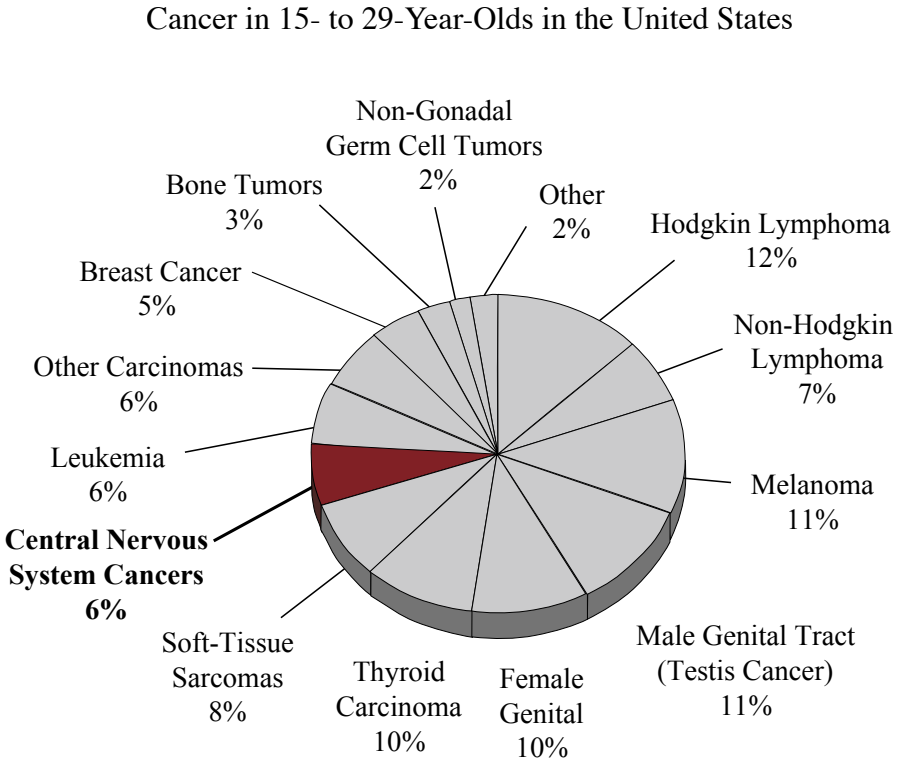
Chapter 6

Central Nervous System Cancer



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HIGHLIGHTS

Incidence

- Central nervous system (CNS) tumors accounted for 6% of all neoplasms in individuals 15 to 29 years of age during the period 1975 to 1998, and were the 7th most common neoplasm in this age group. An estimated 1,500 individuals 15 to 29 years of age were diagnosed with a CNS neoplasm in the U.S. during the year 2000.
- The average incidence of CNS tumors was 22.6 per million per year in the 15- to 29-year age group.
- At all ages, males had a higher incidence of CNS tumors than females.
- White, non-Hispanic individuals at any given age had a higher incidence of CNS tumors compared to African American/black, Hispanic, and Asian/Pacific Islander individuals.
- Between birth and 45 years of age, the incidence of astrocytoma increased and the incidence of ependymoma and PNET decreased with advancing age.
- Astrocytoma accounted for 64% of CNS neoplasms in individuals 15 to 29 years of age, whereas "other gliomas" accounted for 19%, primitive neuroectodermal tumor (PNET) 8%, ependymoma 6%, and miscellaneous CNS tumors 3%.
- The incidence of brain tumors increased slightly since 1975 in individuals 15 to 29 years of age—less so than in younger children, but more so than in 30- to 44-year-olds.
- Adolescents and young adults 15 to 29 years of age—as well as adults 30 to 44 years of age—showed an increasing incidence of "other gliomas" during the period studied (1975 to 1998). "Other gliomas" are defined as malignant glioma not otherwise specified (NOS), mixed oligoastrocytoma, subependymal giant cell astrocytoma, gliosarcoma, oligodendroglioma and monstrocellular sarcoma.

Mortality & Survival

- Mortality for individuals 15 to 29 years of age with CNS tumors showed little variation across racial/ethnic groups and was similar to mortality for children 0 to 14 years of age. Mortality for males at any given age was slightly higher than for females.
- Death rates for CNS tumors improved slightly over time for all age groups.
- The 10-year survival rate for CNS tumors exceeded 50% among patients younger than 20 years of age, but progressively declined with advancing age after age 20 years.
- The age-dependent decline in survival in astrocytoma for those over 20 years of age was dramatic, with a 10-year survival rate of 65% for individuals 15 to 19 years, 40% for those 20 to 24 years and 25% for those 25 to 29 years of age. The 10-year survival rate for 15- to 29-year-olds with PNET was 70%, for those with ependymoma 65%, and for those with "other glioma" 50%.
- Five- and 10-year survival rates for all CNS tumors combined improved slowly but steadily for patients 15 to 29 years of age over the period 1975 to 1998.
- Although the 5- and 10-year survival curves have improved with time, none of the individual age groups or major types of tumors has reached a survival plateau. This suggests that a "cure level" has not been achieved for most CNS neoplasms.
- The improvement in survival rates for CNS tumors in individuals 15 to 29 years of age lags behind that of other age groups.

Risk Factors

- Rare inherited conditions and therapeutic doses of ionizing radiation delivered to the CNS are the only two proven risk factors for CNS tumors, but explain only a small proportion of brain tumors.

INTRODUCTION

Central nervous system (CNS) tumors include both malignant and "benign" neoplasms (see *Classification System*); the latter term is reserved for tumors with a low potential to metastasize. While benign CNS neoplasms are often life-threatening due to local growth in a confined space or invasion/compression of critical structures, data for these tumors were not collected until 2004 and are therefore not included in this chapter. CNS *cancer* is used in the title and throughout the text to refer to malignant tumors of the brain and spinal cord

In the period 1975 to 1998 in the U.S., CNS cancer accounted for 6% of all cancers in adolescents and young adults 15 to 29 years of age, and represented the seventh most common type of cancer in this age group. This is in sharp contrast to individuals 0 to 14 years of age, in whom CNS cancer accounted for 25% of all cancers and were the second most common type of cancer. In the U.S. in the year 2000, 1,500 adolescents and young adults 15 to 29 years of age were diagnosed with a malignant CNS neoplasm (Table 6.1).

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

Malignant CNS neoplasms are histologically diverse and may arise from many different sites in the CNS. They are defined as malignant tumors arising from the brain, meninges, spinal cord, cranial nerves, pituitary gland, pineal gland or the craniopharyngeal duct. The histologic type rather than the site of origin better defines the behavior of CNS tumors, particularly for patients in the first decades of life.

This chapter is limited to primary malignant CNS cancers only; CNS germ cell tumors, CNS lymphoma, and metastases to the CNS from sites outside the CNS are not included. In the International Classification of Childhood Cancer (ICCC), CNS and miscellaneous intracranial and intraspinal neoplasms are divided into five major groups in category III. In the ICCC, astrocytomas appear in category III(b) and other gliomas in III(d). Table 6.2 includes the benign and malignant histologies from the ICCC, but in these analyses only the malignant histologies were used.

The astrocytoma category III(b) includes astrocytomas and glioblastomas regardless of location (categories 9400-9441), gliomatosis cerebri (9381), and malignant glioma of the optic nerve (9380, C72.3). Other gliomas are in category ICCC III(d), including malignant gliomas (9380) of the meninges, acoustic nerve, and other cranial nerves, oligodendroglioma and its variants (9450-9460), mixed gliomas (9382), subependymal giant cell (9384), gliosarcoma (9442), spongioblastoma (9443), and monstrocellular sarcoma (9481).

In the ICCC, primitive neuroectodermal tumors, including medulloblastoma, are in category III(c). These include medulloblastoma (9470), desmoplastic medulloblastoma (9471), primitive neuroectodermal tumor (9473), and medullomyoblastoma (9472). Large cell medulloblastoma (ICD-O-3 9474) is included with III(c).

Table 6.1: *Incidence of Malignant CNS Neoplasms in Persons Younger Than 45 Years of Age, U.S.*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44
U.S. population, year 2000 census (in millions)	19,175	20,549	20,528	20,219	18,964	19,381	20,510	22,706	22,441
Incidence of CNS tumors, 1975-2000, per year per million	33.7	29.9	24.1	19.2	21.2	27.0	33.0	39.8	49.3
Average Annual % Change in incidence of CNS tumors, 1975-1998	2.5%	0.8%	2.1%	0.3%	1.1%	1.6%	0.8%	-0.5%	0.2%
Number of persons diagnosed with CNS tumors, year 2000, U.S.	773	693	576	402	469	629	725	827	1154

Ependymoma is assigned a separate major category, III(a), in the ICCC (Table 6.2) and includes for these analyses malignant subependymal glioma (9383) and choroid plexus papilloma, malignant (9390), as well as the classic ependymomas (9391-9394). Ependymomas described as papillary (9393) or myxopapillary (9394) were only included if they were also described as malignant.

The ICCC assigns miscellaneous intracranial and intraspinal tumors to category III(e) and unspecified intracranial and intraspinal neoplasms to category III(f) (Table 6.2). Many histologies in the miscellaneous group, ICCC III(e) (Table 6.2) are not malignant and were not included in this analyses unless stated to be malignant. Malignant tumors in ICCC III(e) include pituitary carcinomas [chromophobe, acidophil, mixed acidophil-basophil, basophil (8270-8281, 8300)], cerebellar sarcoma (9480), and malignant meningiomas (9530-9539) including menigeal sarcomatosis (9539). Included in the analyses of the Unspec ified group are malignant tumors [(NOS (8000), small cell type (8002), giant cell type (8003), fusiform cell type (8004)], malignant tumor cells (8001) and from ICD-O-3 clear cell tumor (8005). In this chapter, these two ICCC

Table 6.2: *ICCC CNS Tumor Subgroups*

III(a) EPENDYMOMA	III(b) ASTROCYTOMA	III(c) PNET	III(d) OTHER GLIOMAS	III(e) MISCELLANEOUS INTRACRANIAL AND INTRASPINAL NEOPLASMS	III(f) UNSPECIFIED INTRACRANIAL AND INTRASPINAL NEOPLASMS
Ependymoma-NOS, anaplastic, papillary, myxopapillary	Astrocytoma-NOS, pilocytic (juvenile and piloid), fibrillary, protoplasmic, gemistocytic, anaplastic	Medulloblastoma-NOS, desmoplastic	Malignant glioma-NOS, mixed glioma	Pituitary adenoma and carcinoma (chromophobe, acidophil, basophil, mixed)	Malignant and benign primary tumors of the brain, spinal cord and cranial nerves NOS
Choroid plexus papilloma-NOS and malignant	Optic tract glioma	Primitive neuroectodermal tumor	Subependymal giant cell astrocytoma	Prolactinoma	
Subependymal glioma	Pleomorphic xanthoastrocytoma	Medullo-myoblastoma	Oligodendroglioma-NOS, anaplastic	Craniopharyngioma	
	Gliomatosis cerebri		Oligodendroblastoma	Pinealoma	
	Glioblastoma-NOS (GBM, giant cell glioblastoma, spongioblastoma multiforme)		Monstrocellular sarcoma	Pineocytoma	
	Spongioblastoma-NOS, polare		Gliosarcoma	Pineoblastoma	
	Astroblastoma		Primative polar spongioblastoma	Cerebellar sarcoma	
				Ganglioglioma	
				Meningioma-NOS, fibroblastic, psammomatous, angiomatous, hemangioblastic, hemangiopericytic, transitional, papillary	
				Meningioma-malignant (leptomeningeal sarcoma, meningeal sarcoma, meningothelial sarcoma)	
				Meningotheliomatous meningioma	
				Meningiomatosis	
				Meningeal sarcomatosis	

categories of miscellaneous (III(e)) and unspecified neoplasms (III(f)) were combined into one category termed "Miscellaneous" and reported only for malignant neoplasms.

In the ICCC, medulloblastoma (9470, 9471), medullomyoblastoma (9472), primitive neuroectodermal tumors (9473) are considered primitive neuroectodermal tumors forming group III(c). In the SEER modification of ICCC neuroblastomas of the CNS only were moved from IV(a) to III(c) and pineoblastoma (9362) was moved from III(e) to III(c). Primary CNS germ cell malignancies are placed in Germ Cell, Trophoblastic and Other Gonadal Malignancies (ICCC X). Primary CNS lymphomas are included under Lymphoma and Reticuloendothelial Neoplasms (ICCC II). The ICCC category of CNS and miscellaneous intracranial and intraspinal neoplasm does not include chordoma (9370), ganglioneuroblastoma (9490), olfactory neuroblastoma (9522), and retinoblastoma (9510-9512), peripheral primitive neuroectodermal tumors (9364) and nerve sheath tumors (9540-9571). Benign CNS neoplasms such as craniopharyngioma, pituitary adenoma, acoustic neuroma, choroid plexus papilloma, and benign neoplasms NOS are included in the CNS neoplasm group (ICCC III) but are not reported in this chapter.

As explained in the Methods chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

A few clarifications need to be made regarding the placement of some CNS tumors within the ICCC (Table 6.2):

- Benign CNS neoplasms such as craniopharyngioma, pituitary adenoma, acoustic neuroma, choroid plexus papilloma, and benign neoplasms NOS are included in the CNS neoplasm group (ICCC III) but are not reported in this chapter.
- Primary CNS germ cell malignancies are placed in Germ Cell, Trophoblastic and Other Gonadal Malignancies (ICCC X)
- Metastatic tumors to the brain are included in the ICCC according to the site of origin.
- Primary CNS lymphomas are included under
- Medulloblastoma, PNET, neuroblastoma and pineoblastoma are considered primitive neuroectodermal tumors. According to the ICCC, however, pineoblastoma is included in Miscellaneous Neoplasms (ICCC IIIe), and CNS neuroblastoma is included in Sympathetic Nervous System Tumors (ICCC IV).

This chapter will utilize the ICD system to assess mortality rates. Unfortunately, this system categorizes CNS neoplasms by site of origin: brain and other nervous system, spine and cranial nerves. Thus, mortality rates for individual histological types cannot be identified using the ICD.

INCIDENCE

SEER incidence data were analyzed from 1975 to 1998. During these years 3,030 primary CNS neoplasms were diagnosed in individuals 15 to 29 years of age who resided in one of the SEER areas. The average incidence of brain tumors in this age group was 22.6 per million. CNS neoplasms accounted for 6% of all malignancies and were the seventh most common type of cancer in this age group.

Spinal cord tumors represented 6-8% of all primary malignant CNS tumors in individuals 15 to 29 years of age, compared to 10-11% in patients < 15 years of age. The proportion of spinal cord tumors decreased progressively as age increased from 0 to 40 years.

Age-Specific Incidence

Figures 6.1 and 6.2 illustrate the relationship between age at diagnosis and incidence of CNS cancer. The proportion of new CNS tumors relative to all new cancer cases declined steadily with advancing age (Figure 6.1). Malignant CNS tumors accounted for more than one in five cases of cancer in children younger than 5 years of age, but accounted for one in 50 cases in adults 40 to 44 years of age. The decline was due more to an increase in other cancers (Figure 6.1) than to a decrease in CNS tumors (Figure 6.2). When five-year age groups are considered, individuals 15 to 29 years of age had the lowest incidence of CNS neoplasms, followed by individuals 20 to 24 years of age. A steady upward climb in incidence

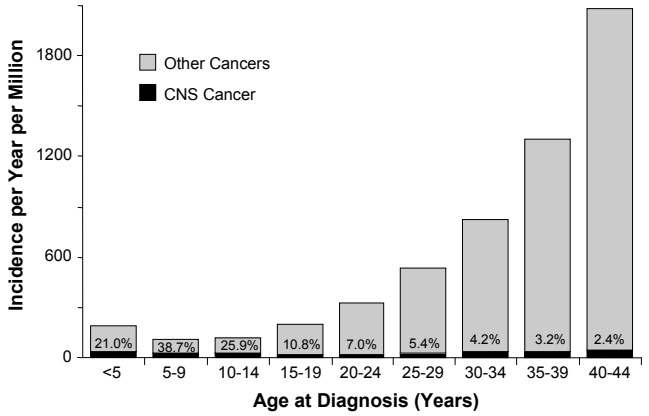

Figure 6.1: Incidence of CNS Tumors Relative to All Cancer, SEER 1975-1998

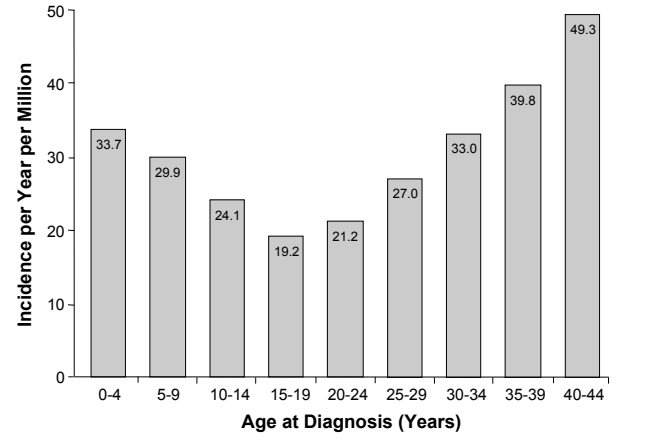

Figure 6.2: U.S. Cancer Incidence: All CNS Cancer, SEER 1975-2000

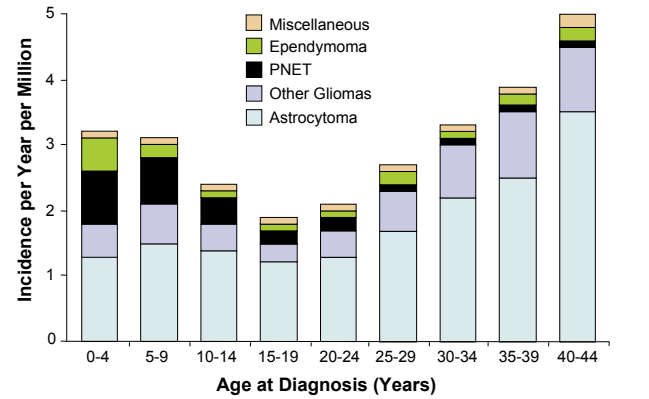

Figure 6.3: Incidence of CNS Tumors by Type (ICCC), U.S. SEER 1975-1998

was seen in those older than 24 years of age, with the rate for 35- to 39-year-olds more than twice that of 15- to 24-year-olds (Figure 6.2).

The incidence of each histological subtype of CNS tumor is displayed in Figure 6.3. In the 15- to 29-year age group, astrocytoma accounted for 64%, "other glioma" 19%, PNET 8%, ependymoma 6%, and miscellaneous 3%. This histologic distribution is more comparable to adults (30 to 44 years of age) than to children (0 to 14 years of age). In children < 15 years of age, astrocytoma accounted for 50%, "other glioma" 15%, PNET 23%, ependymoma 9%, and miscellaneous 3%. The incidence of astrocytoma increased and the incidence of PNET and ependymoma decreased with advancing age (Figure 6.3).

Gender-Specific Incidence

Males at any given age had a higher incidence of CNS tumors compared to females (Figure 6.4), with the male: female incidence ratio never falling below 1.1 (Figure 6.5). The incidence of CNS tumors in males 15 to 29 years of age was 25.1 per million, whereas in females it was 19.3 per million. An average male:female incidence ratio of 1.32 was seen for individuals in this age group. Males had a higher incidence of all histological types of brain tumors as categorized by the ICCC. The male: female incidence ratio for the more common CNS tumors in the 15 to 29 year age group was 1.26 for astrocytoma, 1.32 for ependymoma and "other glioma", and 1.85 for PNET. This male predominance pattern differs from that of all cancers combined, for which the male:female incidence ratio steadily declined with advancing age from age 10 to 45 (Figures 6.5 and 1.3). The gender difference

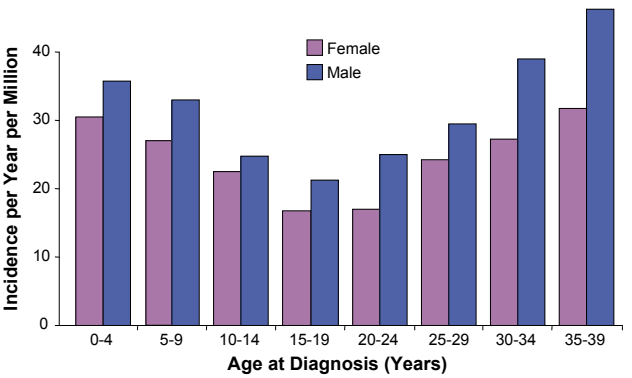

Figure 6.4: Incidence of CNS Tumors (ICCC) by Gender, U.S., SEER 1975-1998

has not been adequately explained. The fact that the male brain is generally larger than the female brain throughout the age span and thereby contains more cells may be a contributing factor.

Racial/Ethnic Differences in Incidence

Figure 6.6 displays CNS tumor incidence from 1990 to 1999 by race/ethnicity. The incidence of CNS neoplasms in all age groups was higher for white non-Hispanic individuals than for African American/black, Hispanic, and Asian/Pacific Islander individuals. In the 15- to 29-year age group, the incidence of CNS neoplasms was 27 per million in white non-Hispanics and 14.4 to 14.8 per million in the other three racial/ethnic groups.

In all racial/ethnic groups, males 15 to 29 years of age had a 20-25% higher incidence of CNS tumors compared to females. The incidence of CNS neoplasms in white non-Hispanic males 15 to 29 years of age was 30.6 per million, compared to 23.2 per million in females. The average incidence of CNS neoplasms for males in the other three racial/ethnic groups was 16 per million, compared to 13 per million for females.

Trends in Incidence

The incidence for all CNS neoplasms based on year of diagnosis (1975 to 1998) is displayed in Figure 6.7. The incidence rate increased for all age groups from 1975 to 1980 and 1987 to 1992. For children 0 to 14 years of age, this data has been rigorously analyzed; this change in incidence did not occur progressively from 1975 to 1994, but, "jumped" to a higher rate after 1985.[1] The timing of the jump was attributed to the wide-scale availability of magnetic resonance imaging (MRI) in the United States—which likely resulted in improved diagnostic sensitivity—rather than an actual increase in incidence.[1] Introduction of MRI may also explain, in part, the increased incidence over time of CNS tumors in individuals older than 15 years of age.

The average annual percent change (AAPC) in incidence of CNS tumors revealed a statistically significant increased incidence of all CNS tumors for children 0 to 14 years of age and for adolescents and young adults 15 to 29 years of age (Figure 6.8; inset). Adults 30 to 44 years of age showed no increase in the incidence of CNS

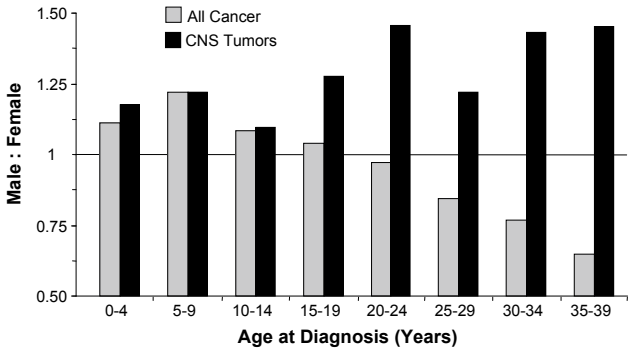

Figure 6.5: Ratio of Male-to-female Incidence for CNS Tumors versus All Cancer, SEER 1975-1998

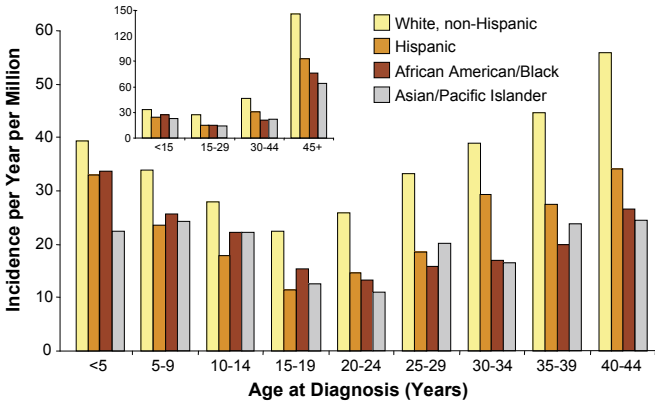

Figure 6.6: Incidence of CNS Tumors by Race/Ethnicity, SEER 1990-1999

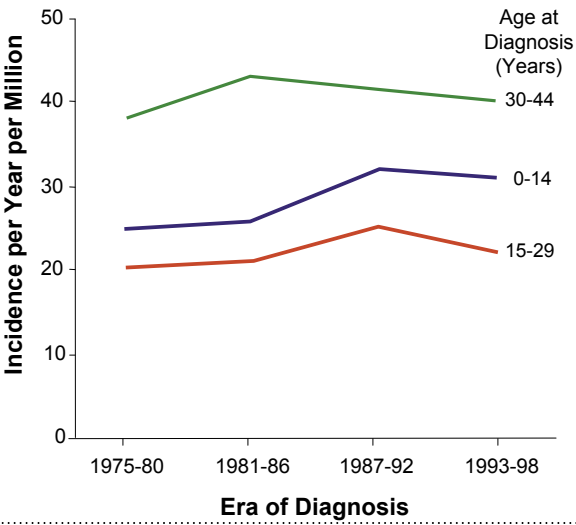

Figure 6.7: Change in Incidence For All CNS Tumors by Era, SEER 1975-1998

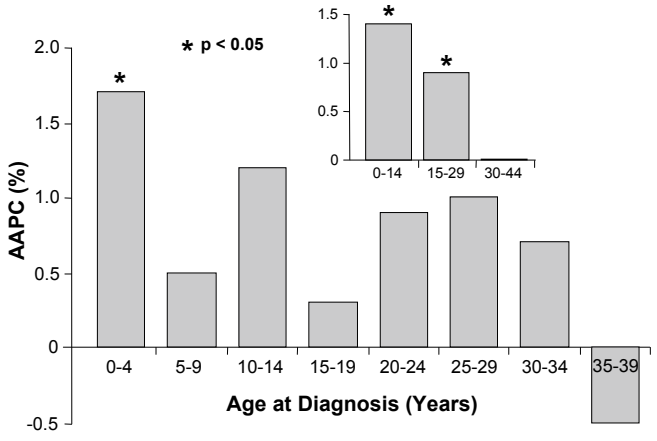

Figure 6.8: Average Annual Percent Change (AAPC) in Incidence for CNS Tumors (ICCC), SEER 1975-1998

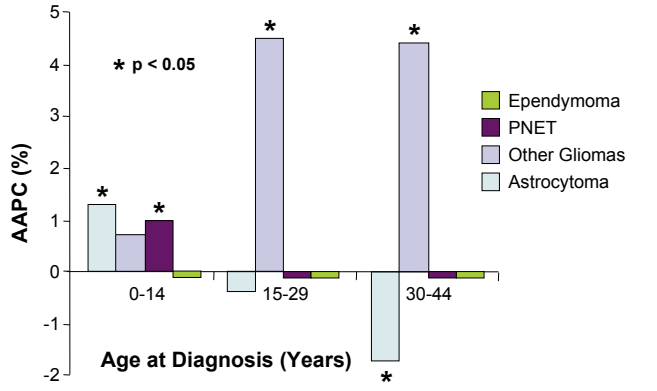

Figure 6.9: Average Annual Percent Change (AAPC) in Incidence by Type of CNS Tumor, SEER 1975-1998

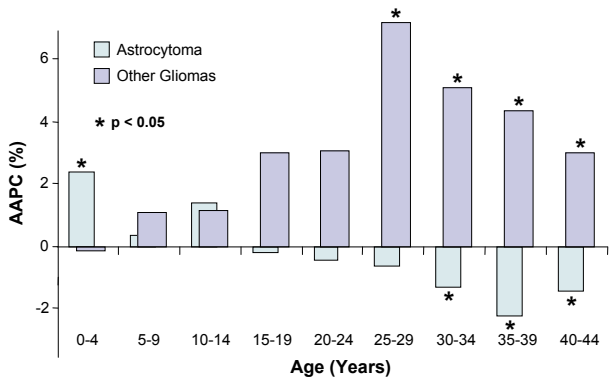

Figure 6.10: Average Annual Percent Change (AAPC) in Incidence for III(b) Astrocytoma and III(d) Other Gliomas, 1975-1998

tumors. The overall pattern of the increase in incidence indicates that most of the increase occurred in the youngest patients (Figure 6.8).

Delineation of incidence by tumor histology revealed a statistically significant increased incidence of astrocytoma and PNET in children 0 to 14 years of age (Figure 6.9). Adolescents and young adults demonstrated a statistically significant increased incidence of "other gliomas" (Figure 6.9). When the AAPC is examined according to five-year age groups and tumor type (Figure 6.10), a significant increase in incidence of "other gliomas" was demonstrated in individuals 25 to 44 years of age (Figure 6.10), and a significant decrease in incidence rate of astrocytoma was observed in individuals 30 to 44 years of age. The change in incidence of "other gliomas" over time in individuals 15 to 29 years of age as compared to those younger and older is displayed in Figure 6.11.

The increased annual incidence in "other gliomas" in adults 30 to 44 years of age despite no change in annual incidence of all CNS neoplasms could be due to better recognition of oligodendroglial elements in glial tumors. This improved recognition could shift the diagnosis from the "astrocytoma" category to the "other glioma" category, resulting in no net change in overall malignant CNS tumors, but explain the significant decrease in annual incidence of astrocytomas in adults aged 30 to 44 years. An explanation for the increased annual incidence of "other gliomas" in 15- to 29-year-olds is less apparent.

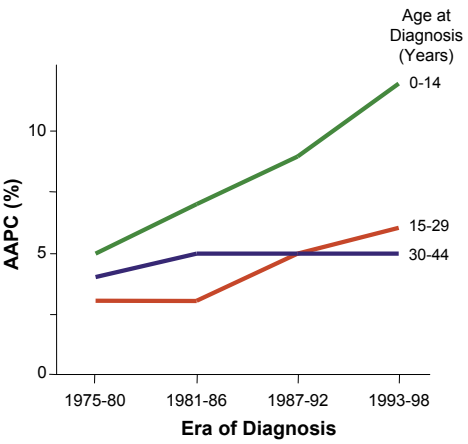

Figure 6.11: Average Annual Percent Change (AAPC) in Incidence for III(d) Other Gliomas by Era, SEER 1975-1998

The trend in incidence of "other gliomas" should be closely observed to determine if the annual incidence is truly increasing or if it is related to the use of improved technology for the diagnosis and classification of glial tumors.

OUTCOME

Mortality

Age- and Gender-Specific Mortality

The death rate for malignant CNS neoplasms was fairly stable for individuals younger than 30 years of age, ranging from 7 to 12 per year per million. The lowest rate was seen in individuals 15 to 24 years of age (Figure 6.12) and is in accordance with the incidence pattern (Figure 6.4). Two discrepancies between the incidence and mortality patterns are apparent: 1) after 25 years of age, the rise in mortality from CNS tumors (Figure 6.12) is out of proportion to the relative higher incidence (Figure 6.4), and 2) the death rate was lower than expected for the incidence in children younger than 5 years of age (Figure 6.12 versus Figure 6.4). These differences imply that survival from CNS tumors is worse for individuals older than 25 years but more favorable for children younger than 5 years of age. Survival data, presented below, confirm the former but do not substantiate the latter.

More males died of CNS tumors than females, regardless of age (Figure 6.12). This appears to reflect the increased incidence in males, which also occurs in all age groups (Figure 6.4).

To adjust for the age-dependent pattern in incidence, Figure 6.13 demonstrates the ratio of the death rate to incidence of CNS tumors by age and gender. The ratio is approximately 0.3 for individuals 15 to 29 years of age, but then steadily increases after 30 years of age to a ratio of 0.6 at 40 to 44 years of age. Thus, individuals older than 25 years are more likely to die due to their CNS tumor when compared to those younger than 25 years of age. This is particularly apparent in males but also in females over 30 years of age (Figure 6.13).

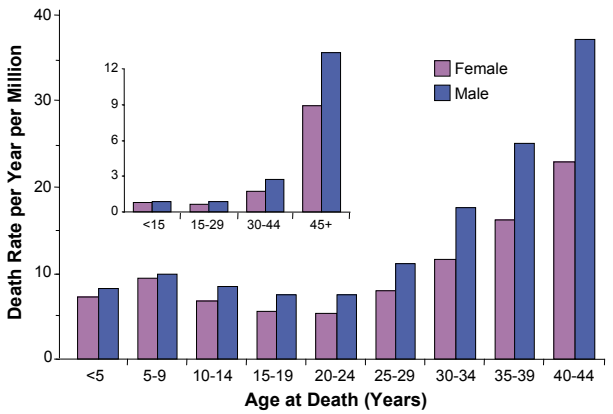

Figure 6.12: National Mortality for CNS Tumors by Gender, 1975-1999

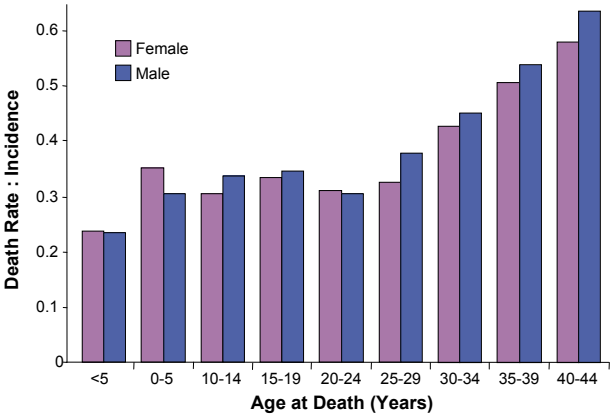

Figure 6.13: Ratio of National Mortality to SEER Incidence for CNS Tumors by Gender, 1975-1999

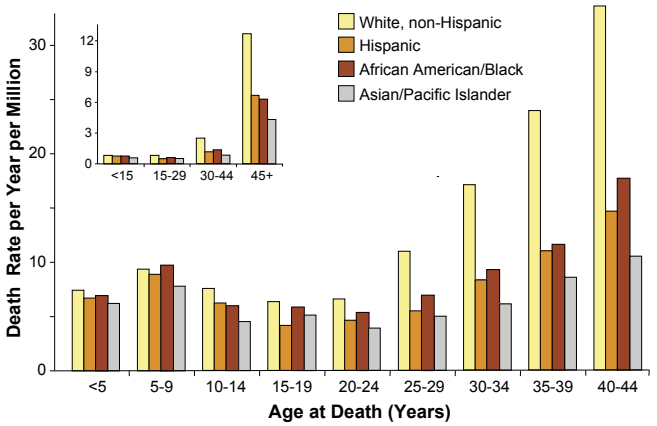

Figure 6.14: National Mortality for CNS Tumors by Race/Ethnicity, 1990-1999

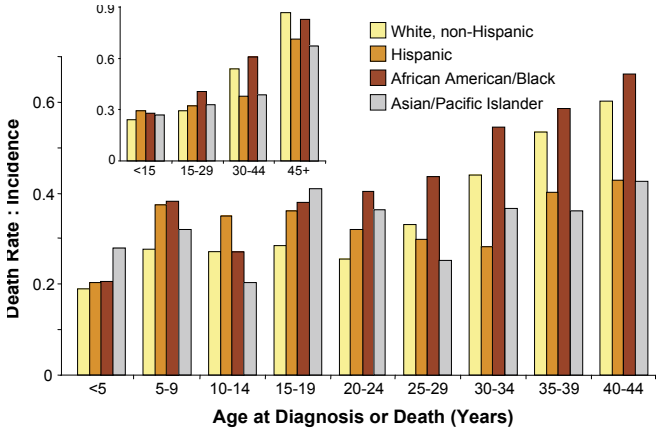

Figure 6.15: Ratio of National Mortality to SEER Incidence for CNS Tumors, 1990-1999

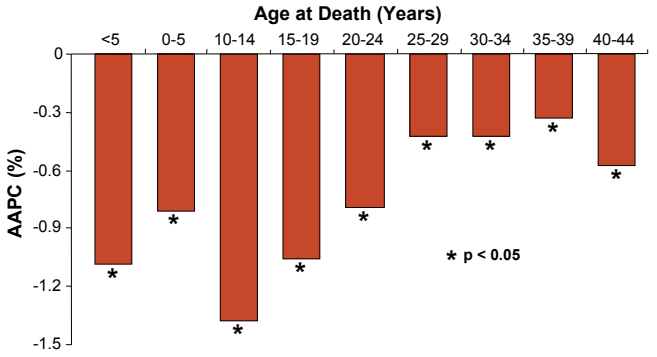

Figure 6.16: Average Annual Percent Change (AAPC) in National Mortality for CNS Tumors, 1975-1999

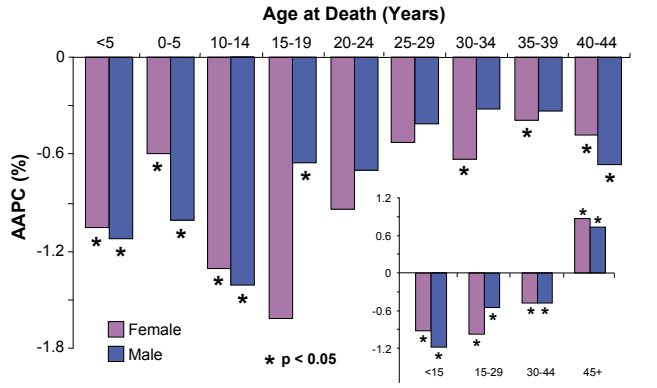

Figure 6.17: Average Annual Percent Change (AAPC) in National Mortality for CNS Tumors by Gender, 1975-1999

Racial/Ethnic Differences in Mortality

Figure 6.14 presents mortality data for CNS tumors according to race/ethnicity and age at death. The death rate was fairly similar across all racial/ethnic groups for 0- to 29-year-olds, but increased for those older than 30 years. The ratio of mortality to incidence by race/ethnicity was slightly higher for 15- to 29-year-olds than for 0- to 14-year-olds, but lower than in those over 30 years of age (Figure 6.15). AfricanAmericans/blacks had the highest ratio of mortality to incidence in the 15- to 29-year-old group compared to the other reported racial/ethnic groups, a pattern that continued through age 44. With advancing age, the ratio of mortality to incidence steadily increased, particularly in white non-Hispanic and African American/black individuals. These data suggest that older individuals, especially white non-Hispanics and African Americans/blacks, are more likely to die of their CNS tumor than younger patients or older Hispanic or Asian/Pacific Islander individuals.

Trends in Mortality

A minimal improvement in mortality was observed over the period 1975 to 1999. Figure 6.16 displays a small but significant decrease in the death rate for all age groups, with the greatest improvement seen in individuals younger than 24 years of age. The improvement in mortality was greater in females than males in the adolescent and young adult age group, particularly for 15- to 19-year-olds (Figure 6.17).

Survival

Survival after the diagnosis of a CNS neoplasm has improved, due in part to advances in diagnostic techniques and histologic classification of tumors, improvement in neurosurgical and radiation oncology techniques, and the utilization of new single and combination chemotherapeutic agents. Unfortunately, improvement in survival and durable remissions has been slower in CNS neoplasms compared to other cancers, especially leukemias and lymphomas. Long-term survivors of CNS tumors often suffer significant long-term sequelae such as hormonal deficiencies, intellectual decline and physical handicaps. These late effects compromise quality of life.

Survival data were collected between 1975 and 1998 and classified by the ICCC, thus allowing analysis across broad

histological subtypes. Racial/ethnic data were analyzed from 1990 to 1999. The 15-year survival progressively declined with advancing age at diagnosis for those older than 20 years of age (Figure 6.18). The 15-year survival for patients younger than 20 years of age exceeded 50%, but was approximately 20% for those 40 years of age and older.

For 15- to 29-year-olds, the 5-year survival rates were not significantly different among the four different racial/ethnic groups, and ranged from 64-72% (Figure 6.19).

Trends in Survival

A slow but steady improvement has been observed in 5- and 10-year survival rates (Figures 6.20 and 6.21). Individuals 15 to 29 years of age diagnosed with a CNS tumor in the period 1993 to 1997 had a 5-year survival rate near 70% and a 10-year survival rate of 55%. Although the 5-year survival rate was nearly identical to the rate for those younger than 15 years of age, the 10-year survival rate declined compared to younger patients. When observing the AAPC in survival for all CNS tumors, 15- to 34-year-olds had less improvement in survival compared to older and younger patients (excluding infants) (Figure 6.22). This observation reinforces the need to target this age group for clinical trials. Males older than 20 years of age had an improved AAPC in survival when compared to females (Figure 6.23).

Survival - Astrocytoma

Individuals diagnosed with astrocytoma between 15 and 19 years of age had 20-year survival rates in excess of 65% (Figure 6.24). However, there was a dramatic difference in survival for those diagnosed between 20 to 24 years (40%) and those diagnosed between 25 to 29 years of age (24%). "Astrocytomas," according to the SEER classification, include both low-grade and high-grade astrocytomas. Children and adolescents are more likely to have low-grade astrocytomas—accounting for the better survival rates— whereas adults are more likely to have high-grade astrocytomas or low-grade astrocytomas that undergo malignant transformation over time. During the period 1975 to 1998, there was a steady improvement in 5-year survival rates for "astrocytoma" (Figures 6.25 and 6.26). Improvement in survival rates was seen for all age groups except 20- to 24-year-olds. The improvement in survival was greatest for older individuals (Figure 6.26),

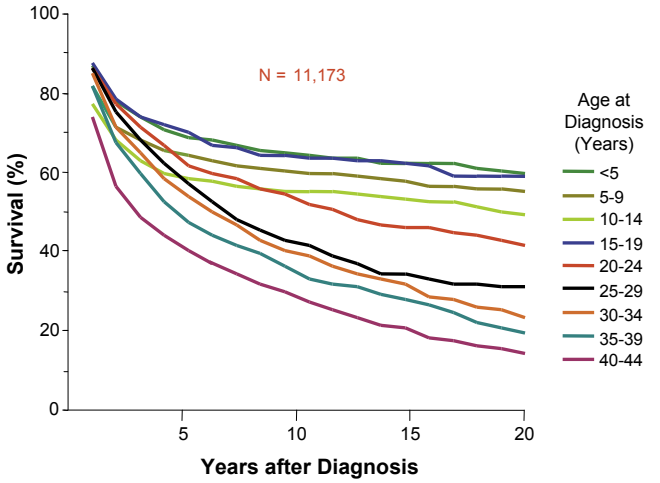

Figure **6.18:** Survival Rates for All CNS Tumors by Age, SEER 1975-1998

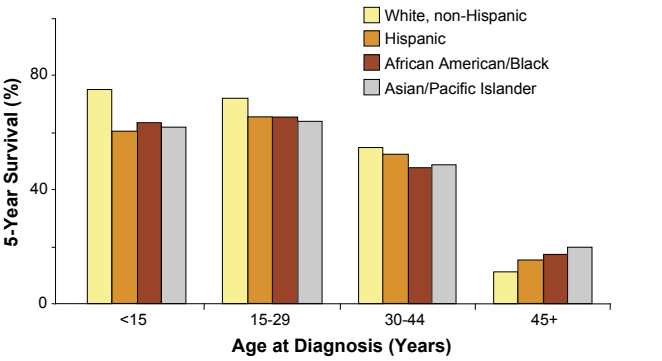

Figure 6.19: 5-Year Survival Rate for CNS Tumors by Race/Ethnicity, SEER 1991-1998

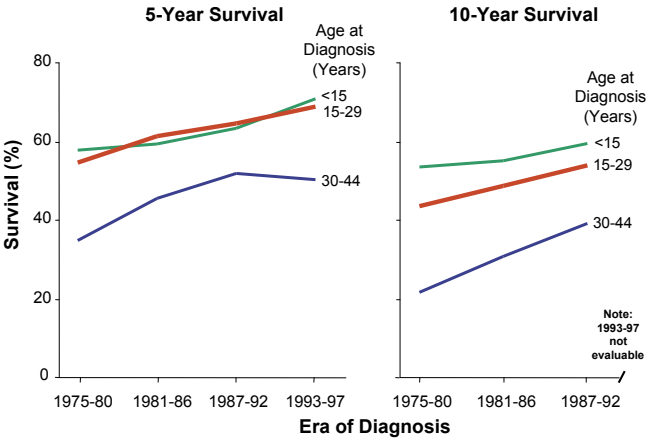

Figure 6.20: Survival Rate versus Era of Diagnosis for All CNS Tumors

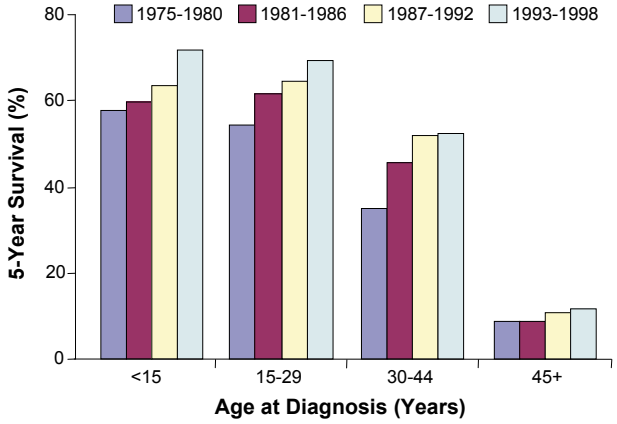

Figure 6.21: 5-Year Survival Rate for All CNS Tumors by Age and Era, SEER 1975-1998

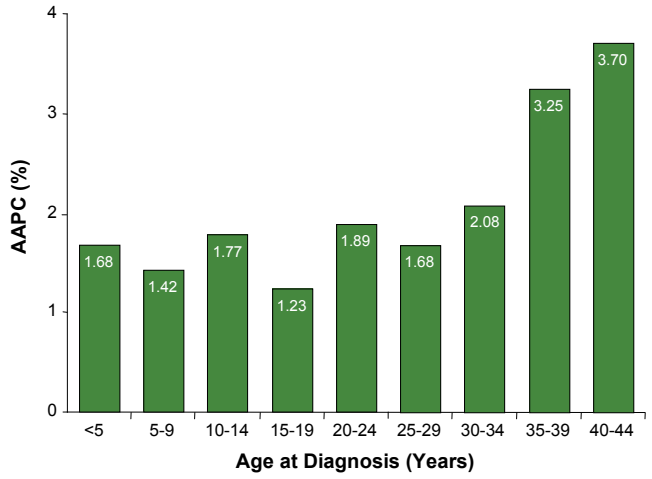

Figure 6.22: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for All CNS Tumors, SEER 1975-1998

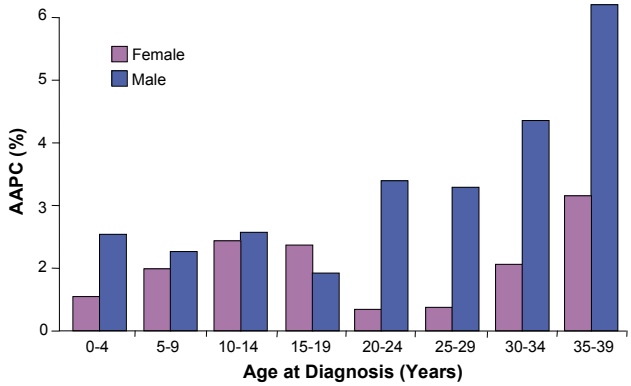

Figure 6.23: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for All CNS Tumors by Gender, SEER 1975-1998

suggesting that true progress is due to advances in the treatment of high-grade astrocytomas. This improvement may be due to the recent addition of temozolomide to the treatment regimen for adults with high-grade astrocytoma. It is unclear why 20- to 24-year-olds had a decline in 5-year survival rates over time.

Survival – Other Gliomas

"Other gliomas" are defined as malignant glioma-not otherwise specified (NOS), mixed glioma, oligodendroglioma-NOS, anaplastic oligodendroglioma, oligodendroblastoma, and other uncommon gliomas, as listed in Table 6.2. As seen in Figure 6.27, 15- to 29-year-olds had the highest survival rates when compared to other age groups, with a 20-year survival rate near 50%. The survival curves for individuals with "other gliomas" have not yet demonstrated a plateau. The continuous decline in all the curves suggests that a "cure level" has not been achieved for any of the age groups. Improvement in survival for "other gliomas" between 1975 and 1998 has occurred in all age groups, although little progress has been made since 1992 (Figure 6.28). Survival improvement was most apparent in the 20- to 24-year age group (Figure 6.29). The improvement in survival over time correlates somewhat but not completely with the first reports—in the late 1980s—of the unique sensitivity of anaplastic oligodendrogliomas to chemotherapy.

Survival - PNET

Five-year survival rates for PNET are displayed in Figure 6.30. Individuals 15 to 29 years of age had superior

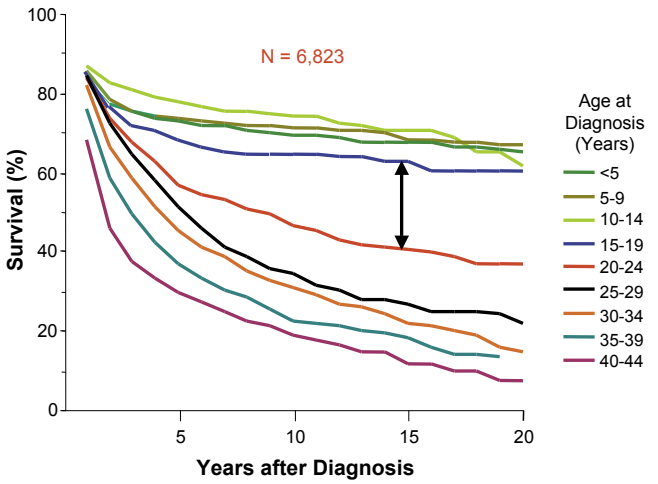

Figure 6.24: Survival Rates for Astrocytoma by Age, SEER 1975-1998

survival rates compared to those 30 to 44 years of age, with a 20-year survival rate of 40-45% compared to that of 25% for older age groups (Figure 6.31). Despite these encouraging results for adolescents and young adults diagnosed with a PNET, no improvement has been seen in this age group since the 1980s. In contrast, a slow, steady rate of improvement in survival has been observed in children (Figure 6.30), most likely due to the use of chemotherapy.

Survival - Ependymoma

Survival at 20 years for 15- to 29-year-olds with ependymoma was 65% (Figure 6.32). Individuals 15 to 44 years of age had the best chance of survival when compared to younger or older patients. The worst survival rates occurred among those younger than 15 years of age. Five-year survival rates for those younger than 1, 1 to 4, 5 to 9 and 10 to 14 years of age were 25%, 46%, 71% and 76%, respectively.[2] Thus, patients with ependymoma diagnosed between ages 5 and 44 years had a survival rate near 70%. The poorer survival in children younger than 5 years of age is likely related to factors such as the frequent posterior fossa tumor location in this age group, which makes total surgical resection more difficult, and the concern regarding administration of adequate doses of radiation therapy to this young age group. It is unclear why individuals diagnosed with ependymoma when older than 44 years of age have such poor survival rates. Although the survival is poorest for the age groups younger than 15 years and older than 44 years, both of these groups have made the greatest improvement in survival over time

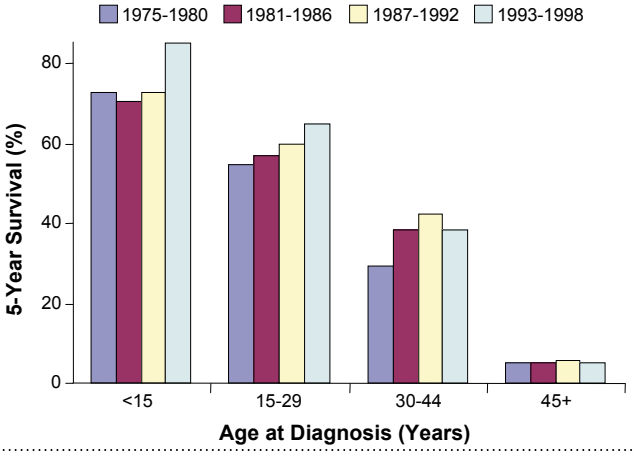

Figure 6.25: 5-Year Survival Rate for III(b) Astrocytomas by Age and Era, SEER

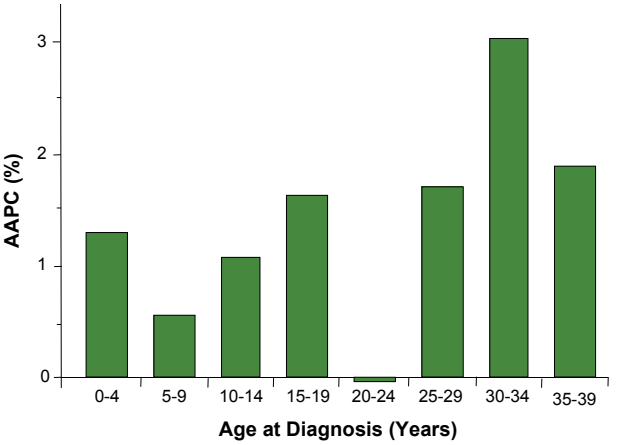

Figure 6.26: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Astrocytomas, SEER 1984-1998

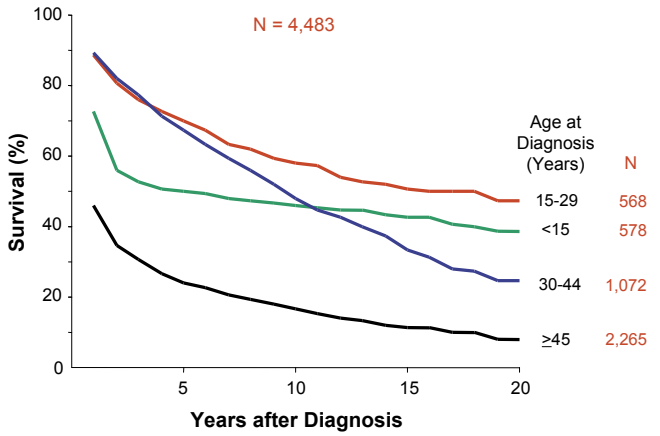

Figure 6.27: Survival Rates for Other Gliomas by Age, SEER 1975-1998

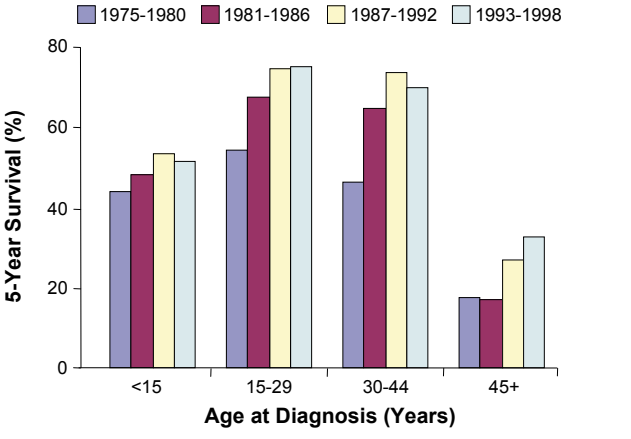

Figure 6.28: 5-Year Survival Rate for III(d) Other Gliomas by Age and Era, SEER 1975-1998

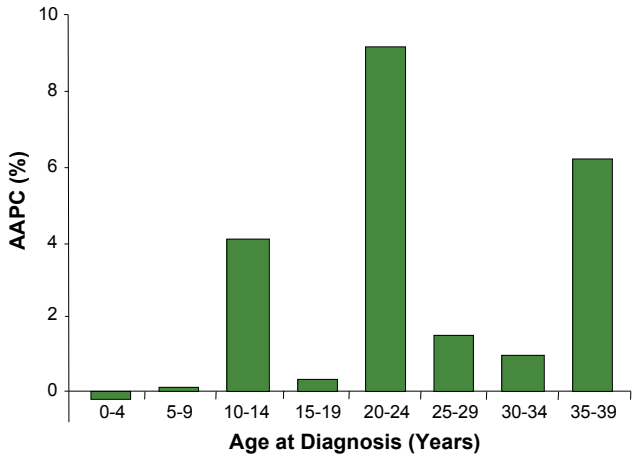

Figure 6.29: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Other Gliomas, SEER 1984-1998

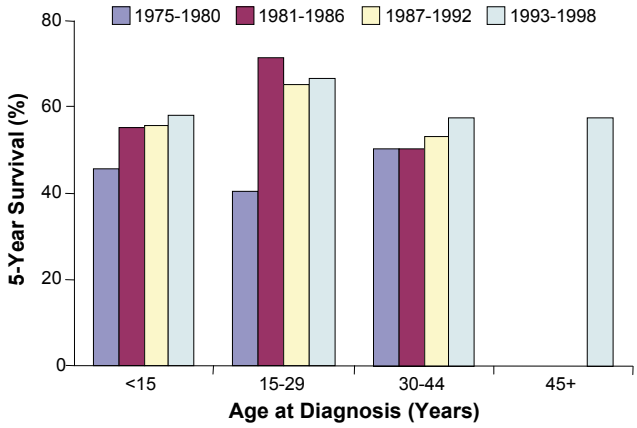

Figure 6.30: 5-Year Survival Rate for III(c) PNET by Age and Era, SEER 1975-1998

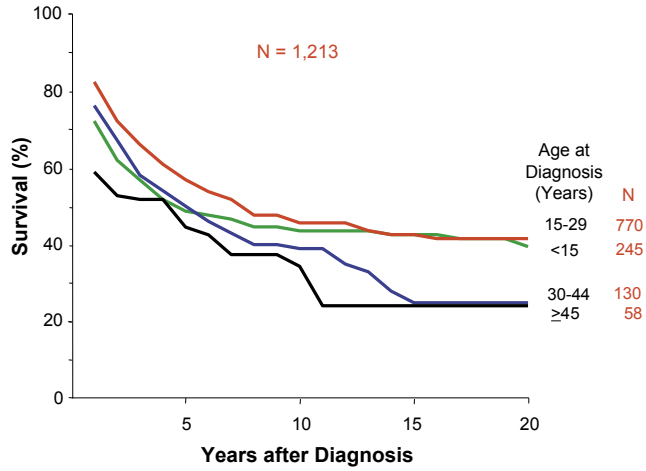

Figure 6.31: Survival Rates for PNET by Age, SEER 1975-1998

(Figures 6.33 and 6.34). Adolescents and young adults 15 to 34 years of age had the poorest improvement in survival over the time period 1984 to 1998, again indicating the need for clinical trials targeted towards this age group.

RISK FACTORS

The only known risk factors for the development of brain tumors at any age are the inheritance of several rare syndromes and previous exposure of the brain to ionizing radiation.[3] However, these factors contribute to a minority of adolescent and young adult CNS neoplasms. Despite many institutional and national cooperative group epidemiological studies, no specific risk factor or set of risk factors has been elucidated in the majority of CNS tumors.

Several inherited syndromes are associated with CNS tumors. Table 6.3 summarizes these syndromes, the related CNS tumors, and the chromosome and gene locations. Each of these syndromes has an inherited mutation in a tumor suppressor gene resulting in an increased incidence of specific types of brain tumors. Although these inherited conditions are rare and account for less than 5 percent of brain tumors, they provide translational tools to investigate the role of specific tumor suppressor genes in the genesis of different types of brain tumors.

The only environmental factor known to cause brain tumors is ionizing radiation. Therefore, individuals of any age who receive radiation therapy to the brain

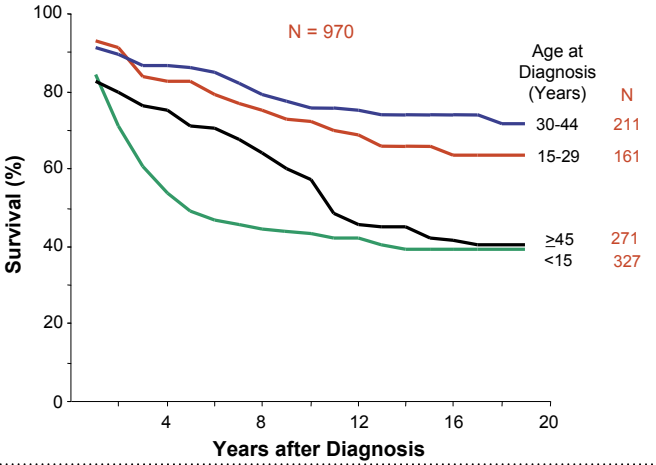

Figure 6.32: Survival Rates for Ependymoma by Age, SEER 1975-1998

for treatment of leukemia, brain tumors or other solid tumors of the head are at an increased risk for secondary CNS neoplasms. The most common secondary CNS neoplasms are gliomas and meningiomas.

The identification of risk factors for the development of brain tumors in adolescents and young adults is confounded by the fact that brain tumors are composed of multiple histologies. Each histological subtype likely has a different mechanism of tumorigenesis and therefore different risk factors. It is difficult to accrue sufficient numbers of patients to test hypotheses about specific histological subtypes of brain tumors. Very few epidemiological studies have been undertaken, and virtually none have incorporated molecular techniques for defining tumor types. Based on current knowledge, there are no immediate preventive measures for the development of adolescent and young adult CNS tumors. Future epidemiological studies may shed more light on the causes of these often debilitating and fatal neoplasms.

SUMMARY

Cancer of the CNS accounted for 6% of all neoplasms in adolescents and young adults 15 to 29 years of age, and was the 7th leading cause of cancer in this age group. The U.S. overall annual incidence of CNS tumors in this age group (approximately 22.6 per million)

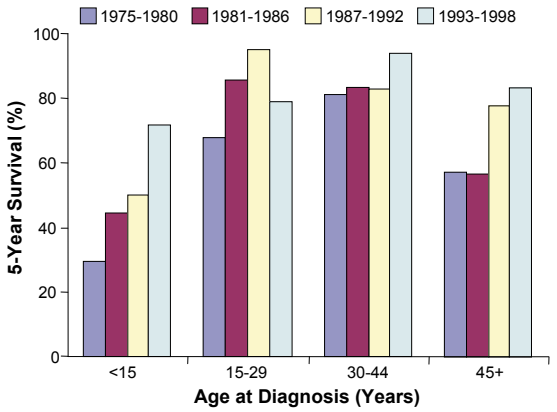

Figure 6.33: 5-Year Survival Rate for III(a) Ependymoma by Age and Era, SEER 1975-1998

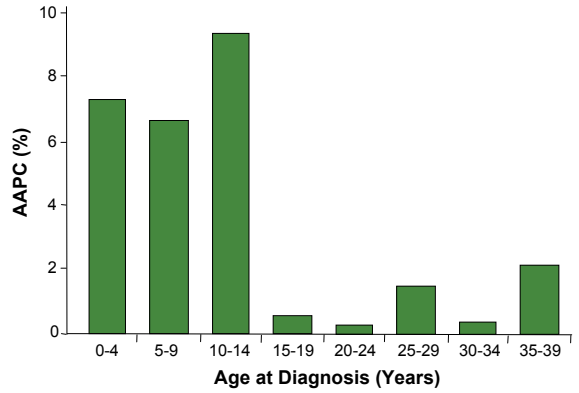

Figure 6.34: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Ependymoma, SEER 1984-1998

Table 6.3: *Inherited Syndromes Associated with CNS Tumors*[3]

SYNDROME	CNS TUMOR	CHROMOSOME LOCATION
Neurofibromatosis Type I	Glioma, Meningioma	17q12-22
Neurofibromatosis Type II	Acoustic neuroma, Schwannoma, Ependymoma, Glioma, Meningioma	22q12
Tuberous Sclerosis Type I and Type II	Subependymal Giant Cell Astrocytoma, Ependymoma, Glioma, Hamaratoma	9q32-34 (Type I) 16p13.3(Type II)
Von Hippel-Lindau syndrome	Cerebellar hemangioblastoma, Glioma	3p25-26
Li-Fraumeni Syndrome	Glioma, Medulloblastoma	17p13 (p53 mutation)
Nevoid Basal Cell Carcinoma syndrome (Gorlin's syndrome)	Medulloblastoma	1q22
Turcot's Syndrome	Medulloblastoma, Glioma	5q21-22
Hereditary Atypical Teratoid/Rhabdoid tumors	Atypical Teratoid/Rhabdoid tumors	22q11.2(INI-1 gene)
Hereditary Retinoblastoma	Pineoblastoma	13q14
Multiple Endocrine Neoplasia I (MEN-I)	Pituitary Adenomas, Ependymoma	11q13

was lower than that of any other age group. Approximately 1,500 individuals between 15 and 29 years of age were diagnosed in the year 2000 with a CNS neoplasm. Males (pediatric through adult ages) had a higher incidence of CNS tumors; the male:female incidence ratio for CNS tumors in the adolescent and young adult age group averaged 1.32. White non-Hispanics had a slightly increased incidence of CNS tumors in this age group compared to African American/black, Hispanic, and Asian/Pacific Islander groups. The distribution of specific types of brain tumors in individuals 15 to 29 years of age differed from that of children younger than 15 years of age and from adults older than 29 years of age. The incidence of astrocytomas increased, while incidence of PNETs and ependymomas decreased with advancing age. Adolescents and young adults, as well as adults up to age 44 years, had an increased annual incidence of "other gliomas". The etiology of this trend may be related to better technology in diagnosing and classifying glial tumors.

National mortality for individuals 15 to 29 years of age showed little variation across racial/ethnic groups and was similar to that of children 0 to 14 years of age. Mortality rose with increasing age. In the 15- to 29-year age group, mortality was higher for males than females and was higher for white non-Hispanic individuals compared to individuals of other races/ethnicities. Mortality improved over the years for all groups younger than 45 years.

Survival of patients with CNS tumors progressively declined as a function of age at diagnosis in individuals over 20 years of age. The overall 10-year survival for all CNS tumors in the adolescent and young adult age group paralleled the survival curves for astrocytoma. The 10-year survival rate for 15- to 29-year-olds with "other gliomas" was 50%, 70% for PNETs, and 65% for ependymomas. The 5- and 10-year survival curves for all CNS tumors have improved with time in the 15- to 29-year age group, but none of the individual age groups or major types of tumors have reached a plateau. This suggests that a "cure level" has not been achieved for most of the CNS neoplasms. Adolescents and young adults 15 to 34 years of age had the poorest improvement in survival over the time period 1984 to 1998, suggesting that this age group should be targeted for clinical trials.

Unfortunately, the causes of CNS neoplasms remain unknown. The only two definitive risk factors for CNS tumors are rare inherited conditions and previous exposure of the brain to ionizing radiation.

Acknowledgments:

Drs. Peter Burger and Bernd Scheithauer kindly reviewed the data regarding incidence and trends in incidence for the different histological subtypes and helped speculate about reasons for these trends.

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