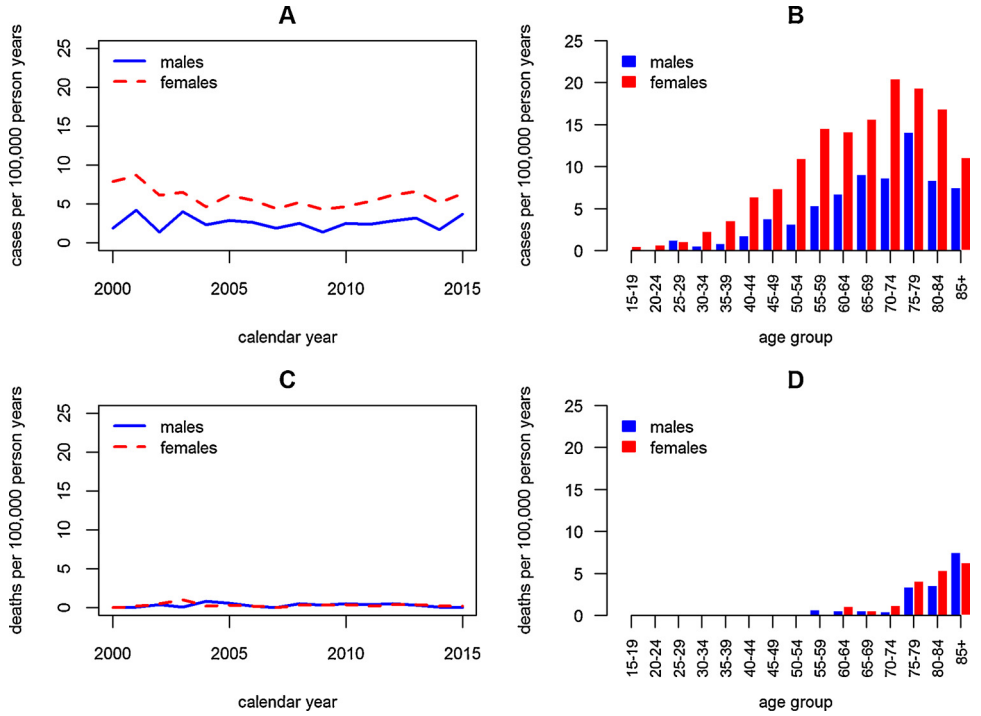

Fig. 1. Age-standardized (A) and age-specific (B) incidence rate (new cases per 100,000 person years) and age-standardized (C) and age-specific (D) mortality rate (deaths per 100,000 person years) of meningiomas (ICD-10: D32, D42, C70) in Saarland between 2000 and 2015.

This observation indicates that resection was offered to meningioma patients with symptomatic and asymptomatic tumors.

As the estimated proportion of patients with tumor extirpation did not include patients with meningiomas notified by death certificate only (DCO), the aforementioned proportion clearly overestimated the proportion of patients who actually had received surgery. If one assumes all patients with DCO-notified tumors to have received conservative treatment only, a proportion of patients with surgery of 85% is derived, which delineates a lower limit of this estimate.

In the aforementioned analysis of SEER data male patients were found to be more likely than female patients to undergo resection [44]. Cahill et al. speculated that this finding may be related to a difference in age and tumor size at diagnosis [44]. Interestingly, in our study higher proportions of WHO grade II and III tumors were observed in men (39%) compared to women (27%), along with a slightly higher likelihood of receiving a resection (93% versus 91%), respectively.

It is well known that females are affected far more frequently by meningiomas than males [3,6–9]. This observation was confirmed by

Table 2
Observed survival, hazard ratios, relative survival and cumulative incidence of tumor recurrence of patients diagnosed between 2000 and 2015 with a first meningioma (ICD-10: D32, D42, C70) up to 10 years after diagnosis overall and by sex, age, WHO grade, and surgery.

		Overall and tumor related survival												Risk of recurrence					
		N1	Observed survival						Relative survival					N2	Cumulative incidence				
			5-year		10-year		p-value	HR		5-year		10-year		p-value		5-year		10-year		p-value
			PE	SE	PE	SE		PE	95% CI	PE	SE	PE	SE			PE	SE	PE	SE	
Overall		930	84.6	1.2	71.6	1.8				94.3	1.3	91.2	2.2		844	5.1	0.8	8.9	1.2	
Sex	male	260	83.3	2.4	69.2	3.5	0.281	1.00	(ref)	95.0	2.7	95.1	4.6	0.243	241	6.0	1.6	11.7	2.6	0.212
	female	670	85.2	1.4	72.5	2.1		0.82	[0.62; 1.08]	94.0	1.5	89.9	2.6		603	4.8	0.9	7.8	1.3	
Age	< = 54	275	96.5	1.2	91.4	2.0	< 0.001	1.00	(ref)	98.5	1.1	95.0	2.1	< 0.001	255	6.8	1.7	12.9	2.5	0.072
	55-74	471	86.8	1.6	71.6	2.5		5.11	[3.16; 8.27]	94.7	1.7	}89.7	}3.2		432	4.4	1.0	7.9	1.6	
	75+	184	60.9	3.8	38.9	4.8		14.1	[8.54; 23.3]	86.7	4.1				157	4.7	1.9	4.7	1.9	
WHO grade	I	550	87.6	1.5	76.8	2.3	< 0.001	1.00	(ref)	96.8	1.6	96.8	2.8	< 0.001	512	3.7	0.9	5.8	1.0	< 0.001
	II	217	85.7	2.4	70.6	3.5		1.10	[0.81; 1.50]	95.6	2.4	90.2	4.5		206	8.7	2.0	16.9	2.9	
	III	22	50.0	10.7	22.9	9.6		5.54	[3.25; 9.46]	61.2	13.1	30.4	12.6		21	23.8	9.6	30.2	11.1	
	missing	141	76.9	3.7	64.0	4.6		1.23	[0.87; 1.74]	87.5	4.5	84.2	6.1		105	1.0	1.0	1.0	1.0	
Surgery	yes	847	85.5	5.1	72.1	1.9	0.096	1.00	(ref)	94.7	1.4	91.1	2.3	0.016[a]	–	–	–	–	–	–
	no	75	75.5	1.2	63.1	6.9		1.07	[0,69; 1.66]	89.9	5.7	NE	NE		–	–	–	–	–	

Abbreviations: N1 = number of patients at risk at t = 0 and contributing survival experience, N2 = number of patients with surgery and contributing survival experience, PE = point estimate, SE = standard error of PE, HR = hazard ratio, 95% CI = 95% confidence interval of the PE, NE = not estimable due to large proportion of patients aged 75 + years. Annotations: [a] of a relative survival model up to 5 years after diagnosis. The Kaplan Meier estimator was used to estimate the observed survival. Cox regression modeling was used to estimate hazard ratios adjusted for sex, age, WHO grade and surgery, respectively. Life table methodology was used to obtain estimates of relative survival. Ten-year estimates of relative survival have not been derived separately for patients aged 75 + due to small numbers of observed and expected deaths within this group. The estimates of the cumulative incidence of meningioma recurrence are based on a generalized Kaplan Meier estimator and the analyses included patients who had received surgery. ICD-O 3 topography and morphology codes of the selected cases were C70 and 9530–9539, respectively.

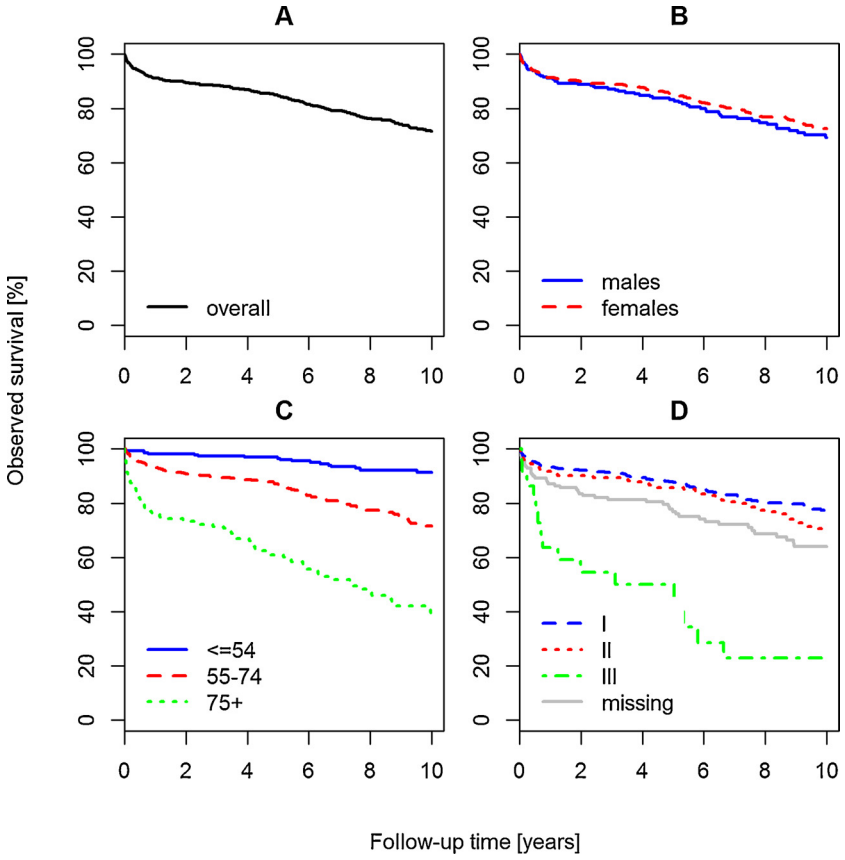

Fig. 2. Observed survival of patients with meningiomas (ICD-10: D32, D42, C70) diagnosed between 2000 and 2015 up to 10 years after diagnosis overall (A) and by sex (B), age at diagnosis (C) and WHO grade (C).

our study. Of the 992 included patients, 72% were females, which corresponds to a female:male ratio of 2.5. A ratio of 2 is cited in many studies (e.g [45,46].); however, ratios of up to 3 have been observed [47,48]. The female:male ratio decresed by WHO grade from 3.0 among patients with benign meningiomas to 1.7 among patients with atypical or anaplastic meningiomas. Several studies have suggested an association between exposure to endogenous or exogenous estrogen and incidence of meningioma [48–50]. The observed age-specific sex ratios did not point to a possible birth cohort effect of a declining excess risk of meningiomas among females after HRT usage in Germany had dropped [51].

The sex ratio was shifted when the tumors were broken down by the overall 10-year cumulative incidence of recurrence. Here, we found a sex ratio of 0.7. This shift confirms earlier reports [8,9,52]. In our study the overall 10-year cumulative incidence of meningioma recurrence was 9%, varying between 12% in males and 8% in females ($p = 0.212$). In a previous study the total risk of recurrence in 661 patients after complete tumor extirpation, with tumors additionally examined by cytogenetic analysis, was 8% [9]. In contrast to these results, in a large study containing 8891 patients with benign meningiomas, 21% recurrences were observed in the first 5 years [9]. In this study, a 5-year risk of recurrence of 4% was observed in patients with benign meningiomas. A possible explanation of this rather large difference might be higher proportions of patients with an incomplete removal of the tumor in the aforementioned study, as a recurrence cannot always exactly be distinguished from a regrowing tumor which had been only partially removed. In the same study [9], among 771 patients with malignant meningioma, a risk of recurrence of 32% was observed, which was similar to the finding of the present study (24% up to 5 years and 30% up to 10 years).

In our study cohort the risk of disease recurrence decreased with age at diagnosis. The age-specific estimates of 10-year cumulative incidence of meningioma recurrences were 13%, 8% and 5% among patients aged ≤ 54, 55–74 and 75+ years, respectively ($p = 0.072$). Similar results were reported by Feun et al. in a descriptive analysis of tumor registry data of patients with intracranial meningioma treated at the Jackson Memorial Hospital [53]. They also found a trend for improved survival for patients with meningiomas for the younger ages [53]. The risk of recurrence further increased with WHO grade. Among patients with benign, atypical and malignant meningiomas, the 10-year cumulative incidences of recurrence were 6%, 17% and 30%, respectively ($p < 0.001$).

Strengths of this study include: (a) the use of a cohort of patients which allowed estimation of the meningioma burden of a population and provided unselected estimates of the outcome of meningioma patients; (b) the availability of information on WHO grade and whether or not the tumors had been extirpated; and (c) the usage of clinical information on recurrence and the availability of death certificates and administrative data of registration offices, which warranted a high completeness of the follow-up of the patients.

The analysis of the recorded tumor morphology according to ICD-O3 revealed a limited utilization of this classification scheme in the daily practice of pathologists and clinicians, as more than two out of three cases were reported as a meningioma of not otherwise specified type. The CRs along with clinicians and pathologists should evaluate which classification and grading system they may use for a more precise categorization of meningeal tumors for epidemiological purposes in the future.

The database of the CR which receives notifications from a variety of sources includes patients receiving both surgical and conservative treatment. The CR further obtains certificates of all deaths in the underlying population. During the study period, the proportion of DCO-

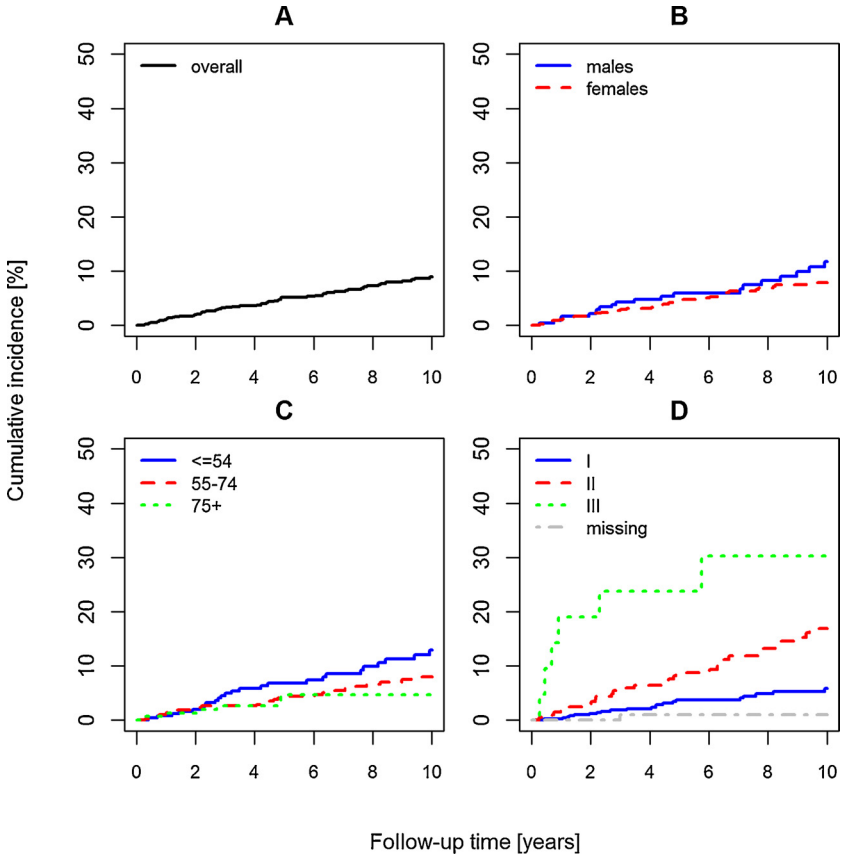

Fig. 3. Cumulative incidence of meningioma recurrence in patients with meningioma (ICD-10: D32, D42, C70) diagnosed between 2000 and 2015 who had received surgery up to 10 years after diagnosis: overall (A) and by sex (B), age at diagnosis (C) and WHO grade (C).

notified cases of all registered invasive malignant tumors was 5% and similar to the observed proportion of DCO-notified meningiomas. Given the rather small proportion of DCO-notified meningiomas, the case ascertainment of meningiomas may be considered as sufficiently complete for the analyses presented. The facts that reporting of recurrent tumors is mandatory by law, that the CR actively collects data of DCO-notified cancers, and that patients with recurrent meningiomas may undergo open resection or receive radiation therapy and often have a favorable prognosis [54] maximize the likelihood of the registration of a recurrent meningioma and an almost complete follow-up of the patients with regard to recurrences.

A major weakness of this study is the lack of more detailed information on the surgical treatment provided and its extent. An analysis of the impact of the extent of surgery on progression-free survival and an assessment of the clinical significance of the Simpson grading system, which has been called into question in recent years [3,55–57], would have added further value to this work. Treatment patterns and outcome may further have been influenced by the treatment facilities. However, no inter-hospital variation in the treatment could be evaluated in this analysis. As the standardized registration of incident benign neoplasms of the meninges and their treatment started in other German regions only very recently, results as presented in this paper will not be available for much larger German populations until the mid 2020s [58].

To summarize, this work presents population-based data on the burden of meningiomas and derived unselected outcome measures of meningioma patients in terms of overall and cancer-related survival and the risk of recurrence after surgery up to 10 years after diagnosis. So far, most published studies reported findings of hospital cohorts or used otherwise selected samples of patients. The findings of this study may therefore be of great relevance for clinicians and their patients and fill a hitherto existing gap in the literature on meningiomas.

Funding statement

This work was supported by the Dr Mildred Scheel Stiftung (111,306) grant to R.K.

Author contributions

B.H. collected patient data, wrote parts of the paper, did the statistics and revised the draft. Z.D. collected patient data and wrote sections of the paper. S.U. wrote a part of the paper and supervised the study. F.S. wrote a part of the paper. A.vD. wrote sections of the paper. J.O. is head of the department and designed and supervised the study. R.K. designed the study, organized the financing and wrote sections of the paper. All authors read and approved the final manuscript.

Authorship

B.H. collected patient data, wrote parts of the paper, did the statistics and revised the draft. Z.D. collected patient data and wrote sections of the paper. S.U. wrote a part of the paper and supervised the study. F.S. wrote a part of the paper. A.vD. wrote sections of the paper. J.O. is head of the department, designed the study and supervised the study. R.K. designed the study, organized the financing and wrote sections of the paper. All authors read and approved the final manuscript.Acknowledgment: We thank Lilli Charlotte Urbschat for proofreading the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest

Acknowledgment

We thank Lilli Charlotte Urbschat for proofreading the manuscript.

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.2019.07.001.

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