Sex-specific aspects of epidemiology, molecular genetics and outcome: primary brain tumours

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ABSTRACT

Recent years have seen a great interest in sex-specific aspects of many diseases, including cancer, in part because of the assumption that females have often not been adequately represented in early drug development and determination of safety, tolerability and efficacy in clinical trials. Brain tumours represent a highly heterogeneous group of neoplastic diseases with strong variation of incidence by age, but partly also by sex. Most gliomas are more common in men whereas meningiomas, the most common primary intracranial tumours, are more common in females. Potential sex-specific genetic risk factors and specific sex biology have been reported in a tumour-specific manner. Several small studies have indicated differences in tolerability and safety of, as well as benefit from, treatment by sex, but no conclusive data have been generated. Exploring sex-specific aspects of neuro-oncology should be studied more systematically and in more depth in order to uncover the biological reasons for known sex differences in this disease.

INTRODUCTION

In the recent years, there has been an emerging awareness of sex-specific aspects of many diseases, including cancer. This interest was in part triggered by observations on the biology of cancer, their potential modulation by the endocrine system, but also concerns that females have often not been adequately represented in early drug development and determination of safety, tolerability and efficacy in clinical trials, or might have less access to care in general. Here, we review sex-specific aspects of epidemiology, risk factors, biology, outcome, access to treatment and safety for the most common primary tumours. 'Sex' was used in this manuscript when discussing biological aspects of disease, whereas 'gender' was used to denote 'sociological considerations.'

EPIDEMIOLOGY

Incidence

Brain tumours represent a highly heterogeneous group of tumours with strong variation of incidence by age, but partly also by sex.[1] In the USA, central nervous system tumours represent the eight most frequent cancer in male and the fifth most frequent cancer in female.[2] Brain tumours in general are more frequent in males (58% vs 41% in females) (table 1).[2] This, however, varies with the tumour type. Malignant tumours are more frequent in males (with an annual incidence rate of 8.3 vs 6.0) and non-malignant tumours more frequent in females (with a rate of 19.8 vs 12.5). The rate of tumours of neuroepithelial tissue origin, the most frequent primary malignant brain tumours, was 5.6 for female versus 7.7 for males between 2012 and 2016 in the Central Brain Tumor Registry of the United States (CBTRUS) report. Notably, the rate of glioblastoma was 4.0 vs 2.5 for females. Germ cell tumours and cysts are also more frequent in males (0.14 in males vs 0.07 in females). The tumour types that are more frequent in females are meningioma (with a rate of 11.5 vs 5) and pituitary tumours (with a rate of 4.5 vs 3.7).[2] In a cohort of 2230 patients who underwent surgery for a pituitary adenoma between 1969 and 1993, more females had prolactinomas, Adreno CorticoTropic Hormone-releasing adenomas and thyroid-stimulating hormone releasing adenomas whereas more males had endocrine inactive adenomas and growth hormone-releasing adenomas.[3]

In a retrospective analysis among glioblastoma patients in the Canton of Zurich, Switzerland, the male/female ratio was 1.27 between 1980 and 1994 vs 1.64 between 2005 and 2009.[4] In the CBTRUS data, the rates of tumours of the meninges and pituitary tumours increased strongly in incidence between the first and the last dataset. No clear sex-specific difference in the evolution of epidemiological data was observed between the data sets of 1990–1994, 2005–2009 and 2012–2016 (table 2),[2 5 6] and any differences would have to be interpreted with caution, given changes in the sources of data and of approaches of data collection over time.

Table 1 Central nervous system tumours diagnosed in the USA in 2012–2016, adapted from Ostrom *et al*, 2019: annual incidence rates by sex

	Female				Male			
	% malignant	% non-malignant	Rate	95% CI	% malignant	% non-malignant	Rate	95% CI
Tumours of neuroepithelial tissue	**92.3**	**7.7**	**5.56**	**5.51 to 5.61**	**92.8**	**7.2**	**7.69**	**7.62 to 7.75**
Pilocytic astrocytoma	100.0	0.0	0.34	0.33 to 0.36	100.0	0.0	0.36	0.34 to 0.37
Diffuse astrocytoma	100.0	0.0	0.40	0.39 to 0.42	100.0	0.0	0.52	0.50 to 0.53
Anaplastic astrocytoma	0.0	0.0	0.36	0.35 to 0.37	100.0	0.0	0.48	0.46 to 0.49
Glioblastoma	100.0	0.0	2.54	2.51 to 2.57	100.0	0.0	4.00	3.96 to 4.05
Oligodendroglioma	100.0	0.0	0.21	0.20 to 0.22	100.0	0.0	0.26	0.25 to 0.27
Anaplastic oligodendroglioma	99.9	0.1	0.10	0.09 to 0.10	100.0	0.0	0.12	0.12 to 0.13
Ependymal tumours	61.3	38.7	0.37	0.35 to 0.38	55.9	44.1	0.49	0.47 to 0.50
Choroid plexus tumours	16.0	84.0	0.05	0.05 to 0.06	16.0	84.0	0.05	0.05 to 0.06
Neuronal and mixed neuronal glial tumours	18.4	81.6	0.29	0.27 to 0.30	21.6	78.4	0.34	0.33 to 0.35
Tumours of the pineal region	46.9	53.1	0.06	0.05 to 0.06	67.9	32.1	0.04	0.04 to 0.05
Embryonal tumours	95.7	4.3	0.20	0.19 to 0.21	97.8	2.2	0.27	0.26 to 0.29
Tumours of cranial and spinal nerves	**0.7**	**99.3**	**2.02**	**1.99 to 2.05**	**0.7**	**99.3**	**2.01**	**1.98 to 2.04**
Nerve sheath tumours	0.7	99.3	2.02	1.99 to 2.05	0.7	99.3	2.01	1.98 to 2.04
Other tumours of cranial and spinal nerves	0.0	100.0	--	--	0.0	100.0	0.00	0.00 to 0.00
Tumours of meninges	**1.2**	**98.8**	**11.89**	**11.82 to 11.96**	**2.8**	**97.2**	**5.37**	**5.32 to 5.42**
Meningioma	0.9	99.1	11.63	11.56 to 11.70	1.9	98.1	5.08	5.03 to 5.13
Mesenchymal tumours	28.7	71.3	0.09	0.08 to 0.09	34.5	65.5	0.09	0.08 to 0.10
Primary melanocytic lesions	58.3	41.7	0.01	0.00 to 0.01	82.0	18.0	0.01	0.01 to 0.01
Other neoplasms related to the meninges	8.7	91.3	0.17	0.16 to 0.18	8.6	91.4	0.20	0.19 to 0.21
Lymphomas and hematopoietic neoplasms	**99.8**	**0.2**	**0.40**	**0.39 to 0.42**	**99.9**	**0.1**	**0.48**	**0.47 to 0.50**
Lymphoma	100.0	0.0	0.39	0.38 to 0.41	100.0	0.0	0.47	0.45 to 0.48
Other hematopoietic neoplasms	91.8	8.2	0.01	0.01 to 0.01	95.6	4.4	0.02	0.01 to 0.02
Germ cell tumours and cysts	**48.7**	**51.3**	**0.07**	**0.06 to 0.07**	**75.8**	**24.2**	**0.14**	**0.13 to 0.15**
Germ cell tumours, cysts, and heterotopias	48.7	51.3	0.07	0.06 to 0.07	75.8	24.2	0.14	0.13 to 0.15
Tumours of sellar region	**0.2**	**99.8**	**4.69**	**4.65 to 4.74**	**0.3**	**99.7**	**3.94**	**3.89 to 3.98**
Tumours of the pituitary	0.2	99.8	4.51	4.46 to 4.56	0.3	99.7	3.74	3.70 to 3.79
Craniopharyngioma	**0.2**	**99.8**	**0.19**	**0.18 to 0.20**	**0.7**	**99.3**	**0.19**	**0.18 to 0.20**
Total	**23.2**	**76.8**	**25.84**	**25.73 to 25.95**	**40**	**60**	**20.82**	**20.72 to 20.92**

The bold values correspond to a group of tumor subtypes, data by subtype are provided below.
CI, confidence interval.

Table 2 CBTRUS data between the data sets 1990–1994, 2005–2009 and 2012–2016, adapted from Surawicz *et al*; Dolecek *et al*; Ostrom *et al*

	1990–1994				2005–2009				2012–2016			
	Female		Male		Female		Male		Female		Male	
Histology	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Tumours of neuroepithelial tissue	**5.05**	**4.90 to 5.20**	**7.2**	**7.01 to 7.38**	**5.59**	**5.54 to 5.64**	**7.77**	**7.70 to 7.84**	**5.56**	**5.51 to 5.61**	**7.69**	**7.62 to 7.75**
Pilocytic astrocytoma	0.26	0.22 to 0.30	0.27	0.23 to 0.31	0.32	0.31 to 0.34	0.33	0.32 to 0.34	0.34	0.33 to 0.36	0.36	0.34 to 0.37
Diffuse astrocytoma	0.15	0.12 to 0.17	0.16	0.13 to 0.19	0.5	0.48 to 0.52	0.68	0.66 to 0.70	0.4	0.39 to 0.42	0.52	0.50 to 0.53
Anaplastic astrocytoma	0.4	0.36 to 2.16	0.57	0.52 to 0.62	0.3	0.28 to 0.31	0.43	0.42 to 0.45	0.36	0.35 to 0.37	0.48	0.46 to 0.49
Glioblastoma	2.07	1.98 to 2.16	3.24	3.11 to 3.36	2.53	2.49 to 2.56	3.98	3.94 to 4.03	2.54	2.51 to 2.57	4	3.96 to 4.05
Oligodendroglioma	0.25	0.2 to 0.29	0.33	0.30 to 0.37	0.24	0.23 to 0.25	0.3	0.29 to 0.31	0.21	0.20 to 0.22	0.26	0.25 to 0.27
Anaplastic oligodendroglioma	0.04	0.03 to 0.06	0.09	0.07 to 0.11	0.1	0.09 to 0.11	0.13	0.12 to 0.14	0.1	0.09 to 0.10	0.12	0.12 to 0.13
Ependymal tumours					0.37	0.35 to 0.38	0.46	0.45 to 0.48	0.37	0.35 to 0.38	0.49	0.47 to 0.50
Choroid plexus tumours	0.04	0.03 to 0.05	0.04	0.03 to 0.06	0.05	0.05 to 0.06	0.05	0.05 to 0.06	0.05	0.05 to 0.06	0.05	0.05 to 0.06
Neuronal and mixed neuronal–glial tumours	0.11	0.09 to 0.13	0.16	0.13 to 0.19	0.25	0.24 to 0.26	0.29	0.28 to 0.30	0.29	0.27 to 0.30	0.34	0.33 to 0.35
Tumours of the pineal region	0.03	0.02 to 0.04	0.02	0.01 to to 0.03	0.05	0.04 to 0.05	0.03	0.03 to 0.04	0.06	0.05 to 0.06	0.04	0.04 to 0.05
Embryonal tumours	0.2	0.17 to 0.23	0.32	0.28 to 0.36	0.22	0.21 to 0.24	0.29	0.28 to 0.31	0.2	0.19 to 0.21	0.27	0.26 to 0.29
Tumours of cranial and spinal nerves					**1.71**	**1.69 to 1.74**	**1.7**	**1.67 to 1.73**	**2.02**	**1.99 to 2.05**	**2.01**	**1.98 to 2.04**
Nerve sheath tumours	0.77	0.72 to 0.83	0.73	0.68 to 0.79	1.71	1.68 to 1.74	1.7	1.67 to 1.73	2.02	1.99 to 2.05	2.01	1.98 to 2.04
Tumours of meninges	**3.51**	**3.39 to 3.62**	**1.95**	**1.86 to 2.05**	**10**	**9.93 to 10.07**	**4.58**	**4.53 to 4.63**	**11.89**	**11.82 to 11.96**	**5.37**	**5.32 to 5.42**
Meningioma	3.37	3.25 to 3.48	1.79	1.70 to 1.88	9.76	9.69 to 9.83	4.28	4.23 to 4.33	11.63	11.56 to 11.70	5.08	5.03 to 5.13
Lymphomas and hemopoietic neoplasms					**0.4**	**0.38 to 0.41**	**0.54**	**0.52 to 0.55**	**0.4**	**0.39 to 0.42**	**0.48**	**0.47 to 0.50**
Lymphoma	0.28	0.24 to 0.31	0.6	0.55 to 0.65	0.39	0.37 to 0.40	0.52	0.51 to 0.54	0.39	0.38 to 0.41	0.47	0.45 to 0.48
Germ cell tumours and cysts					**0.06**	**0.06 to 0.07**	**0.13**	**0.12 to 0.14**	**0.07**	**0.06 to 0.07**	**0.14**	**0.13 to 0.15**
Germ cell tumours, cysts and heterotopias	0.04	0.03 to 0.06	0.14	0.11 to 0.16	0.06	0.06 to 0.07	0.13	0.12 to 0.14	0.07	0.06 to 0.07	0.14	0.13 to 0.15
Tumours of sellar region					**3.36**	**3.32 to 3.41**	**2.96**	**2.92 to 3.00**	**4.69**	**4.65 to 4.74**	**3.94**	**3.89 to 3.98**
Tumours of the pituitary	0.89	0.83 to 0.96	0.93	0.87 to 1.00	3.18	3.14 to 3.22	2.78	2.74 to 2.81	4.51	4.46 to 4.56	3.74	3.70 to 3.79
Craniopharyngioma	0.11	0.09 to 0.14	0.11	0.09 to 0.13	0.18	0.17 to 0.19	0.18	0.17 to 0.19	0.19	0.18 to 0.20	0.19	0.18 to 0.20
Total	**10.97**	**10.76 to 11.19**	**12.07**	**11.83 to 12.31**	**22.25**	**22.15 to 22.35**	**18.8**	**18.69 to 18.90**	**25.84**	**25.73 to 25.95**	**20.82**	**20.72 to 20.92**

The bold values correspond to a group of tumor subtypes, data by subtype are provided below.
CBTRUS, Central Brain Tumour Registry of the United States; CI, confidence interval.

Age

In a large cohort of the US National Cancer Database (NCDB), age at diagnosis was similar between males and females for glioblastoma (N=2073) or for WHO grade 2 or 3 glioma (N=2963) patients.[7] In a large cohort of meningioma patients, age at diagnosis was also similar between women and men.[8]

Risk factors

Only two non-genetic risk factors have been reported in primary brain tumours: ionising radiation (which increases the risk) and medical history of allergies (which decreases the risk).[9]

There are only a few explanations supporting a difference between incidence in females and males. In a first Genome-Wide Association Study (GWAS), a significant association between a diagnosis of all glioma and glioblastoma and one single nucleotide polymorphism (SNP) (rs11979158) at 7p11.22 locus, near epidermal growth factor receptor (EGFR) in males only and an association between all glioma and glioblastoma and a large region on 3p21.31 was noted for females only supporting a potential sex-specific risks (Ostrom 2018).[10] Another GWAS study identified differences in risk alleles for glioma development between males and females.[11] In this last study using three different algorithms, an association between EGFR and all glioma and glioblastoma in males and between telomerase reverse transcriptase (TERT) and all gliomas in females was found, supporting the hypothesis of a potential sex-specific genetic risk factor affecting the telomerase pathway.

In a large study from the UK, several types of brain tumours, notably meningioma but also other tumours were associated with the intake of oestrogen-only (vs oestrogen-progestin) menopausal hormone therapy, identifying among women a potential hormonal impact of brain tumourigenesis.[12] This hormonal impact is substantiated by an observation of increased risk of meningiomas and prolactinomas in transgender individuals, but transwomen only, not transmen.[13]

However, the influence of oestrogen may vary depending on whether they are exogenously supplied oestrogen or endogenous hormones.[14]

SEX-SPECIFIC TUMOUR BIOLOGY

Why males have a higher risk of developing glioblastoma than females is unknown. In an effort to model the preferential affection of males by glioblastoma, Sun *et al* explored astrocytes from neurofibromin-deficient mice with concurrent expression of a dominant negative p53 variant.[15] When these cells were treated with EGF, astrocytes from male mice responded stronger with regard to neoplastic transformation, providing at least a model system to explain the differential incidence of these tumours by sex.

Bayik *et al* explored immunosuppressive myeloid-derived suppressor cells (MDSC) in mouse models of glioblastoma and noted sex-specific differences in the contribution of monocytic and granulocytic MDSC, with monocytic MDSC elevated in tumours of male mice and granulocytic MDSC elevated in blood of female mice. The depletion of granulocytic MDSC in the blood increased the survival in female mice. The authors also report patient data in favour of a predominant proliferation of monocytic MDSC in tumours of males and reported that an elevated granulocytic MDSC/interleukin-1β gene signature was associated with poor survival in females.[16]

In a study exploring the response to serum deprivation or etoposide-induced DNA damage in neurofibromin-deficient and p53-deficient astrocytes, female cells exhibited an increased p16 and p21 activity and cell arrest, whereas male cells continued to proliferate with an accumulation of chromosomal alterations, showing sex-specific effect of cytotoxic and targeted treatments.[17]

An analysis of 590 grade 4 gliomas, including 278 confirmed isocitrate dehydrogenase (IDH) wildtype glioblastomas, 266 grade 3 gliomas and 249 grade 2 gliomas from The Cancer Genome Atlas (TCGA) indicated higher overall and subclonal mutational burden in females which were in part attributed to X-chromosomal mutations. The type of clonal mutations varied also in that mutations in genes of the mitogen-activated protein kinase pathway (MAPK) were more often clonal in females with glioblastoma. In contrast, mutations in genes of receptor tyrosine kinase signalling pathways were more often clonal in males with lower grade gliomas.[18]

Using data available in the public domain, it was described that female glioblastoma patients had lower volumes of necrosis at diagnosis than male patients and that the level of necrosis correlated with MYC activity in females, but was linked to P53 activity in males, consistent with the notion that there are sex-specific mechanisms of necrosis in glioblastoma.[19]

Heat maps of the TCGA glioblastoma cohort showed distinct patterns of female-specific and male-specific transcriptome components.[20] Five female-specific and five male-specific gene-clusters were identified, with 116 genes shared by both. Survival was also different when comparing female and male clusters. For the current standard of care (surgery, radiation, temozolomide), when comparing the female cluster associated with the best survival and the male cluster associated with the best survival to other female and male clusters, different pathways were identified (integrin signalling pathway for female and cell cycle regulation for male). Of note, the best female cluster was dominantly composed of IDH-1-mutant tumours. However, the hypothesis of a sex-specific role of the integrin pathway was not confirmed in the CENTRIC trial in patients with O^6-methylguanine DNA methyltransferase (MGMT) promoter-methylated glioblastoma: the survival was 25.3 vs 26.8 months for males with cilengitide vs control (HR 1.04, 95% CI 0.75 to 1.43) whereas it was 27.2 vs 26.2 months (HR 0.97, 0.69 to 1.36) for females. While there is a trend, this is obviously far from significant.[21] In the CORE trial that included only

patients with MGMT promoter-unmethylated glioblastoma there were three arms: a control arm, a standard dose arm of cilengitide, and a dose-intensified cilengitide arm.[22] Median survival for males with the standard cilengitide arm vs the control arm was 14.9 vs 13.6 months (HR 0.86, 95% CI 0.56 to 1.34) whereas for females it was 18.1 vs 12.5 months (HR 0.50, 95% CI 0.28 to 0.89), apparently confirming the trend. However, looking at the high dose cilengitide arm, the signal was not reproduced: males 14.7 vs 13.6 months (HR 0.90, 95% CI 0.58 to 1.40), females 13.6 vs 12.5 months (HR 0.73, 95% CI 0.42 to 1.26). Further studies, potentially requiring more active agents than cilengitide, will be required to confirm the role of preferential integrin signalling in glioblastoma in females.

Regarding the presumed role of cell cycle regulation in males, it has to be recognised that the current standards of care of radiotherapy and alkylating agent chemotherapy all target DNA and thus likely the cell cycle directly or indirectly, although in a less targeted fashion. However, it appears to be too far-fetched to link the overall poorer outcome in males with glioblastoma to this difference in cell cycle regulatory gene expression.

In another TCGA study, methylation analysis revealed sex-specific genome-wide DNA methylation differences, with distinct sex-specific methylation patterns among four glioma subtypes from 587 participants (IDH wild type glioblastoma, IDH wild type non-glioblastoma, IDH mutated and 1p19q codeleted glioma, IDH mutated 1p19q non codeleted glioma), with variable number of hypermethylated differentially methylated probes (DMP) for females and males among the different tumour entities. Most of the hypermethylated DMP were characteristics of the tumour subtype, and hypermethylation seemed to be associated with a reduction of the expression of promigratory genes in females and was associated with downregulation of proapoptotic genes in males.[23]

In a cohort of 114 glioma patients, a concomitant AIB1 and HER2 amplification was claimed to be associated with resistance to radiotherapy and a worse prognosis in women only.[24]

Females were found to have a greater proportion of MGMT promoter methylated tumours (56% vs 43%) among 83 male and 57 female glioblastoma patients in an Italian registry.[25] This was also observed (44% vs 38%) in a large cohort of 1250 male and 823 female glioblastoma patients from the NCDB.[7] No sex difference was noted in the 1p19q codeletion status in the non-glioblastoma cohort.

In another TCGA-based study, the presence of some genomic mutations varied depending on glycolytic gene expression and the authors reported a discordant prognostic value of IDH status between males and females when stratifying for the level of glycolytic gene expression.[26]

The proportion of male patients increased with the grade of meningioma in a cohort of 252 patients.[27] These results were confirmed in a German cohort of 992 patients with a first diagnosis of meningioma between 2000 and 2015, where the WHO grade differed significantly between women and men, with a greater proportion of grades 2 and 3 meningioma in males.[8] The CBTRUS registry confirmed these data.[28]

With the exception of NF2 mutation, oncogenic mutations have been reported in less than 10% of meningiomas,[29] and there are, thus, limited data to assess whether there is a sex association. However, a predominance of women were reported among patients with SMO mutation (5% vs 2% in males), KLF4 mutation (8% vs 4% in males), TRAF7 mutation (19% vs 9% in males), and PI3KCA mutation (6% vs 2% in males), whereas 1p loss (60% vs 21% in females), 6p loss (33% vs 9% in females), 7p loss (16% vs 2% in females), CDKN2A loss (16% vs 2% in females), 14p loss (34% vs 8% in females) and 19p loss (9% vs 1% in females), was more frequently found in tumours of males. No significant difference was observed between women and men for the frequency of TERT promoter mutations[27] (table 3).

SEX-SPECIFIC DIFFERENCES IN OUTCOME

The efficacy of treatment by sex is rarely reported in large randomised trials. Different outcome by sex among brain tumour patients can have various different reasons including time from symptom onset to diagnosis, differing management patterns and true differences of biological tumour behaviour or benefit from treatment.

Longer survival was reported in glioblastoma patients treated with surgery between 2000 and 2008 in a Surveillance, Epidemiology and End Results (SEER) analysis, with a 5-year cancer-specific survival of 8.3% in women vs 6.8% in men.[30] Prolonged survival of females with glioblastoma was confirmed in the National Cancer Institute SEER programme and a validation cohort from Ohio, with the interpretation that this difference was independent of treatment, age, performance score or IDH mutation status.[31] A better survival was also observed for women in several large cohorts of the US NCDB in patients with a diagnosis of glioblastoma between 2004 and 2015,[7 32 33] independently of the extent of resection.[33] Improved survival in female glioblastoma patients has also been reported specifically in the elderly population using SEER data.[34] Similar results were obtained in an extensive cohort of 16'717 patients aged 65 years old or more, diagnosed from 2005 to 2011 in another US NCDB study.[35]

SEER data were also used to estimate prognostic factors in patients with WHO grade 3 gliomas. Females had improved survival, but only on multivariable and not on univariable analysis, which makes it difficult to derive conclusions. Furthermore, such studies suffer from none standardised histological diagnostic procedures and therapy.[36] The analysis of the US NCDB, assessing data of the years 2010–2014, found no superior survival for females with lower grade (grades 2 or 3) gliomas.[7] Further, no significant survival difference between females and

Table 3 Molecular, signatures and actionable targets

	N, total patients	Female	Male	References
Glioblastoma				
MGMT promoter methylation	140	56% (32/57)	43% (36/83)	Franceschi *et al*,[25] 2018
	2073	44% (363/823)	38% (480/1250)	Glittema*et al*[7], 2019
Meningioma				
Overall cohort	*150*	*95*	*55*	Abedalthagafi *et al*,[29] 2016
AKT mutation	9 (6%)	5 (5%)	4 (7%)	
SMO mutation	6 (4%)	5 (5%)	1 (2%)	
KLF4 mutation	10 (7%)	8 (8%)	2 (4%)	
TRAF7 mutation	23 (15%)	18 (19%)	5 (9%)	
NF2 mutation	55 (37%)	31 (33%)	24 (44%)	
PI3KCA	7 (5%)	6 (6%)	1 (2%)	
1p loss	53 (35%)	20 (21%)	33 (60%)	
4p loss	9 (6%)	5 (5%)	4 (7%)	
6p loss	27 (18%)	9 (9%)	18 (33%)	
7p loss	11 (7%)	2 (2%)	9 (16%)	
CDKN2A loss	11 (7%)	2 (2%)	9 (16%)	
10q loss	14 (9%)	3 (3%)	11 (20%)	
11p loss	4 (3%)	3 (3%)	1 (2%)	
14p loss	27 (18%)	8 (8%)	19 (34%)	
18p loss	24 (16%)	10 (10%)	14 (25%)	
19p loss	6 (4%)	1 (1%)	5 (9%)	
Monosomy 2	85 (57%)	49 (52%)	36 (65%)	
3p gain	2 (1%)	1 (1%)	1 (2%)	
Overall cohort	*252*	*161*	*91*	Sahm *et al*,[27] 2016
TERT mutations	16 (6.4%)	6 (37.5)	10 (11)	

CDKN2A, cyclin-dependent kinase inhibitor 2A; MGMT, O^6-methylguanine DNA methyltransferase; NF2, neurofibromatosis type 2; TERT, telomerase reverse transcriptase.

males was observed in an analysis of 542 Swedish low-grade glioma patients over 10 years (2005–2015).[37]

Only a few studies have been conducted in non-malignant brain tumours, leaving opportunities for further research. A relatively large population based study of 9092 patients newly diagnosed with meningioma from Germany revealed no significant differences in outcome (risk of recurrence, survival) between males and females, although the preponderance of females in this patient population was confirmed.[8]

ACCESS TO TREATMENT

Several studies have explored whether females have less access to diagnostic procedures, standard of care treatments, or clinical trials. In a large US NCDB cohort of glioblastoma patients, males were more treated with chemotherapy.[38] These results were also observed in another US NCDB study of elderly patients: males were more likely to receive chemoradiotherapy where as women were more likely to receive no further treatment.[35]

A Swedish study reported worse preoperative performance status in females with 'low-grade' gliomas consistent with delayed diagnostic workup, however, the interval time to surgery, the type of surgical procedure and the complications did not differ by sex.[37] No difference in the Karnofsky performance score at diagnosis was found in another NCDB cohort of glioblastoma or non-glioblastoma patients.[7] Further, no difference was observed regarding healthcare insurance or size of the tumour, type of surgery, or chemotherapy or radiotherapy in non glioblastoma patients.[7]

Gender was not identified as a significant factor in a multivariate analysis exploring the association between rates of gross total resection and radiotherapy and racial and socioeconomic disparities among 71 098 meningioma patients in the USA.[39]

ARE THERE TREATMENT-RELATED DIFFERENCES IN OUTCOME?

A difference in outcome has been substantiated also for female vs males with gliomas receiving comparable treatment defined by extent of resection.[23 33 40]

A comprehensive study based on serial MRI proposed that women indeed respond better to temozolomide chemoradiotherapy than men,[20] but these surprising findings require independent validation.

An Italian study indicated that the survival advantage of female patients with glioblastoma was restricted to patients with tumours with MGMT promoter methylation; yet, the sample size was small and sex and methylation status were combined as one parameter in the multivariable analysis which may at least be considered unusual.[25]

In a TCGA cohort, the median overall survival and the age-adjusted median survival was similar by sex for patients with IDH wildtype non-glioblastoma patients or for patients with IDH-mutant glioma without 1p19q codeletion. Data for patients with IDH-mutant glioma with 1p19q codeletion were not mature at the time of the analysis.[23]

Sex was not identified as a prognostic factor in a multivariate analysis exploring 71 098 meningioma patients in the USA.[39]

ARE THERE SEX-SPECIFIC DIFFERENCES IN SAFETY, TOLERABILITY AND TOXICITY FROM TREATMENT?

In a prospective cohort of 100 patients operated for a suspicion of low or high-grade glioma, new postoperative neurological deficits were noted in 37% of patients and a worsening of a pre-existing deficit was noted in 4%. No difference was observed between both sexes.[41] In another study on 1016 patients aged 65–89 years with a craniotomy for primary supratentorial malignant intraaxial tumours, risk factors for morbidity and mortality were not associated with sex, among the 816 admitted from home, around 34% had a change in living disposition which was associated with female sex among other factors.[42] In another cohort of 92 patients with gliomas and metastases involving the motor pathway, female sex, among other factors, was associated with a poorer functional prognosis and a poorer quality of life.[43]

In a recent cohort of 112 low-grade diffuse glioma, a high fatigue according to the European Organisation for Research and Treatment of Cancer (EORTC) fatigue subscale was noted in 45% of the patients preoperatively and in 42% of the patients post-operatively. Female sex was associated with preoperative fatigue only, whereas male sex was not associated with fatigue.[44]

Early after the introduction of temozolomide, it was noted that females experience myelosuppression with temozolomide more often than males, whereas there was no such effect for other adverse events of temozolomide.[45] Female sex was also identified as a risk factor for acute haematological toxicity from temozolomide in India[46] and in the USA.[47 48] The higher risk of severe myelotoxicity associated with concomitant and maintenance temozolomide in newly diagnostic glioblastoma in females has been confirmed,[49] but in this study there were only four patients with (common terminology criteria for adverse events) grade 3 or 4 haematological toxicity, and these were all females.

A higher risk of venous thromboembolism in male patients was reported in a large cohort of glioblastoma patients.[50]

COMPLEMENTARY AND ALTERNATIVE MEDICINE USE

Use of complementary and alternative medicine (CAM) may disclose differences in attitudes towards cancer, access to care or compliance with measures of evidence-based medicine not only in a country-specific and culture-specific, but also in a sex-specific manner. Several recent retrospective analyses have covered this issue. In older cohorts, a gender difference was observed in regards to CAM use,[51–53] with 47% of women and 35% of men using CAM,[52] whereas in the most recent cohorts, no gender difference was noted among CAM user,[54 55] with 53% of women and 46% of men using CAM.[54]

CONCLUSION

Sex differences are observed in epidemiology and biology, and should be considered in early drug development and determination of safety, tolerability and efficacy in clinical trials. The efficacy and tolerance of treatment by sex should be reported in large randomised trials. Future clinical trials might also consider including sex as a stratification factor and a sex-specific determination of maximum tolerated doses. Prospective studies also need to determine whether access to care may be more limited for women with primary brain tumours in certain parts of the world.

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