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Malignant brain tumours in South Australia

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Preface

This monograph describes patterns of primary malignant brain tumours (cancers that start in the brain) for South Australia over the past 30 years.

Malignant brain tumours are relatively rare cancers but are of concern to the public because of the generally poor outcomes for people affected. While malignant brain tumours occur mainly in older people, they can also develop in children and young people, and are in fact the second most common type of cancer in children and the second leading cause of cancer death in people under 25 years of age. Rates of malignant brain tumours have remained stable in all age groups except those aged 65 years and over, where rates appear to have increased. The increase in older people is thought to be due to better diagnosis and more investigation of neurologic symptoms in this age group over time.

Despite considerable research interest in brain tumours globally, little is known about the causes of these cancers and very little progress has been made in treating the disease. Currently there are no known preventive strategies to reduce people's risk of developing malignant brain tumours.



Professor Brenda Wilson
Chief Executive
Cancer Council SA

Acknowledgements

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Principal authors: Kerri Beckmann and David Roder, with assistance from Tom Vreugdenburg and Jennifer Owen.

Contents

Preface	i
Acknowledgements	ii
Table of contents	iii
Summary	1
Introduction	5
Types of malignant brain tumours	6
Signs and symptoms	6
Treatments and outcomes	7
Patterns and trends	8
Risk factors	9
Descriptive epidemiology	11
Methodology	12
Patterns and trends in South Australia	12
Survival	18
Regional comparisons	20
Highlights	24
Resources	25
Bibliography	27
Glossary	29

Summary

Summary

This monograph describes patterns of primary malignant brain tumours (cancerous tumours that develop from cells within the brain) among South Australians, over the past 30 years. Benign tumours and tumours that develop in the spinal cord or peripheral nerves are not included. Data described in this report were collected by the South Australian Cancer Registry, which has been operating within the Epidemiology Branch of SA Health for over 30 years.

Malignant brain tumours are relatively rare cancers but generally have a high case fatality rate. Currently around 125 primary malignant brain tumours are diagnosed in South Australia each year and there are approximately 100 deaths from these tumours annually. Malignant brain tumours rank 15th in terms of common cancers and 11th in terms of cancer deaths across South Australia.

The overall incidence of malignant brain tumours in South Australia is similar to that for Australia as a whole and does not vary significantly from that for any other state or territory. Generally rates of brain tumours are highest in more developed countries, hence by world standards the incidence in South Australia/Australia is high compared with many other parts of the world. Higher rates are thought to reflect better detection of malignant brain tumours through the availability of imaging technologies in developed countries. Because of the high case fatality rate, mortality rates for Australia are also comparatively high.

Brain tumours are classified according to the cell type from which they originate and the grade (aggressiveness) of the tumour. There are a large number of different subtypes of malignant brain tumours that affect South Australians, the most common being glioblastoma-multiforme, one of the most aggressive/high grade forms of brain cancer, which accounts for 40% of all malignant brain tumours diagnosed. Astrocytomas (which are lower grade cancers) are the next most common subtype, accounting for 32% of malignant brain tumours diagnosed.

Subtypes vary according to age. Glioblastoma-multiforme is more common in older people than in children (48% of cases among South Australians aged 65 years or older compared

with 5% among children aged under 15 years). On the other hand children are more likely to be diagnosed with astrocytomas (48% of cases in children) and medulloblastomas (27% of cases in children).

Patterns and trends observed in South Australia are reflective of patterns for malignant brain tumours in other industrial countries. The age distribution is bimodal, with a small but distinct peak in incidence in children, very low incidence during adolescence and increasing incidence with increasing age from early adulthood. Males are more likely to develop malignant brain tumours than females (overall gender ratio 1.5 to 1).

Overall the incidence rate of malignant brain tumours has remained stable in South Australia, although the number of cases diagnosed annually has almost doubled over the past 30 years, as the population of South Australia ages. Age specific incidence has also remained stable in all age groups except those aged over 65 years, where the rate has increased significantly. There is some debate internationally about whether the increasing incidence in older people is a 'real' increase or represents increased investigation and detection in this age group. The later seems more likely given the consistent rates in other age groups.

As well as an increase in the proportion of older people being diagnosed with malignant brain tumours, there has also been a shift toward a higher proportion of the glioblastoma-multiforme (GBM) subtype occurring over the past 30 years (which is related to the changes in age profile). During the most recent decade of cancer registration, 50% of malignant brain tumours recorded were glioblastoma-multiforme. This compares with 31% during the first decade of cancer registration in South Australia.

While incidence has remained stable in South Australia, mortality (particularly among males) has increased. The most likely reason for the increasing mortality rate is the increase in older patients being diagnosed and the increase in proportion of cases of a more aggressive type (e.g. GBM which are more common in older people).

Malignant brain tumours are one of the most rapidly fatal forms of cancer and survival outcomes are poor. Currently around 20% of people diagnosed with a malignant brain tumour in

South Australia are alive five years after diagnosis. Survival varies considerably according to age and tumour subtype. Children, adolescents and young adults have the best survival outcomes (five year survival~60%) while older adults 65 years and over have the worst outcomes (five year survival~4%). Five year survivals range from 68% for oligodendromas, to 32% for astrocytomas and only 3% for glioblastoma-multiforme.

Overall survival outcomes for malignant brain tumours have not improved over the past three decades. South Australian data for all subtypes together actually show a decline in five year survival over this period. Declining survival is likely to be due to the increase in portion of older patients and patients with more aggressive cancers (GBM subtype) among brain cancer cases. When these factors are taken into consideration using multivariate analyses, survival has actually increased.

The causes of brain tumours are not well understood. These are a diverse group of cancers and the various subtypes are likely to have different causal factors. The only known risk factor for malignant brain tumours is exposure to high dose ionising radiation. Most people in the population would not be exposed to ionising radiation in high doses, and the risk from low dose exposures (e.g. X-rays) is not clear. Other factors that have been investigated, for which some positive associations have been noted include: electromagnetic radiation, various occupational and chemical exposures (e.g. welding, pesticides), infectious agents and medical conditions such as multiple sclerosis and epilepsy. However most repeated studies have yielded mixed results. Lifestyle factors such as smoking, obesity, high alcohol consumption and physical inactivity do not appear to be associated with increased brain cancer risk. The one exception is diet, where there is some evidence to suggest high consumption of cured meats and fish may be linked to brain tumour development. However existing evidence is inconclusive.

Introduction

Introduction

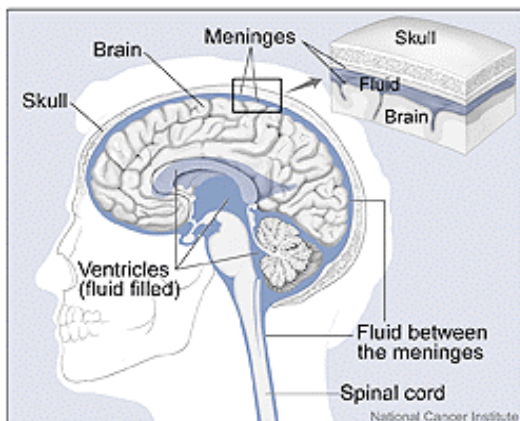
Tumours of the central nervous system (CNS) include tumours of the brain, spinal cord and meninges (the protective layers covering the brain and spinal cord). Brain tumours account for 85% of CNS tumours. This report focuses only on primary malignant brain tumours.

'Primary' indicates that the tumour started in cells within the brain (as distinct from secondary tumours or metastases which have spread to the brain from other organs). 'Malignant' refers to tumours that are cancerous, which are likely to grow rapidly and can spread to other parts of the body. About three quarters of all brain tumours are malignant and one quarter benign. While benign brain tumours are potentially life threatening since they can grow and press on nearby parts of the brain, benign tumours are not recorded on the South Australian Cancer Registry (as is the case with most other registries outside of the USA) so we are unable to present data on their occurrence.

Similarly this report will only focus on malignant tumours that start in the brain—primary tumours. The brain is often the site of 'metastatic' tumours, i.e. tumours that have developed elsewhere in the body and spread to the brain. This report does not include any data on metastatic brain tumours.

Comparisons of malignant brain tumour patterns over time and across regions are difficult because of differences in the ability to diagnose these cancers and because some countries include benign tumours along with malignant tumours when recording brain tumour data, while others do not.

Figure 1 Structure of the brain



Types of malignant brain cancer

There are over one hundred different types of tumours affecting the central nervous system.

Tumours are classified according to their location and cell type (histology). See *Table 1*. Gliomas are the most common type of brain tumour, arising from glial cells which provide the supporting structure for the nerve cells in the brain, and are usually malignant. There are several types of glial cells including astrocytes, which can develop into astrocytomas and oligodendrocytes, which can develop into oligodendrogliomas. Other common tumour types include ependymomas, which begin in cells that line the fluid filled spaces of the brain (also glial cells) and medulloblastomas which arise from a type of embryonic cell that forms in the fetus (sometimes referred to as primitive neuroectodermal tumours or PNETs). PNETs usually occur in children. Some brain tumours will contain mixed cell types. The most common types of benign brain tumours are meningiomas, which are tumours that start in the meninges (protective layers covering the brain).

Brain tumours are also grouped according to the extent to which the cells have changed from their normal appearance (tumour grade). Astrocytomas tend to be low grade malignant (cancerous) tumours while glioblastomas are high grade malignant tumours. On the other hand, meningiomas are almost always benign tumours though very occasionally they can be cancerous. Subtypes vary considerably according to age, for example glioblastomas are rare in children but quite common in people over 45 years of age. Prognosis also differs greatly according to subtype. Generally those diagnosed with astrocytomas (lower grade cancers) have better survival outcomes than those diagnosed with glioblastomas (higher grade cancers).

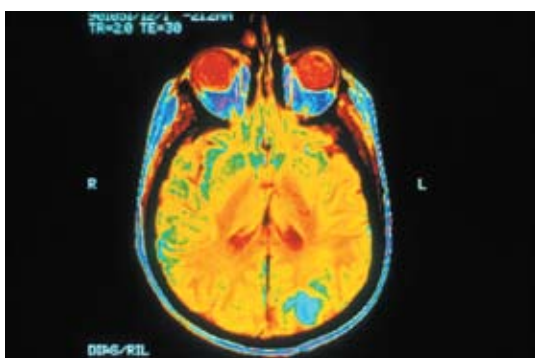
Signs and symptoms

Presenting symptoms may be localised and specific or more generalised, depending on the location of the cancer and the degree of spread. Generalised symptoms, which are usually caused by increasing intracranial pressure from the growing tumour, include headache, nausea or vomiting and seizures. Specific symptoms which depend on location may include muscle weakness, loss of balance, sensory loss, changes to mood, personality or memory and visual problems.

Table 1 Classification of tumours of the central nervous system

CNS subsite	ICD-9/10 code	ICD-10 code
brain	191.0	C71.1–C71.9
cranial nerve	192.0	C72.2–C72.5
cerebral meninges	192.1	C70.0
spinal cord	192.2	C72.0
spinal meninges	192.3	C70.1
histological (cell) type	ICD-O code	predominant form
gliomas	9380–9481	
astrocytoma	9384, 9400–21	borderline/malignant
glioblastoma-multiforme (GBM)	9440–42	malignant
medulloblastoma/primitive neuroectodermal tumours (PNET)	9470–73	malignant
oligodendroglioma	9450–60	malignant
other gliomas	9380–83, 9422–30, 9472–81, 9443, 9390	malignant
meningioma	9530–39	benign
nerve sheath tumours	9540–60	benign
other	9120–61	

Malignant brain tumours are often difficult to diagnose because they can be located in very inaccessible parts of the brain and may present with quite generalised symptoms. Diagnosis often involves advanced medical technology involving neuro-imaging using MRI (magnetic resonance imaging) and CT (computed tomography).

**Photo: MRI of the brain**

Treatments and outcomes

Treatment varies according to the type of brain tumour, its location, size and grade, as well as the patient's age and other prognostic factors.

Ideally malignant brain tumours are treated by removing all or as much of the cancer as possible via surgery. Sometimes surgery is not possible because of the location and/or extent of spread of the tumour, and would cause damage to brain functioning. In these cases radiotherapy, which uses high energy radiation to kill cancer cells, and/or chemotherapy drugs, that target cancer cells, are possible treatments. Even when surgeons can see no remaining cancer after surgery, radiotherapy or chemotherapy may also be given to kill any cells that are left and to improve the chances of survival. Children are more likely to have chemotherapy than adults.

The chances of recovery from primary malignant brain tumours also depend on the characteristics of the cancer (type, size, location and grade) and the patient (age and general health) as well as whether the cancer was surgically operable and whether any cancer cells were left behind. Prognosis is generally poor for malignant brain tumours. They are one of the most rapidly

fatal types of cancer with only around 50% of patients alive one year after diagnosis. In developed countries between 20% and 30% of patients survive five years after diagnosis. Little improvement in survival has been observed over the past 50 years. Outcomes vary considerably according to the type and grade of cancer at diagnosis. Five year survival from astrocytoma is around 30% compared with 3% for glioblastoma-multiforme. Children and young adults generally have better outcomes than older adults. Outcomes are similar for males and females.

Patterns and trends

Primary malignant brain tumours are relatively rare cancers but are of public interest because they are associated with very poor outcomes. After stroke they are the next leading cause of death from a neurological disorder. Brain tumours can affect people at an early age and are the second most common form of cancer in children under 15 years of age. Despite considerable research effort, little is known about the causes of brain tumours and little progress has been made in terms of treatment outcomes over the past five decades.

In most developed countries, malignant brain tumours (collectively) rank just outside the top 10 cancers in terms of incidence and mortality. There are about 5–6 new cases of malignant brain tumours diagnosed per 100,000 persons per year (age standardised to the World Population) and around 3–5 brain cancer deaths per 100,000 persons per year. Around 1,400 cases are diagnosed each year in Australia and approximately 175,000 worldwide.

The age distribution of malignant brain tumours is bimodal. There is an early peak in incidence among children under 10 years of age followed by a decline in incidence rates between the ages of 10 and 20 years. Rates tend to rise again during adulthood until the age of 70 when they again appear to decline. Rates among young adults are in the order of 4 cases/100,000 per year (age standardised to World Population) whereas there are more than 20 cases/100,000 per year for those aged over 60 years. The decline in later life may actually be due to under-diagnosis either because of a lack of investigation of symptoms or misclassification as stroke or dementia in the elderly. While malignant brain tumours are relatively rare in the population as a whole, accounting for 1–2% of all cancers diagnosed

in developed countries, they are the second most common cancer type occurring in children, accounting for around 20% of cancers in those aged under 15 years.

Rates of malignant brain tumours are higher for males than females with a ratio of 1.5 cancers among males for every 1 cancer among females. Gender differences are less pronounced among children. (Interestingly females have higher rates of benign brain tumours than males). There is a clear trend toward increasing incidence with increasing social class in developed countries, particularly for males. One possible explanation for this trend is increased exposure to medical X-rays (e.g. dental X-rays) among higher socio-economic status (SES) groups. However this does not explain the gender differences.

Regional comparisons are problematic due to variation in the ways brain tumours are classified, availability of resources for diagnosing brain tumours, the extent to which symptoms are investigated in older patients and variations in autopsy practices across different countries. Global differences in rates tend to correspond to the level of economic development, with the highest rates in North America, Australasia and Western Europe and the lowest rates in Asia, South and Central America. The variation in rates is more modest than for many other cancers with known lifestyle or environmental risk factors, and may be even less when taking into account the variations in diagnostic effectiveness across countries. Rates among immigrants from poorer countries tend to increase toward levels seen in the host country. This could be due to increased exposure to (unknown) environmental risk factors in the host country or, more likely, increased ascertainment of tumours in the host country.

Similarly it is difficult to interpret changes in incidence over time because of the likelihood of improved diagnosis and differences in reporting to registries over time. Registry data from industrial countries suggest an increase in the incidence of brain cancer over the past few decades. However there is considerable debate about whether these increases are artificial, reflecting improved diagnostics, or do in fact indicate changes in incidence due to environmental exposures or other risk factors. Most of the observed increase has been confined to older people, suggesting increased investigation of symptoms among the elderly may be the main factor driving the upward trend in rates.

Risk factors

Very little is known about the causes of malignant brain tumours. Research into the causes is difficult due to the diversity of subtypes which may have different causes, and because information about exposures is often difficult to obtain from patients with brain cancer due to memory and communication difficulties and poor survival outcomes. Conventional lifestyle factors that are often associated with common cancers such as lung, colorectal and breast cancer do not appear to play an important role in relation to tumours of the brain. The only well established risk factor is exposure to high dose ionising radiation. Since few individuals are exposed to high doses of ionising radiation this is unlikely to account for many of these cancers. Other risk factors that have been investigated include occupational and environmental exposures (chemicals and non-ionising radiation), dietary factors, infections, brain trauma and other medical conditions.

Genetic factors

An increased risk of malignant brain tumours is associated with several genetic and familial syndromes (for example Li Fraumeni's syndrome). Risk is also slightly elevated if a relative has been diagnosed with a brain tumour. Genetic and familial traits are likely to account for only 1–5% of cases. There may be some environmental-gene interactions that explain a larger proportion of cases but the nature of these remains unclear at this stage.

Radiation

Several forms of radiation have been studied in relation to brain tumour risk. These include ionising radiation (IR), electromagnetic radiation (EMR) and radio-frequency radiation (RF) which is a low level form of EMR.

Studies of atomic bomb survivors and of people exposed to high dose radiation for treatment of medical conditions indicate a strong link between high dose ionising radiation and both malignant and benign brain tumours. Timing of exposure appears to be important, with greater risk if exposed at an early age. A dose response is evident, with higher doses of ionising radiation leading to greater risk and shorter latency periods. Malignant brain tumours occur more frequently in patients who have had treatment for an earlier primary cancer, especially those who had childhood cancers.

Evidence is less clear in relation to exposure to low dose ionising radiation. Studies of occupational exposure to ionising radiation have yielded mixed results. There is some evidence of an increase in risk from exposure to diagnostic X-rays (e.g. dental X-rays) in early studies but more recent studies, since radiation standards were tightened, have failed to show a link.

Electromagnetic radiation has been implicated as a potential causal factor in the development of brain tumours from a number of studies indicating an increased incidence in children living in close proximity to EMR sources (e.g. powerlines) or having high exposure in the home. The earlier studies have been criticised for lacking power or relying on indirect measures of exposure while more recent studies have not yielded consistent findings. Increased risk among some electrical-related occupations has also led to suspicions around a link between EMR and malignant brain tumours but results are mixed for studies that have looked at direct measures of exposure.

Studies focussing on radio-frequency exposure and the risk of brain tumours have yielded no consistent or convincing evidence to indicate a causal relationship. Sources of RF exposure include microwaves, radar and occupational exposures (e.g. telecommunications). Mobile phones are another source of radio-frequency radiation and their potential to increase risk of brain tumours has been of great interest and concern. Radio-waves can cause damage through heating tissue, however the amount of heat produced by mobile phones is not thought to be sufficient to cause damage to brain tissue. Results from the majority of studies have found no association between hand-held mobile phone use and malignant brain tumours. However some, but not all, long-term studies have suggested slightly increased risks for benign tumours. A few have also found a link between the side of the brain on which a tumour is located and preferred side of the head for mobile phone use. Further studies on long-term use of mobile phones are being undertaken.

Diet and lifestyle

Tobacco consumption does not appear to be associated with increased risk of brain tumours. Most studies have shown no association between smoking and risk of developing tumours, though one study has shown an association with unfiltered cigarettes. Results are conflicting in

relation to maternal smoking with an increased risk of childhood brain cancer found in some studies but not others. Results relating to passive smoking are also mixed and inconclusive.

Little research has been undertaken in relation to alcohol and the risk of brain tumours but the limited evidence available does not suggest any association with alcohol consumption in general, or with any specific types of alcoholic beverages. Studies of maternal alcohol use have yielded inconsistent findings but also tend to indicate no association. Physical activity and obesity have not been evaluated to any great extent as risk factors for brain tumours.

There is limited evidence of a weak association between certain dietary factors and malignant brain tumours. High consumption of cured meats and fish appears to be associated with increased risk of developing brain tumours, while high consumption of fruits and vegetables appears to be negatively associated with risk, suggesting a protective effect. More research is required to confirm these findings. One hypothesis that is being explored is the role of nitroso-compounds (NOCs), which have been found to increase the incidence of malignant brain tumours in animal models. Fish and nitrate-cured meats contain large amounts of nitrate (which can form NOCs), while fruits and vegetables contain vitamin C and E, which inhibit the formation of nitroso-compounds.

Occupational/chemical exposures

Several occupations have been identified as being associated with a higher risk of malignant brain tumours. These include: electrical-related occupations where exposure to EMR may be a

factor; various health professions (e.g. pathologists, dentists, physicians, vets) where exposure to radiation or toxic chemicals, or better access to health care/diagnosis may be potential factors; petrochemical and rubber industries where certain chemical exposures may be important; and agricultural workers where exposure to pesticides may be a factor. Findings from occupational studies have been mixed and somewhat inconsistent and, as yet, no specific chemicals or compounds have been identified as causative agents.

Medical factors

Several medical conditions including epilepsy and previous brain trauma have been linked with an increased risk of developing malignant brain tumours, but the exact nature of these associations is unclear due to difficulties distinguishing causation from symptoms and the potential for bias to influence findings.

Associations with multiple sclerosis, specific blood types and certain infections have also been noted in isolated studies but the relevance of these factors is unclear. There is some evidence to suggest that a history of colds, flu or allergies such as hay fever, asthma or eczema may reduce the risk of malignant brain tumours. While the evidence is not compelling it is interesting in the context of findings that first-born children are at increased risk (which may be related to a lack of, or later, exposure to an infectious agent).

In summary, exposure to high dose radiation is the only established risk factor for malignant brain tumours. Other areas that require further investigation include the role of dietary nitroso-compounds, infectious agents, electromagnetic radiation and specific chemical agents.

Descriptive epidemiology

Descriptive epidemiology

Methodology

Data sources

Data analysed on all cases of malignant brain tumours diagnosed among South Australians between 1977 and 2006 were provided by the South Australian Cancer Registry. This included all cases with an ICD-9 site code of 191 which were coded as invasive cancers (i.e. malignant brain tumours), but excluded other central nervous system tumours that developed in the spinal cord or peripheral nerves, as well as tumours of the eye and pituitary and pineal glands. Descriptors obtained from the South Australian Cancer Registry included date of diagnosis, age at diagnosis, date and cause of death, gender and histological subtype.

National and interstate data were accessed through the Australian Institute for Health and Welfare's report 'Cancer in Australia: an overview 2008'. Confidence intervals for published incidence rates were estimated using PEPI software.

International data were accessed through the Globocan 2002 database, which has been developed and maintained by the International Agency for Research on Cancer (IARC). Data from this source are estimates of incidence and mortality for 2002, standardised by age to the new World Population.

Analysis

Incidence and mortality rates

The cancer incidence rate is defined as the number of new cases of cancer diagnosed in a specific time period (usually one year), divided by the number of people at risk of developing cancer within the population of interest. The cancer mortality rate is defined as the number of deaths from cancer during a specific time period, divided by the number of people at risk within the population of interest.

In this monograph, incidence and mortality are reported as the number of new cases of

malignant brain tumours/deaths from malignant brain tumours per 100,000 people per year. The estimated residential population for each year, by gender and five year age groups, was provided by the Australian Bureau of Statistics and was used to calculate the population at risk for South Australia. For comparisons over time or between subgroups, incidence and mortality rates were age standardised to the Australian population profile for 2001 (except in the case of international comparisons where they were standardised to the World Population). South Australian incidence and mortality rates, along with 95% confidence intervals, were derived using STATA software.

Survival

Survival outcomes presented in this monograph are disease-specific survivals obtained using the Kaplan-Meier product limit method with STATA software. For comparisons between groups, survival outcomes are generally presented as five year survival fractions (i.e. the percent who were alive five years after diagnosis). Log rank tests were undertaken to determine statistically significant differences between groups. All cases were censored at 31 December 2007.

Patterns and trends in South Australia

Malignant brain tumours are a relatively rare form of cancer. The most current data for South Australia indicate that there are approximately 125 cases of malignant brain tumours diagnosed in the state each year (2002–2006). The average annual incidence rate for malignant brain tumours (1997–2006) is 7.1 per 100,000 people, age standardised to Australian Population 2001, making it the 15th most common type of cancer diagnosed in South Australia (excluding non-melanocytic skin cancers).

While malignant brain tumours account for 1.5% of all cancers diagnosed, they account for 3% of deaths from cancer and rank as the 11th leading cause of cancer death in the state. Recent figures indicate approximately 100 deaths from malignant brain tumours per year (2002–2006), with an average annual age standardised mortality rate of 6.6 deaths per 100,000 people (1997–2006).

The most common form of brain tumour diagnosed in South Australia is glioblastoma-multiforme (a high grade form of glioma) which

accounts for 40% of all malignant brain tumours recorded in the Cancer Registry. Astrocytoma (a low grade form of glioma) is the second most common type of brain tumour diagnosed, accounting for about one third of the malignant brain tumours. Other gliomas (14%) make up the next largest group of brain tumours recorded in the South Australian Cancer Registry.

Differences by age and gender

Malignant brain tumours predominantly affect older people.

Incidence rates in South Australia vary from just under 2 cases per 100,000 persons per year among adolescents to just over 20 cases per 100,000 persons per year among those aged over 65 years. There is an early peak in incidence among young children (under the age of 10 years) after which incidence declines until early adulthood (around 20 years). From early adulthood, the incidence of malignant brain tumours increases to peak at around 70–75 years of age, after which it evidently declines again.

Despite the higher incidence rates in older people, malignant brain tumours account for a much higher proportion of all cancers diagnosed in children (~15%) than among people aged 65 years or older (1.1%, SA 1997–2006).

Age profiles are similar for males and females, however males have a higher incidence overall, which is evident from early adulthood (*Figure 2*). The annual average age standardised incidence

among males (of all ages) is 8.6 per 100,000 per year compared with 5.7 per 100,000 per year for females (1997–2006). The overall male to female incidence ratio in South Australia is 1.5 to 1.

Due to the high case fatality rate for malignant brain tumours, mortality rates across the age ranges mirror those seen for incidence, with the highest mortality rates for males aged 65 years and older (26 deaths per 100,000 persons, age standardised) and lowest among adolescents and young adults (<1 death per 100,000 per year). See *Figure 3*. Mortality rates are higher for males across all age ranges, however these differences are not statistically significant for children (0–14 years) and adolescents and young adults (15–24 years). The overall male to female mortality ratio is 1.6 to 1.

As is the case with incidence, malignant brain tumours account for a substantial proportion of childhood cancer deaths (32%) but only a small proportion of cancer deaths overall among older people (2% among those 65 years and older).

The mix of brain tumour subtypes also varies with age. *Table 2* shows the proportions of major histological types according to age grouping, as well as mean age at diagnosis for each type. Astrocytomas (lower grade gliomas) are more common among children and young adults than among older adults, whereas glioblastoma-multiforme (higher grade gliomas) are rarely diagnosed in children but account for around half of the brain tumours diagnosed in adults from the age of 45 years. Likewise, medulloblastomas (also

Figure 2 Annual age specific incidence of malignant brain tumours by gender, South Australia 1977–2006

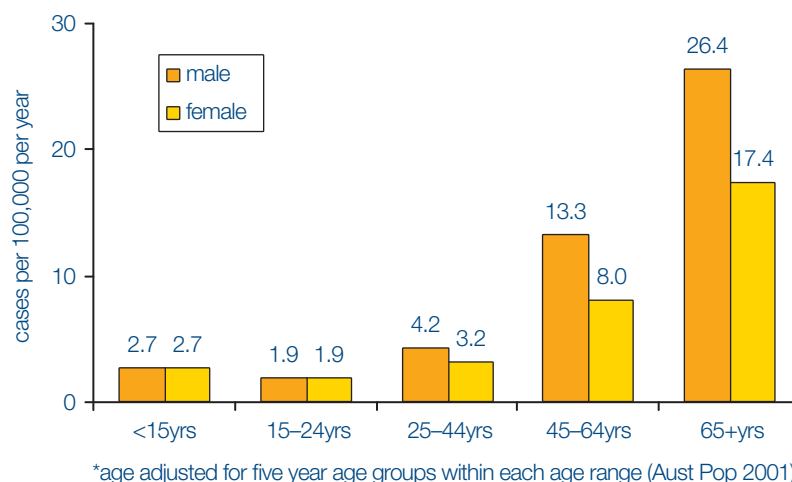
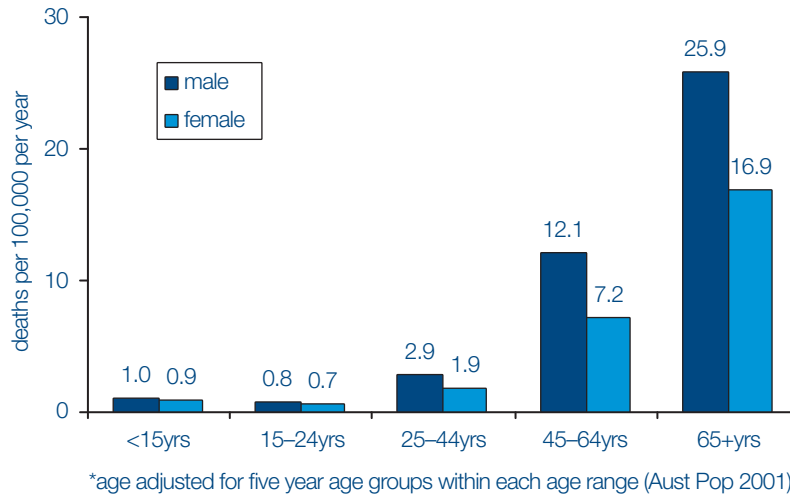


Figure 3 Annual age specific mortality for malignant brain tumours by gender, South Australia 1977–2006



known as primitive neuroectodermal tumours) account for just over one quarter of brain tumours in children but are rarely diagnosed in adults.

The mean age at diagnosis for astrocytoma in South Australia is 48 years, while the mean age for GBM is 62 years and medulloblastoma, 13 years.

Time trends

The total number of malignant brain tumours per year in South Australia (i.e. the burden of brain cancer) has almost doubled over the past three decades, from around 76 cases per year (1977–1981) to 125 cases per year (2002–2006). However the increase in number of cases is mainly restricted to people aged 45 years and

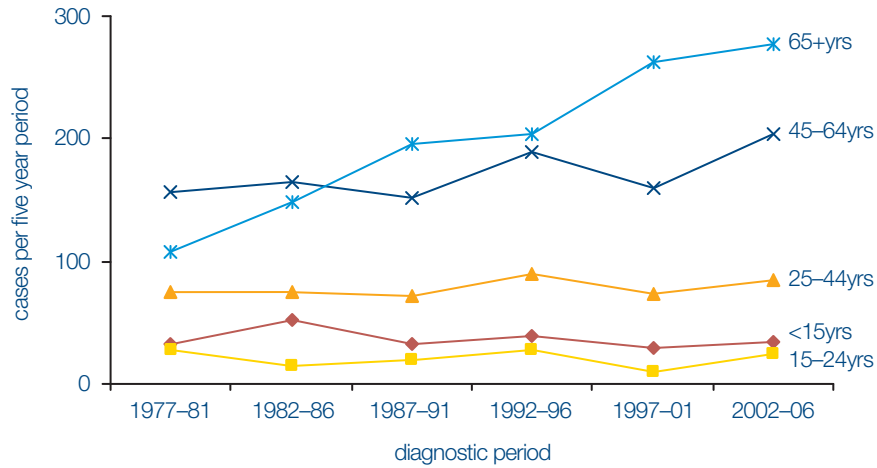
older, with little change in numbers of brain tumours diagnosed in children, adolescents and young adults (*Figure 4*). When taking into account changes in the population profile, the only age group in which the rate of malignant brain tumours appears to have increased is among those aged 65 years and older (*Figure 5*). This trend has also been observed internationally in more developed countries and is thought to be due to improved diagnostic techniques and more investigation among older people, although there is still some debate about the extent to which diagnostic effectiveness account for the increasing trend.

Overall, the age standardised incidence of malignant brain tumours has remained reasonably stable in South Australia over the past 30 years,

Table 2 Distribution of malignant brain tumour subtypes, by age group (SA 1977–2006) percent of cases in each age group

histological subtype	<15	15–24	25–44	45–64	65+	all ages	mean age at diagnosis (yrs)
astrocytoma	43.0	48.4	49.7	31.5	22.5	32.3	48.3
glioblastoma-multiforme	5.4	13.9	21.4	50.0	47.7	40.0	61.5
ependymoma	5.8	5.7	3.2	0.9	0.3	1.6	33.0
medulloblastoma (PNET)	27.2	11.5	1.7	0.0	0.1	2.7	12.6
oligodendroglioma	1.8	2.5	10.2	3.5	1.2	3.5	45.5
other gliomas	11.8	13.1	8.5	10.0	19.5	13.8	60.9
other malignant brain tumours	5.0	4.9	5.3	4.1	8.7	6.2	61.3

Figure 4 Trends in number of malignant brain tumours according to age group, South Australia 1977–2006



for both males and females, though there can be considerable variation from year to year due to the relatively small number of cases diagnosed annually (*Figures 6 and 8*). Mortality rates, however, do appear to have increased among males (from 6.9 per 100,000 per year for the period 1977–86 to 8.3 per 100,000 per year for 1997–2006, after adjusting for changes in the age

profile of the population). See *Figures 7 and 8*. The slight increase observed among females was not statistically significant (hence could be due to chance variation). Increasing mortality rates are likely to be due to the increase in cases among older people who are generally diagnosed with higher grade tumours (see below) and have poorer survival outcomes.

Figure 5 Trends in age specific rates for malignant brain tumours, South Australia 1977–2006

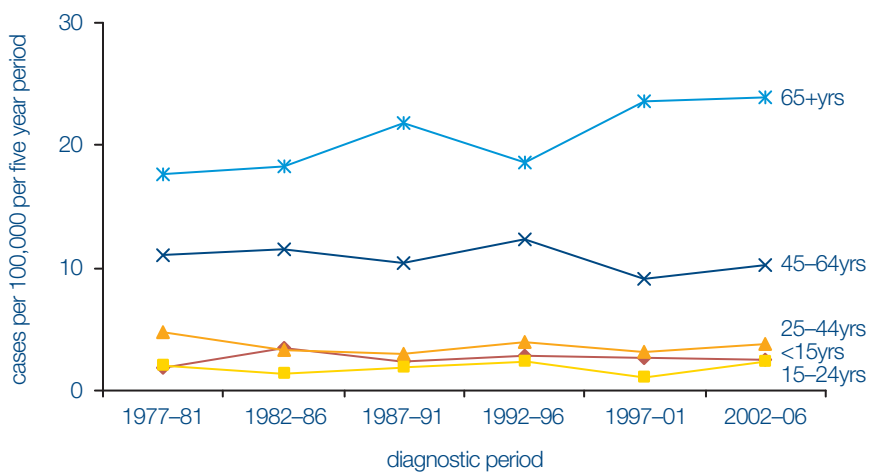
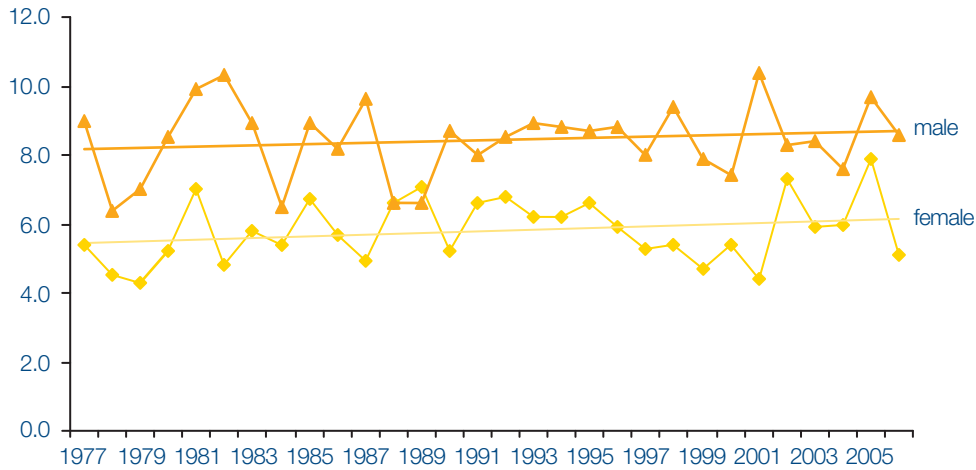


Figure 6 Trends in age standardised incidence rates for malignant brain tumours by gender, South Australia 1977–2006 (cases per 100,000 per year)



Time trends also indicate changes in the proportions of histological subtypes diagnosed and the age profile of those being diagnosed. Nearly half (47%) of all malignant brain tumours diagnosed between 1997 and 2006 occurred among people aged 65 years or older, whereas only 30% of those diagnosed between 1977 and 1986 were in this age range (*Figure 9*). The histological profile of malignant brain tumours

has also changed in line with the increasing age profile, with 50% of cases diagnosed in the most recent decade being classified as higher grade GBMs, compared with 31% and 37% in the previous two decades. The reverse pattern is noted in relation to astrocytomas which accounted for 41% of malignant brain tumours diagnosed in the period 1977–1986 but only 25% for the period 1997–2006 (*Figure 10*).

Figure 7 Trends in age standardised mortality rates for malignant brain tumours by gender, South Australia 1977–2006 (deaths per 100,000 per year)

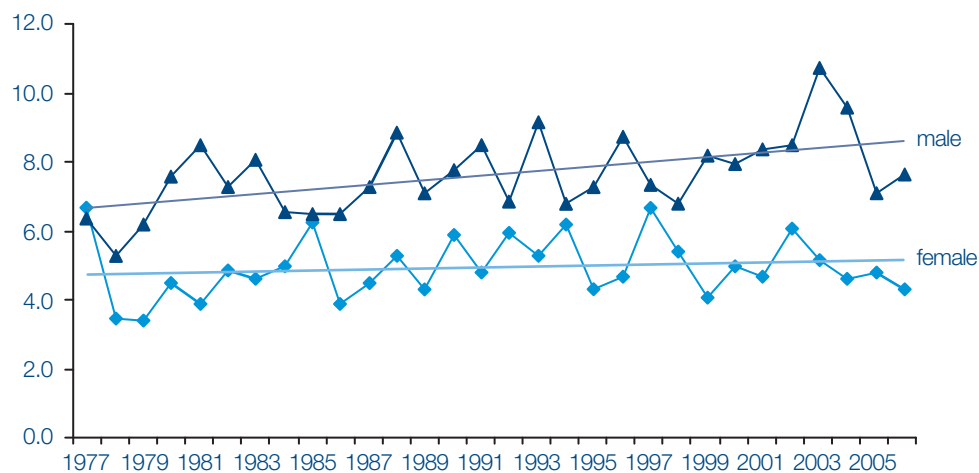


Figure 8 Average annual age standardised incidence and mortality rates per 100,000 for malignant brain tumours, by time period and gender (South Australia 1977–2006)

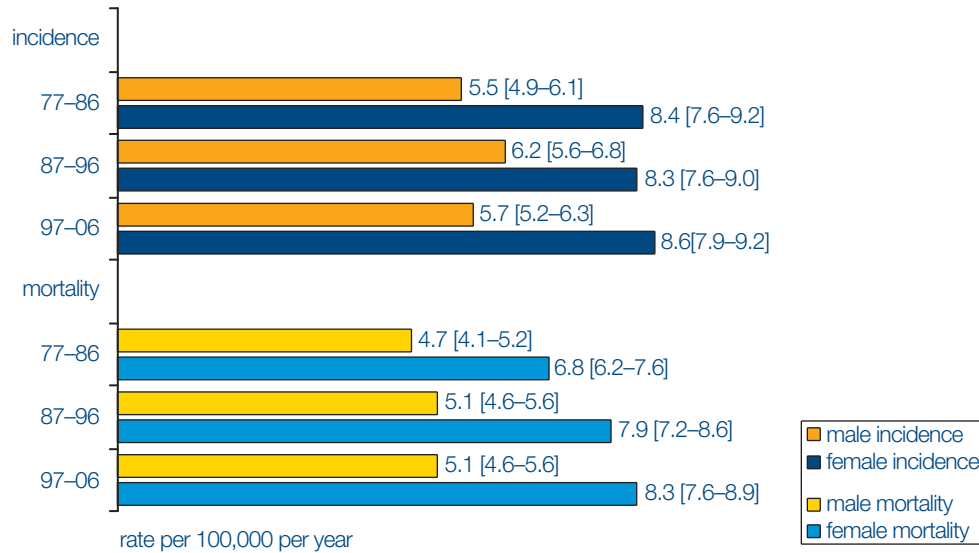


Figure 9 Distribution of age group at diagnosis according to diagnostic period, South Australia 1977–2006

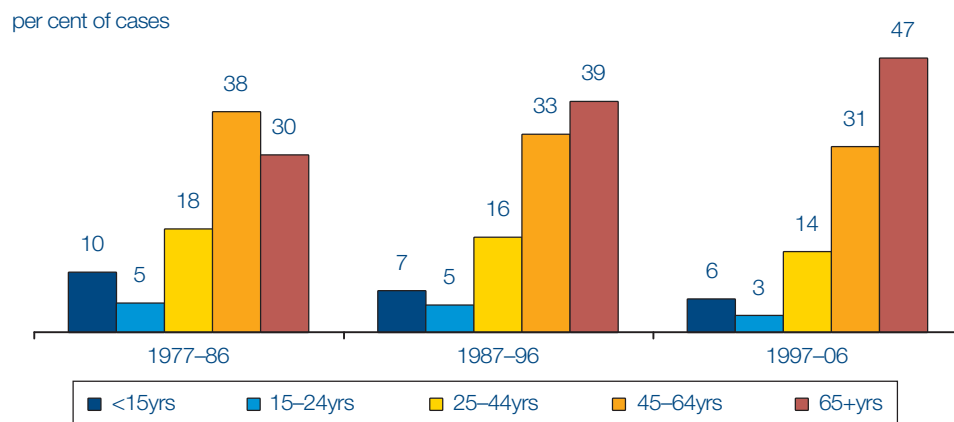
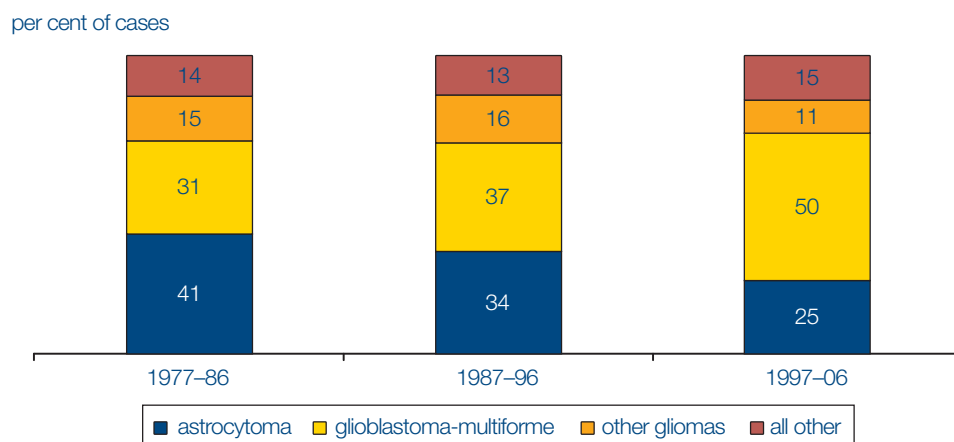


Figure 10 Distribution of histological subtypes according to diagnostic period, South Australia 1977–2006



Survival

Survival outcomes for malignant brain tumours are among the poorest, relative to other types of cancer. On average only 40% of patients diagnosed with malignant brain tumours in South Australia (1977–2006) were alive 12 months after the date of diagnosis. Five year survival for all malignant brain tumours combined was in the order of 20% and 10 year survival around 16%.

There is, however, considerable variation in survival outcomes according to histological subtype (*Figure 11*), with relatively favourable outcomes for those diagnosed with oligodendromas and ependymomas (five year survivals of 69% and 66% respectively). The poorest outcomes are seen for the high grade form of glioma (glioblastoma-multiforme), with around 3% survival five years post-diagnosis. Five year survival for those with astrocytoma is 32% (see *Figure 12*).

Figure 11 Survival to five years following diagnosis of a malignant brain tumour according to histological subtype, South Australia 1977–2006 (disease-specific survival)

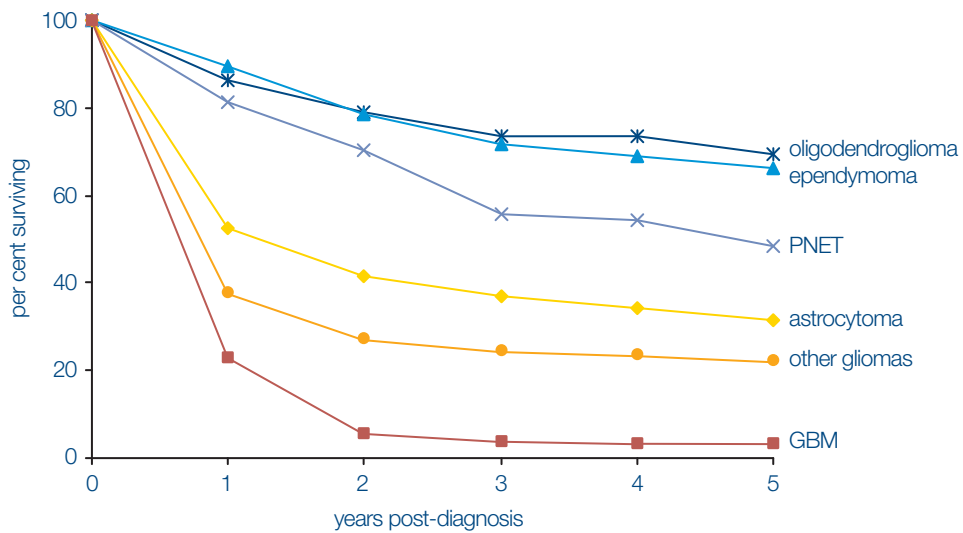
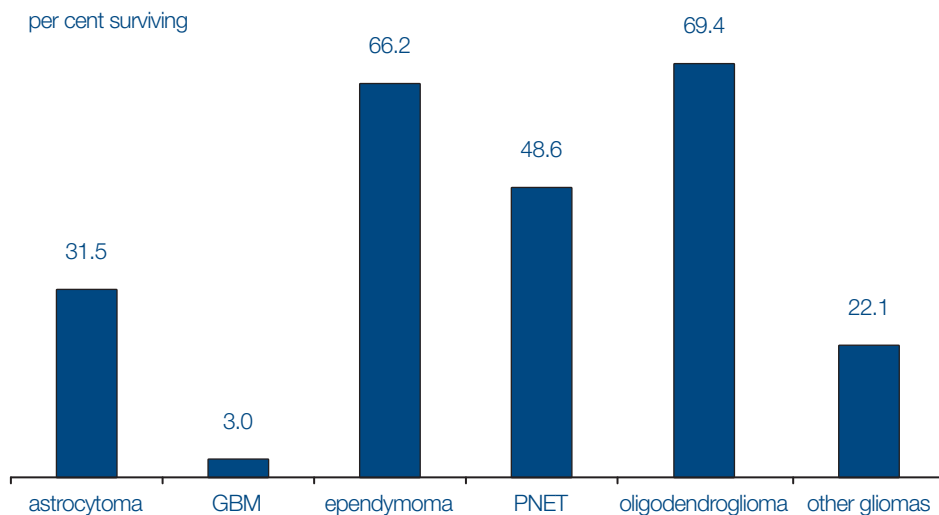


Figure 12 Five year survival from malignant brain tumours according to histological subtype, South Australia 1977–2006 (disease-specific survival)



Age is also a prognostic indicator, with significantly poorer survival associated with increasing age among adults. Five year survival was around 59% for children with brain tumours and 60% for adolescents and young adults (1977–2006). This compares with five year survival rates of 48% for adults aged 25–44yrs, 13% for those aged 45–64yrs and 4% for those aged 65yrs or older (see *Figure 13*). While these patterns in part reflect the profile of cancer types occurring in each age range (i.e. higher proportion of GBMs

in older people), significant differences are seen across age groups for each of the major tumour subtypes, indicating the independent effect of age.

Survival also varies according to gender. Overall women had better survival rates than males (five year survival of 23% for females compared with 19% for males for all brain tumours combined 1977–2006). See *Figure 13*. While the difference is not great it is statistically significant. Similar gender differences have been observed in other

Figure 13 Five year survival percent according to age group, gender and diagnostic period, South Australia 1977–2006 (disease-specific survival)

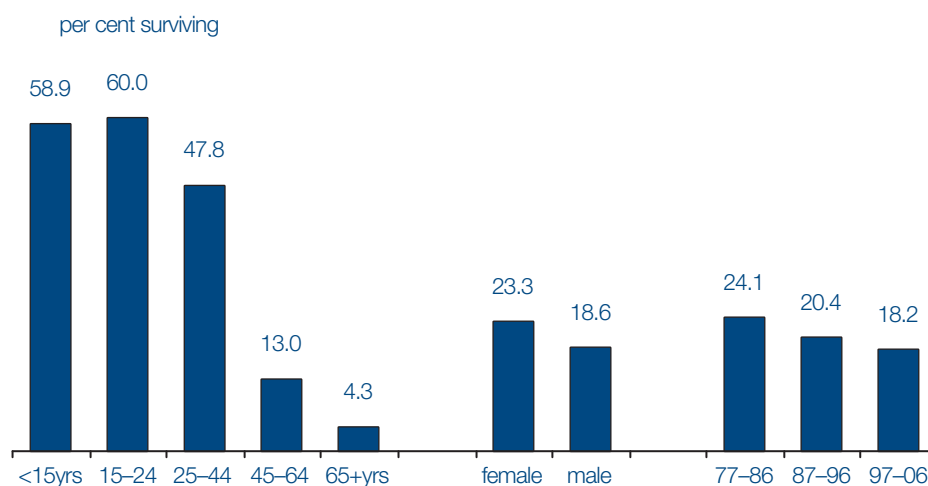


Table 3 Cox multivariate model of risk of death from malignant brain tumours

factors	hazard ratio*	95% CI
female	1.00	
male	1.03	0.94–1.11
<15 yrs	1.00	
15–24 yrs	1.12	0.81–1.53
25–44 yrs	1.63	1.31–2.05
45–65 yrs	3.43	2.76–4.26
65+ yrs	7.12	5.73–8.85
all subtypes except GBM	1.00	
glioblastoma-multiforme	1.84	1.69–2.02
1977–1986	1.00	
1987–1996	0.92	0.83–1.02
1997–2006	0.80	0.72–0.89

(*risk of death compared with reference group; higher than 1 = increased risk, lower than 1 = decreased risk of death)

developed countries, but the reasons for these differences remain unclear.

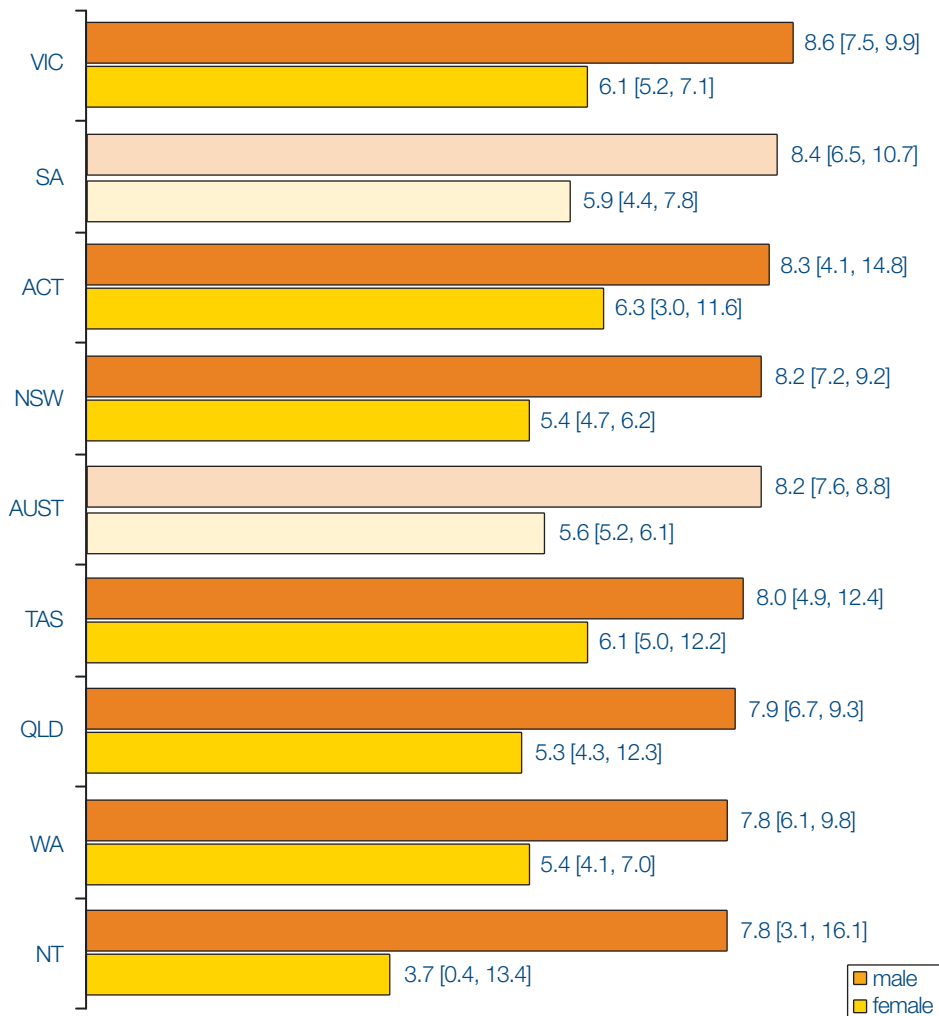
Trends over the past three decades do not indicate any improvement in overall survival from malignant brain tumours in South Australia. In fact comparison of five year survivals across each decade shows a statistically significant decrease from 24% for those diagnosed between 1977 and 1986 to 18% for those diagnosed between 1997 and 2006. See *Figure 13*. However when changes in the age profile and cancer subtype are taken into account (via Cox regression modelling) an improvement in survival over time can be seen, as indicated by the hazard ratios of less than one (see *Table 3*).

Regional comparisons

Within Australia

As shown in *Figure 14*, there is little variation in the incidence of malignant brain tumours across the states and territories of Australia. The incidence rate in South Australia is comparable to that for the whole of Australia and for all other states or territories, for both males and females. Neither are there any statistically significant differences between any of the other states and territories.

Figure 14 Incidence of malignant brain tumours per 100,000 by gender for states and territories of Australia (2001–2005)



age standardised to Australian 2001 population
source AIHW

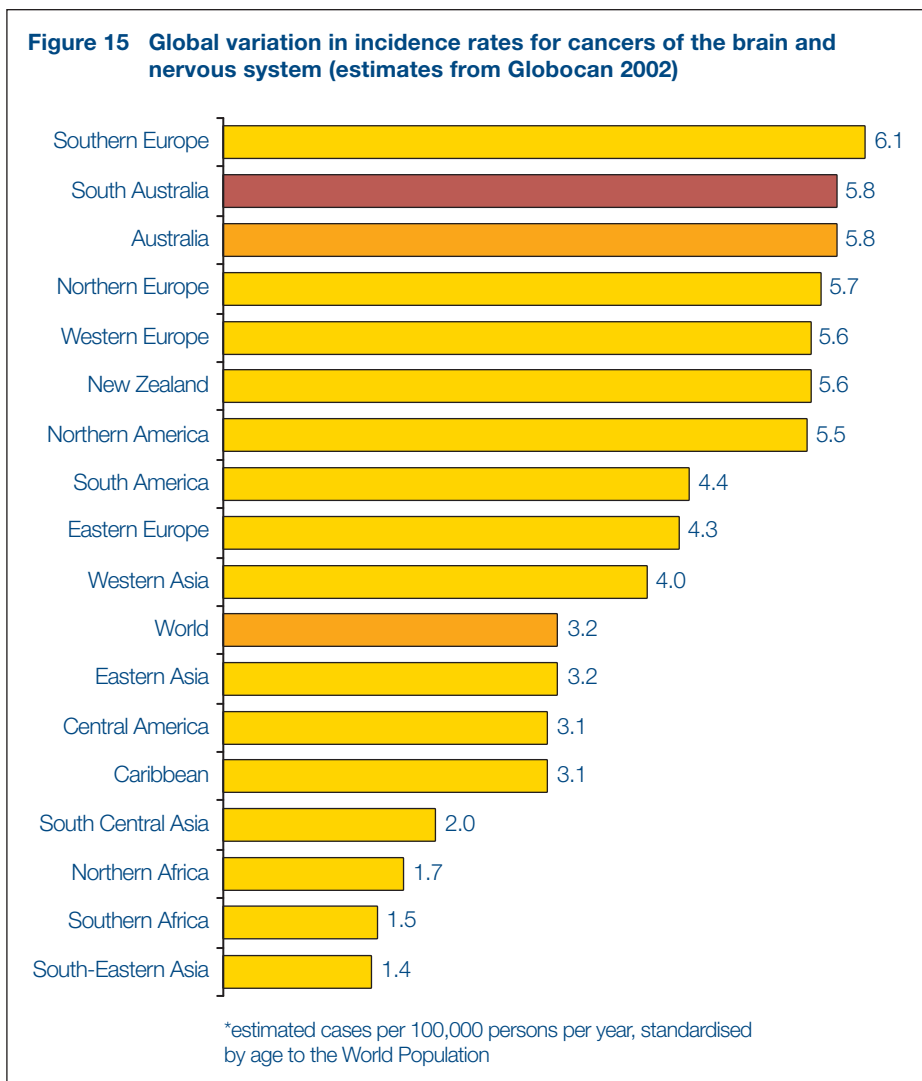
Global

Interpretation of regional differences in the incidence and mortality rates for malignant brain tumours is problematic due to differences in tumour classification and reporting requirements across different cancer registries, as well as variations in diagnostic capabilities, autopsy rates and other investigative practices in different regions of the world. While there may be some, as yet unknown, environmental factors that contribute to regional variations, it is most likely that higher rates reflect greater diagnostic sensitivity in regions that have well-resourced health care sectors (e.g. they have access to enhanced imaging technologies for better detection of brain tumours).

Estimates from IARC (via Globocan 2002) include malignant brain tumours that are grouped together

with other malignant central nervous system (CNS) tumours. Malignant tumours of the brain account for the vast majority of central nervous system cancers, therefore patterns in cancers of the CNS collectively are generally indicative of patterns for malignant brain tumours.

Globocan data indicate higher rates of cancers of the nervous system in more developed countries/regions compared with less developed countries/regions (see *Figure 15*). In the case of both males and females, the incidence rates for Australia (hence South Australia) are among the highest in the world. Southern Europe experiences the highest rates among males and females, while South Eastern Asia experiences the lowest rates of cancers of the CNS. Regional variation in malignant brain tumours is around fourfold and is likely to reflect differences in diagnostic methods as discussed above.



As with incidence rates, Australia and hence South Australia has relatively high mortality rates for cancers of the nervous system, compared with other regions of the world (Figure 16). This is largely due to the high case fatality rate for malignant tumours of the brain in general, which means countries with high incidence rates are also likely to have high mortality rates.

tumours, survival outcomes are better than many other regions of the world. The highest death-to-case ratios are seen for Eastern Europe, and parts of Asia and Africa. The lowest ratios are seen for Europe, North America and eastern Asia (China, Japan and Korea)

Comparisons of the ratio of mortality and incidence rates for a particular period of time are indicative of variations in survival between regions (the higher the ratio, the poorer the outcomes for individuals with cancer in that particular region.) Figure 17 shows the deaths per 100 cases across various regions based on incidence and mortality estimates available from Globocan. The ratio of deaths to cases for Australia and South Australia is equivalent to the world average, indicating that while we have high rates of malignant brain

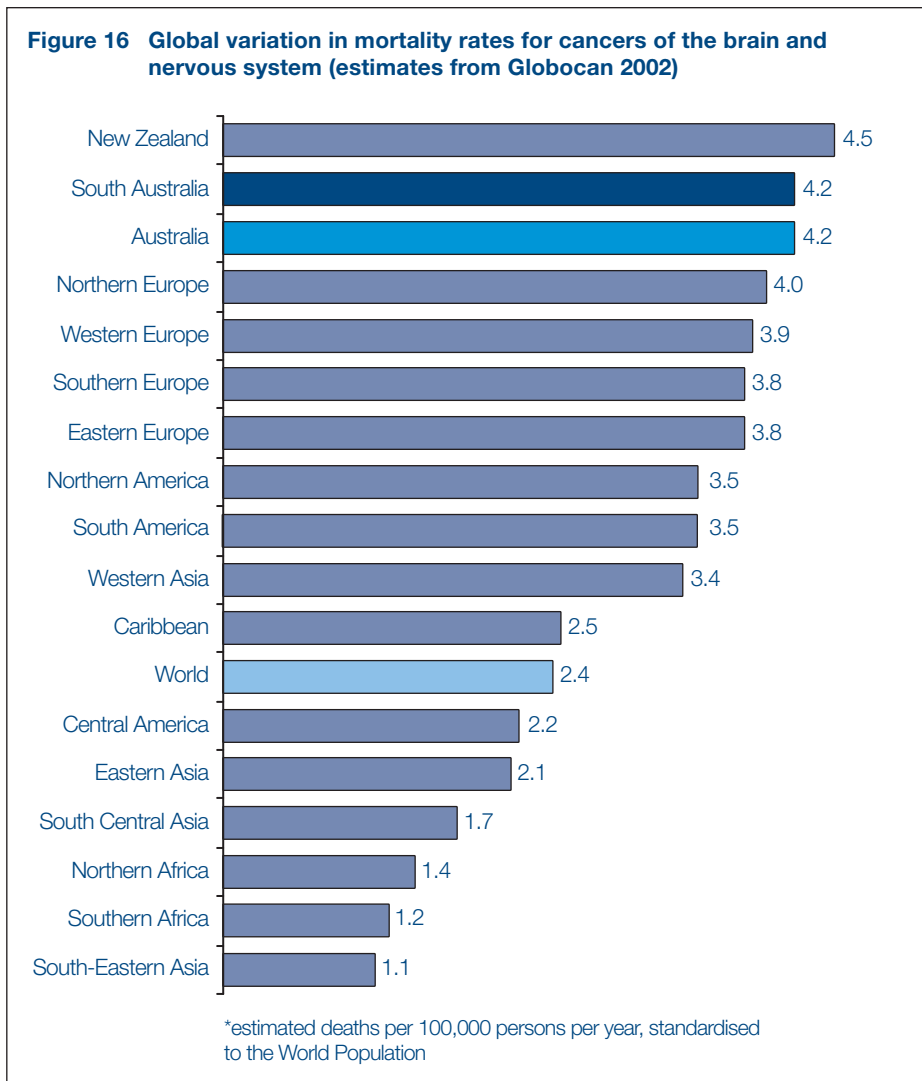
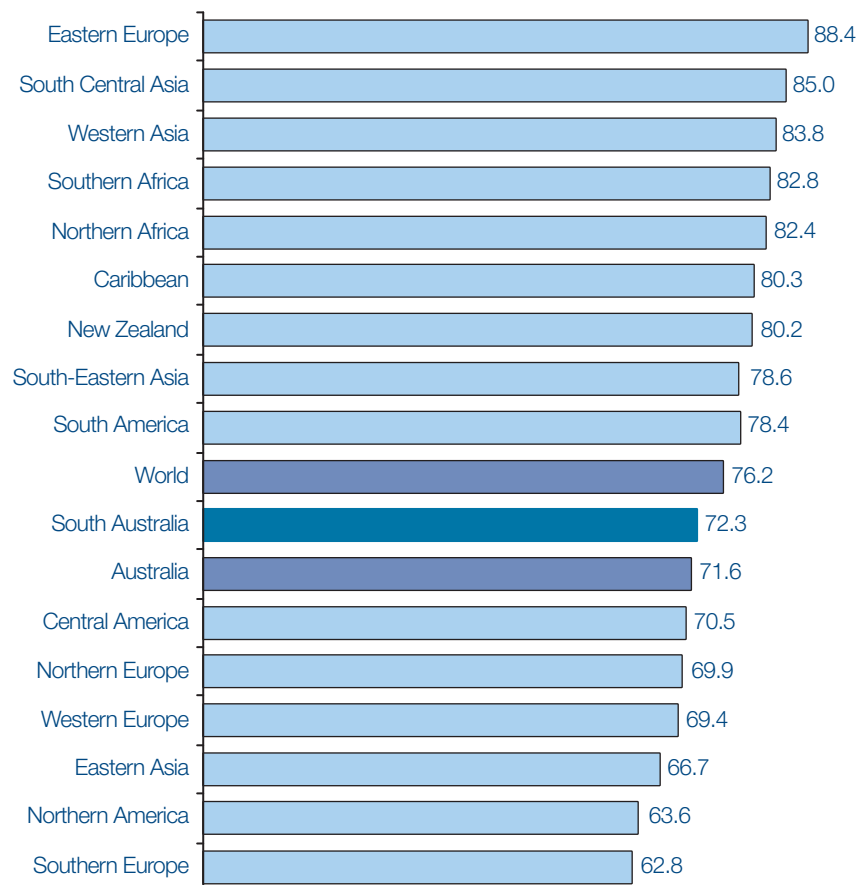


Figure 17 Global variation in numbers of deaths per 100 cases for cancers of the brain and nervous system (based on incidence and mortality estimates from Globocan 2002) (age standardised to World Population)



Highlights

- Malignant brain tumours are relatively rare, accounting for only 1.5% of all cancers diagnosed in South Australia and 3% of all cancer deaths.
- Collectively, malignant brain tumours rank 15th in terms of most common cancers and 11th in terms of leading cause of cancer death in South Australia.
- The incidence of malignant brain tumours tends to be higher in more developed countries, hence rates in South Australia/Australia are relatively high by world standards. This may be due to the availability of more advanced diagnostic technologies than in many other countries.
- Because of the high case fatality for malignant brain tumours, mortality rates are also high in Australia compared with other regions of the world.
- While brain tumours predominantly affect older people, they can also occur at a young age. As a proportion of all cancers, brain tumours account for 20% of childhood cancers and 32% of cancer deaths in children.
- Males are more likely than females to develop and die from malignant brain tumours (Incidence ratio 1.5 to 1.0).
- 40% of malignant brain tumours diagnosed in South Australia are glioblastoma-multiforme (GBM), a very aggressive type of brain cancer which occurs mainly in older people.
- The overall incidence rate in South Australia has remained relatively stable over the past three decades. However the number of cases diagnosed each year has doubled, due largely to the changing age profile in South Australia.
- Age specific rates have remained steady in all age groups, except those aged 65 years or older, where there has been an increase. This pattern has also been seen in other industrial countries and may reflect an increase in diagnostic investigation in older people.
- The mortality rate for malignant brain tumours in South Australia has increased over the past three decades. This is due largely to the increase in incidence among older people and the increase in cases that are of a more aggressive form (glioblastoma-multiforme).
- Survival outcomes are poor for South Australia, as they are elsewhere. Only 40% of people diagnosed with malignant brain tumours in South Australia were alive 12 months after diagnosis. Five year survival was 20% while 10 year survival was 16%.
- Survival outcomes are clearly associated with age at diagnosis and histological subtype. Five year survival for children under 15 years was 59%, while five year survival for those aged 65 years or older was 4%. People diagnosed with astrocytoma have a five year survival of 32% compared with just 3% for glioblastoma-multiforme.
- When age and histological subtype are taken into account, survival outcomes for malignant brain tumours have actually improved in South Australia over the past two decades.

Resources

Resources

For further information on brain cancer or support for patients and families contact:

Cancer Council Help Line 13 11 20

Publications

Brain cancer—a Cancer Council SA publication

A Primer of Brain Tumors—a publication from the American Brain Tumor Association

<www.abta.org/index.cfm?contentid=170>

Understanding Brain Tumours: A guide for people with brain or spinal cord tumours and their families and friends—a Cancer Council NSW publication

<www.nswcc.org.au/editorial.asp?pageid=1226>

Websites

National Cancer Institute, US

<www.meb.uni-bonn.de/cancernet/201143.html>

Cancerbackup, UK

<www.cancerbackup.org.uk/Home>

Brain tumour medical database

<www.brainlife.org/>

Cancer Institute, NSW

<www.cancerinstitute.org.au/cancer_inst/patients/>

Support groups

Adult Brain Cancer Support Group—Adelaide

<web.me.com/adultbraincancersa/Site/Home>

Brain Injury Network of SA

Ph 08 8252 3711

<www.binsa.org/>

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Glossary

Glossary

adolescent

a young person in the developmental stage between puberty and maturity.

astrocytoma

a tumour that begins in the brain or spinal cord in small, star-shaped cells called astrocytes. The location of the tumour depends on the age of the person. In adults, astrocytomas most often arise in the cerebrum whereas in children, they may arise in the brain stem, cerebrum and cerebellum.

benign brain tumour

a tumour or abnormal growth of cells that occurs in the brain but is not malignant (does not contain cancerous cells). Benign tumours can be fatal if they grow and press on particular parts of the brain.

case fatality rate

the proportion of individuals with a disease that die of that disease.

central nervous system

pertaining to the brain, cranial nerves and spinal cord. It does not include muscles or peripheral nerves.

chemotherapy

treatment by means of chemicals that selectively destroy cancerous tissue (anti-cancer therapy).

computed tomography (CT)

a special radiographic technique that uses a computer to compile multiple X-ray images into a two-dimensional cross-sectional image.

diagnostic

refers to procedures or tests that are used to determine the cause of an illness or disorder.

eczema

a form of dermatitis (inflammatory skin condition) occurring as a reaction to many internal and external agents.

electromagnetic radiation (EMR)

radiation (such as radio waves, microwaves, infrared, visible light, ultraviolet, X-rays and gamma rays) which consists of associated, interacting electric and magnetic field waves which travel at the speed of light.

ependymoma

a type of brain tumour derived from the cells that line the cavities within the ventricles of the brain and the central canal of the spinal cord. Because cerebrospinal fluid (CSF) normally flows through the cerebral ventricles and the central canal of the spinal cord, blockage due to an ependymoma can cause build-up of fluid, pressure on the brain with the associated symptoms of headaches, nausea and vomiting.

epilepsy

a transient disturbance of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances or disruption of the autonomic (involuntary) nervous system.

glioblastoma-multiforme

a type of tumour that forms from glial (supportive) tissue in the brain. It is highly malignant, grows very quickly and has cells that look quite different from normal glial cells. Early symptoms may include sleepiness, headache and vomiting. Also called a grade IV astrocytoma.

glioma

a brain tumour that begins in a glial or supportive cell, in the brain or spinal cord. Malignant gliomas are the most common primary tumours of the central nervous system (the brain and spinal cord). There are many types of gliomas.

incidence rate (cancer)

the rate at which cancers arise in the population. It may be expressed as the number of new cases diagnosed annually per 100,000 people.

ionising radiation (IR)

radiation sufficiently energetic to dislodge electrons from an atom. Ionising radiation includes X-rays and gamma radiation, electrons (beta radiation), alpha particles (helium nuclei) and heavier charge atomic nuclei.

Li Fraumeni's syndrome

an inherited family trait carrying an increased risk of cancer during childhood and early adulthood.

magnetic resonance imaging (MRI)

a special imaging technique used to image internal structures of the body, particularly the soft tissues. An MRI image is often superior to a normal X-ray image.

malignant brain tumour

a tumour in the brain that contains cancer cells (i.e. is cancerous).

medulloblastoma

a tumour that usually arises in the cerebellum. It is the most common brain tumour in children. It is sometimes called a primitive neuroectodermal tumour.

meninges

the surrounding membranes of the brain and spinal cord. There are three layers: the dura mater (outer), arachnoid membrane (middle) and the pia mater (inner layer).

meningioma

a common (usually benign) brain tumour that arises from the pia-arachnoid cells of the meninges.

mortality rate (cancer)

the rate at which deaths from cancer occurs in the population. It may be expressed as the number of deaths occurring annually per 100,000 people.

multiple sclerosis

a neurodegenerative disease characterised by the gradual accumulation of patches within the brain where the myelin sheath around the nerve cells has been damaged/destroyed. Peripheral nerves are not affected. The cause of this disease is still unknown.

nitroso-compounds (NOCs)

a group of chemical compounds that contain a nitroso group (NO) attached to a carbon or nitrogen atom. They can occur in man-made products or they can occur naturally and/or be formed within the body.

oligodendroglioma

a rare, slow-growing type of brain tumour that begins in cells called oligodendrocytes, which provide support and nourishment for cells that transmit nerve impulses. Also called an oligodendroglial tumour.

prognostic indicator

a sign or symptom indicating the likely course or outcome of a disease.

radio-frequency radiation (RF)

a low energy form of electromagnetic radiation.

radiotherapy

the treatment of disease by ionising radiation.

socio-economic status

pertaining to social or economic status.

