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Abstract: PURPOSE OF REVIEW: Age has remained one of the most important determinants of risk for the development of certain brain tumors, of benefit from and tolerance of brain tumor treatment, and overall outcome. Regarding these three aspects, there are major differences across the spectrum of primary brain tumors depending on specific histology. Here, we review recent advances in understanding the biological basis of the prognostic marker 'age' in neuro-oncology. RECENT FINDINGS: Contemporary population-based studies confirm the strong prognostic impact of age in many brain tumors. Elderly patients continue to be treated less aggressively than younger patients with the same tumors. However, biological factors may contribute to the negative prognostic impact of age. For instance, among gliomas, mutations of the isocitrate dehydrogenase genes, which are prognostically favorable, are much more common in younger patients. Moreover, complete responses defined by neuroimaging were much less durable in elderly as opposed to younger patients with primary central nervous system lymphoma in the German Primary Central Nervous System Lymphoma Study Group trial. SUMMARY: A combination of age-adapted patterns of care and treatment-independent, tumor-intrinsic factors contributes to the poorer outcome of elderly patients with brain tumors. These factors need to be better distinguished and understood in order to improve outcome in elderly brain tumor patients.

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Geriatric Neuro-Oncology: from Mythology to Biology

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ABSTRACT

Purpose of review: Age has remained one of the most important determinants of risk for the development of certain brain tumors, of benefit from and tolerance of brain tumor treatment, and overall outcome. Regarding these three aspects, there are major differences across the spectrum of primary brain tumors depending on specific histology. Here we review recent advances in understanding the biological basis of the prognostic marker “age” in Neuro-Oncology.

Recent findings: Contemporary population-based studies confirm the strong prognostic impact of age in many brain tumors. Elderly patients continue to be treated less aggressively than younger patients with the same tumors. However, biological factors may contribute to the negative prognostic impact of age. For instance, among gliomas, mutations of the isocitrate dehydrogenase (IDH) genes, which are prognostically favourable, are much more common in younger patients. Moreover, complete responses defined by neuroimaging were much less durable in elderly as opposed to younger patients with primary central nervous system lymphoma in the G-PCNSL-SG-1 trial.

Summary: A combination of age-adapted patterns of care and treatment-independent, tumor-intrinsic factors contributes to the poorer outcome of elderly patients with brain tumors. These factors need to be better distinguished and understood in order to improve outcome in elderly brain tumor patients.

Introduction

The population of Western societies undergoes a dramatic change in that the proportion of the elderly, overall less fit population increases steadily. This will result in altered incidences and prevalences of age-associated diseases and may necessitate specific therapeutic approaches to diseases, notably cancer, when these are diagnosed in the elderly [1]. Yet, for many diseases, including many types of cancer, the best treatment, its tolerability and efficacy, are vaguely defined in elderly patients because clinical trials may have had an upper age limit or because these patients were considered too frail to be included in a clinical trial. A retrospective analysis of 59,300 patients from 495 cooperative group trials sponsored by the National Cancer Institute, performed from 1997 through 2000, showed that 32% of the participants in phase II and III clinical trials were elderly defined as aged 65 or more. In contrast, the relative contribution of this patient population to cancer diagnoses in general in the United States was 61%, illustrating that elderly patients are strongly underrepresented in clinical trials. This pattern of preferential enrolment of younger patients was not specific to brain tumors [2]. The diagnosis of brain tumors in elderly patients who often exhibit significant comorbidity (see below) raises distinct questions that differ from those relevant for younger patients where this diagnosis is usually the major limitation of life expectancy. In the elderly, the treatment of brain tumors is less often curative and will focus more strongly on preservation of quality of life respectively maintaining functional independence. Moreover, as our health care systems and our treatment options evolve, the definition of “elderly” has changed and will continue to do so. The current cut-off of

younger *versus* elderly is likely to be in the range of 70, but this may vary in a disease-specific manner, for instance, in the field of brain tumors, the likely cut-off would be 60 to 65 in primary central nervous system lymphoma where the question focuses on the decision between high-dose *versus* conventional dose chemotherapy or the benefit from intrathecal treatment , but more likely to be 65-70 for malignant gliomas where the choice is between single modality *versus* multimodality management approaches, that is, radiotherapy or chemotherapy alone *versus* their combination. Importantly, for the future, it is mandatory to better distinguish the concepts of *elderly cancer patients* from *cancer patients with frailty*, a poorly defined constellation of being less fit and at higher risk of intolerance of cancer treatment that is strongly age-related.

Brain tumor epidemiology by age

The most reliable and extensive data to estimate the risk of brain tumor development by age are provided by the Central Brain Tumor Registry of the United States (www.cbtrus.org). The table shows median ages at diagnosis and age-specific survival by histology. Embryonal tumors with a median age at diagnosis of 9 years, and pilocytic astrocytomas 13 years, are predominantly tumors of childhood whereas glioblastomas and lymphomas as well as meningiomas are typical brain tumors associated with advanced age. Moreover, looking at outcome by age, it has long been recognized how strong the impact of age at diagnosis is on outcome in most types of glioma as well as brain lymphoma. In contrast, this seems not be true for ependymomas, neuronal/glial

tumors and embryonal tumors. Many of the differences by age are therefore more likely caused by age-specific changes in the biology of some tumors rather than age-specific treatment approaches alone.

Comorbidity and complications of treatment

It is often assumed that elderly patients tolerate brain tumor treatment less well and that the natural course of brain tumors in the elderly is more aggressive. However, these assumptions are only partially true and disease-specific considerations are required (see below). It is important to understand that it is probably not age *per se*, but rather the increased prevalence of significant comorbidities that increases the risk of side effects and decreases the tolerability of most treatments for cancer, including major surgery, radiotherapy and chemotherapy. Moreover, polypharmacy associated with age may be more predictive of side effects from chemotherapy than age alone.
Specifically the brain of the elderly is considered more sensitive to the possible detrimental effects of therapeutic irradiation. This has been demonstrated most clearly in patients with primary central nervous system lymphoma who were treated with combined systemic and intrathecal chemotherapy plus whole brain radiotherapy. In this patient population, age was a powerful predictor of severe neurotoxicity [3]. However, the latter is less clear than generally assumed when looking at focal irradiation. An analysis of acute and late grade 3 neurological toxicities among 2761 patients from 14 RTOG trials accrued from 1983 to 2003 showed an age association only on univariate

analysis, but not on multivariate analysis [4]. Moreover, the risk of cerebral radiation necrosis in glioma patients treated with focal radiotherapy was not age-related [5]. The recently published German Primary Central Nervous System Lymphoma trial (G-PCNSL-SG-1 trial) on the role of whole brain radiotherapy in primary central nervous system lymphoma is particularly useful to study the link between age and tolerability of treatment. Although the dose of high-dose methotrexate was adapted to the glomerular filtration rate, hematogical WHO grade III/IV toxicity was twice as common in patients aged 60 more than in younger patients whereas no relevant difference was observed for non-hematogical toxicity [6].

Finally, there is a significant risk of cognitive impairment with increasing age and the ability to consent to treatment is more often questionable than in younger patients. This limits the suitability of many, particularly less fit brain tumor patients for inclusion in clinical trials as well as the use of experimental treatment strategies outside clinical trials. Moreover, not only therapeutic irradiation, but also chemotherapy has increasingly been reported to promote cognitive decline [7]. While the concept of the “chemobrain” is currently of concern predominantly in long-term survivors of cancer who are less frequent in the elderly, it can nevertheless be predicted that such chemotherapy-associated cognitive changes may affect elderly patients more severely than younger adult patients, simply because of less neurological comorbidity, e.g., dementing and cerebrovascular diseases.

Tumor-specific considerations

Gliomas

Among the astrocytic gliomas, there is a clear age-dependent differential distribution of histological subtypes corresponding to grade of malignancy, molecular features such as epidermal growth factor receptor (*EGFR*) amplification and *p53* mutation, and outcome (Table). WHO grade I pilocytic astrocytomas are typical tumors of children and adolescence and are probably biologically unrelated to the astrocytic gliomas of higher grades (II-IV). They are the most common brain tumor in children aged 5-14.

For astrocytic and oligodendroglial tumors of grades II to IV, a strong negative impact of age probably irrespective of treatment intensity is not disputed. Age has been identified as a prognostic factor both in the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) score for malignant gliomas [8,9] as well as the prognostic score for patients with low grade gliomas derived from analyses of the European Organization for Research and Treatment of Cancer (EORTC) trials 22844 and 22845 [10]. A more contemporary series of low grade gliomas from France showed that elderly patients aged ≥ 60 more often presented with a clinical deficit, a lower Karnofsky performance score, a larger tumor, and a lower rate of tumor resection. Exclusive chemotherapy was more often used as the first-line treatment in elderly glioma patients . Of patients dying from progressive tumor, 55% of the elderly had not received radiotherapy compared to 11% in the younger patients [11].

Among malignant gliomas, the same treatment confers less benefit to elderly patients as compared with younger patients, both in anaplastic glioma [12] and in glioblastoma [13].

The elucidation of the age-dependent frequency and prognostic role of mutations of the isocitrate dehydrogenase (IDH) genes in gliomas has provided the first major molecular marker that may account for the negative prognostic impact of age. Within one histological entity, *IDH* mutations are prognostically favourable, and they are virtually absent in malignant gliomas in patients aged 60 or more: in fact, a retrospective analysis of patients from the NOA-04 anaplastic glioma trial and the German Glioma Network provided evidence that the *IDH*1 status is more prognostic for overall survival than standard histological criteria that differentiate high-grade astrocytomas (Hartmann et al. 2010). Among 382 patients with grade III/IV gliomas, *IDH1* mutation status was the most prominent single prognostic factor, followed by age, diagnosis and O6-methylguanylmethyltransferase (*MGMT) status*. The sequence from more favorable to poorer outcome was (i) anaplastic astrocytoma with *IDH1* mutation, (ii) glioblastoma with *IDH1* mutation, (iii) anaplastic astrocytoma without *IDH1* mutation and (iv) glioblastoma without *IDH1* mutation [14]. Recent analyses in elderly glioblastoma patients have revealed an increased prevalence of *MGMT* promoter hypermethylation (50-60%) compared with the general population of glioblastoma patients [15,16]. Nonetheless, prognosis in this patient group is considerably worse and the prognostic value of MGMT less clearly defined. It remains to be determined whether these differences are tumor-specific or reflect an age-related increase in methylation [17].

Specifically in the controversial field of glioblastoma in the elderly, a series of clinical trials have been designed to clarify the best treatment: a French trial demonstrated the

superiority of radiotherapy over best supportive care [18] and a Canadian trial indicated that hypofractionated radiotherapy at 2.66 Gy in 15 fractions to 40 Gy is as effective as convential fractionation at 2 Gy in 30 fractions to 60 Gy [19]. More recently, two larger phase III trials showed that there is probably little difference between radiotherapy alone and temozolomide alone in terms of overall survival [20,21]. Also, in elderly (≥ 70 years) and less independent (KPS < 70) patients with glioblastoma, temozolomide seems to be a well-tolerated and effective option [22]. Importantly, there are concerns that combined modality treatment may be both less active and less well tolerated in the elderly [23]. A National Cancer Institute of Canada / EORTC trial comparing radiotherapy alone and radiotherapy plus temozolomide is ongoing.

Finally, the introduction of anti-angiogenic agents into the management of malignant gliomas has probably for the first time led to the identification of a preferential benefit from a given treatment in the elderly: in a phase II trial of the vascular endothelial growth factor (VEGF) antibody bevacizumab alone, the median progression-free survival for patients with a median age of 53 years or older was 30 weeks *versus* a median progression-free survival of 11 weeks for younger patients [24], and patients of older age (≥55 years) and poor performance status (Karnofsky performance score ≤80) had significantly better progression-free survival when treated with bevacizumab, and bevacizumab-treated older patients had significantly increased overall survival, in a single institution report [25]. These observations indicate that glioblastomas in the elderly may be more VEGF-dependent than glioblastomas in younger patients.

Primary central nervous system lymphoma

As outlined above, the dramatically increased risk of severe neurotoxicity with higher age has been most clearly delineated in patients with primary central nervous system lymphoma. However, this patient population has also revealed that there are clear age-dependent differences in response rate, duration of response, and benefit from salvage treatment. In the G-PCNSL-SG-1, median overall survival was 14.2 months for patients aged 60 or more *versus* 38.4 months for patients aged 59 or less [6]. As in glioblastoma, there is now general agreement that separate clinical trials for younger and elderly patients with cerebral lymphoma are required, with cure as the goal in younger patients and maintaining remission and (neurocognitive) function as the goal in the elderly.

Brain and leptomeningeal metastases

Brain metastases are the most common brain tumors in adults. For elderly patients with systemic cancer who develop brain or leptomeningeal metastases, most of the above-mentioned considerations regarding maintenance of quality of life and tolerance of treatment may be even more relevant than for patients with primary brain tumors. Specifically for patients with leptomeningeal metastases, aggressive treatment is typically administered preferentially to younger patients [26]. However, given the increasing repertoire for pharmacological treatments for systemic cancer, the likelihood

of achieving control of systemic disease should guide treatment decisions more than age alone, and clinical trials on central nervous system involvement in systemic cancer should probably consider the histology of the primary tumors more than in the past. The first widely used prognostic score had already incorporated an age cut-off of 70 [27]. More recent revisions of prognostic score concepts stress the relevance of age and even introduced three age categories of 49 or less, 50-59, and 60 or more [28,29]. Accordingly, future studies on the optimization of brain metastasis treatment should consider age at least as a stratification factor or even as a stratum to design age-dependent trials such as in glioblastoma or primary central nervous system lymphoma.

Conclusions

Age remains to be one of the most important prognostic factors in the clinical course of brain tumors. Commonly age is a negative prognostic factor as exemplified by a plethora of data on patients with gliomas, primary central nervous system lymphomas and brain metastases. Specifically in gliomas, the poorer outcome in the elderly may not result only from less aggressive treatment, but also from a distinct pattern of molecular changes rendering tumors in the elderly less responsive to treatment. Moreover, there is a relative paucity of data on treatment in the elderly from clinical trials. The underrepresentation of elderly patients in clinical trial populations has probably multiple reasons: previously, many trials had upper age limits because an increased rate of side effects was feared; pharmaceutical companies may have been particularly concerned

about severe side effects in the elderly, affecting the safety profile and thus reputation of new drugs in general; elderly patients are very likely to exhibit more comorbidity rendering compliance with inclusion and exclusion criteria less likely.

Key points

- Age strongly determines the risk of development for specific types of brain tumors.
- Age is a major therapy-independent prognostic factor for brain tumor patients.
- Age is associated with less aggressive treatment of brain tumors.
- Age is associated with specific molecular features of glial brain tumors, e.g., presence of *EGFR* amplification and absence of *IDH* and *p53* mutations.

References

1. Balducci L, Colloca G, Cesari M, et al. Assessment and treatment of elderly patients with cancer. Surg Oncol 2010; 19:117-123.

2. Lewis JH, Kilgore ML, Goldman DP, et al: Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003; 21:1383-1389.

3. Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. J Clin Oncol. 2000; 18:3144-3150.

4. Lawrence YR, Wang M, Dicker AP, et al. Early toxicity predicts long-term survival in high-grade glioma. Br J Cancer 2011; 104:1365-1371.

5. Ruben JD, Dally M, Bailey M, et al. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. Int J Radiat Oncol Biol Phys 2006; 65:499-508.

6. Thiel E, Korfel A, Martus P, et al. G-PCNSL-SG-1 randomised phase III trial of high-dose methotrexate with or without whole brain radiotherapy for primary central nervous system lymphoma. Lancet Oncol 2010; 11:1036-1047.

***Age is confirmed as a major negative prognostic factor in the largest primary central nervous system lymphoma trial ever performed.**

7. Weiss B. Chemobrain: a translational challenge for neurotoxicology. Neurotoxicology 2008; 29:891-898.

8. Curran WJ, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993; 85:704-710.

9. Scott CB, Scarantino C, Urtasun R, et al. Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: A report using RTOG 90-06. Int J Radiat Oncol Biol Phys 1998; 40:51-55.

10. Pignatti F, Van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low grade glioma. J Clin Oncol 2002; 20:2076–2084.

11. Kaloshi G, Psimaras D, Mokhtari K, et al. Supratentorial low-grade gliomas in older patients. Neurology 2009; 73:2093-2098.

12. Wick W, Hartmann C, Engel C, et al., for the Neurooncology Working Group (NOA) of the German Cancer Society. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. J Clin Oncol 2009; 27:5874-5880

13. Stupp R, Hegi ME, Mason WP, et al., on behalf of the European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups and the National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10:459-466.

14. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astroctytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavourable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol 2010; 120:707-718.

***IDH mutation is more prognostic than grade among patients with malignant gliomas (WHO grades III/IV).**

15. Gerstner ER, Yip S, Wang DL, et al. MGMT methylation is a prognostic biomarker in elderly patients with newly diagnosed glioblastoma. Neurology 2009; 73:1509-1510.

16. Weller M, Hentschel B, Felsberg J, et al., for the German Glioma Network. Profound predictive impact of *MGMT* promoter methylation in glioblastoma of the elderly [abstract]. Proc ASCO. J Clin Oncol 2011; 29:LBA2001.

17. Christensen BC, Houseman EA, Marsit CJ, et al. Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. PLoS Genet 2009; 5

18. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007; 356:1527–1535.

19. Roa W, Brasher PM, BaumanG, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 2004; 22:1583–1588.

20. Malmstrom A, Gronberg BH, Stupp R, et al. Glioblastoma (GBM) in elderly patients: a randomized phase III trial comparing survival in patients treated with 6-week radiotherapy (RT) versus hypofractionated RT over 2 weeks versus temozolomide single-agent chemotherapy (TMZ) [abstract]. Proc ASCO. J Clin Oncol 2010; 28:LBA2002.

***Randomized trial suggesting similar efficacy of radiotherapy alone *versus* temozolomide alone in glioblastoma of the elderly (ABSTRACT).**

21. Wick W, Engel C, Combs SE, et al. NOA-08 randomized phase III trial of 1-week-on/1-week-off temozolomide versus involved-field radiotherapy in elderly (older than age 65) patients with newly diagnosed anaplastic astrocytoma or glioblastoma (Methusalem) [abstract]. Proc ASCO. J Clin Oncol 2010; 28:LBA2001.

***Randomized trial suggesting similar efficacy of radiotherapy alone *versus* temozolomide alone in glioblastoma of the elderly (ABSTRACT).**

22. Gállego Pérez-Larraya J, Ducray F, Chinot O, et al. Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial. J Clin Oncol 2011; 29:3050-3055.

23. Sijben AE, McIntyre JB, Roldan GB, et al. Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. J Neurooncol 2008; 89:97-103.

24. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009; 27:740-745.

25. Nghiemphu PL, Liu W, Lee Y, et al. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. Neurology 2009; 72:1217-1222.

26. Oechsle K, Lange-Brock V, Kruell A, et al. Prognostic factors and treatment options in patients with leptomeningeal metastases of different primary tumors: a retrospective analysis. J Cancer Res Clin Oncol 2010; 136:1729-1735.

27. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997; 37:745–751.

28. Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008; 70:510-514.

29. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multiinstitutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010; 77:655-661.

***This study incorporates the primary cancer diagnosis into a prognostic score for patients with brain metastases.**

Table. Brain tumor epidemiology: median age at diagnosis and survival by age (www.cbtrus.org) (nd no data).

Histology (median age at diagnosis)	Age group	Cases (n)	1-year survival rate	2-year survival rate	5-year survival rate	10-year survival rate
Pilocytic astrocytoma (13)	0-14	1,366	98.7%	98.6%	97.3%	96.1%
	0-19	1,644	98.4%	98.4%	96.8%	95.6%
	20-44	491	96.8%	95.2%	91.0%	87.9%
	45-54	88	94.3%	88.0%	82.4%	72.4%
	55-64	40	95.4%	84.0%	81.0%	nd
	65-74	22	nd	nd	nd	nd
	75+	Nd	nd	nd	nd	nd
Diffuse astrocytoma (47)	0-14	89	93.1%	84.3%	84.3%	82.1%
	0-19	110	94.4%	85.1%	85.1%	79.6%
	20-44	243	91.6%	81.4%	58.5%	40.7%
	45-54	81	71.6%	52.8%	39.5%	Nd
	55-64	96	55.1%	29.5%	nd	Nd
	65-74	58	nd	nd	nd	Nd
	75+	38	nd	nd	nd	Nd
Anaplastic astrocytoma (52)	0-14	150	59.7%	43.5%	32.0%	27.7%
	0-19	200	63.7%	44.5%	33.6%	30.1%
	20-44	933	87.3%	72.7%	48.5%	36.5%
	45-54	532	70.1%	48.2%	28.6%	18.6%
	55-64	485	46.9%	21.6%	8.2%	5.7%
	65-74	411	30.7%	11.0%	3.3%	Nd
	75+	285	12.9%	5.2%	nd	nd
Glioblastoma (64)	0-14	155	46.6%	26.0%	20.9%	13.3%
	0-19	239	54.5%	29.5%	18.6%	12.7%
	20-44	2,052	66.1%	34.3%	16.1%	9.7%
	45-54	3,561	51.8%	18.7%	5.6%	3.1%
	55-64	4,931	39.8%	12.4%	3.3%	0.8%

	65-74	4,831	22.3%	5.5%	1.4%	0.8%
	75+	4,183	9.7%	2.4%	0.7%	c
Oligodendroglioma (41)	0-14	114	97.3%	96.4%	95.3%	90.6%
	0-19	191	97.4%	95.1%	92.5%	88.6%
	20-44	1,304	98.0%	95.7%	84.7%	67.2%
	45-54	526	94.3%	88.9%	76.8%	55.8%
	55-64	255	87.2%	78.0%	65.0%	46.9%
	65-74	109	78.4%	68.6%	51.5%	35.1%
	75+	68	57.9%	42.6%	30.4%	Nd
Anaplastic oligodendroglioma (49)	0-14	nd	nd	nd	nd	nd
	0-19	27	88.5%	nd	nd	nd
	20-44	395	93.2%	81.8%	65.9%	46.8%
	45-54	238	83.3%	70.0%	52.9%	40.1%
	55-64	170	72.3%	55.4%	32.5%	16.7%
	65-74	100	50.3%	35.1%	nd	nd
	75+	40	nd	nd	nd	nd
Ependymoma and anaplastic ependymoma (40)	0-14	433	93.4%	85.6%	69.9%	60.5%
	0-19	520	94.2%	86.9%	72.8%	63.3%
	20-44	564	95.9%	94.4%	90.9%	87.1%
	45-54	304	94.3%	90.4%	84.9%	81.8%
	55-64	209	92.5%	88.3%	84.4%	83.6%
	65-74	100	88.6%	76.2%	72.0%	58.6%
	75+	51	83.2%	74.1%	63.4%	32.4%
Malignant neuronal/glial, neuronal and mixed (26)	0-14	92	86.3%	76.0%	69.6%	69.6%
	0-19	112	86.9%	75.5%	67.4%	67.4%
	20-44	134	93.3%	87.7%	77.2%	66.0%
	45-54	114	91.4%	88.7%	75.8%	58.9%
	55-64	87	89.9%	72.1%	61.1%	54.7%
	65-74	43	72.4%	62.6%	60.5%	nd

	75+	36	77.3%	65.8%	55.5%	nd
Embryonal/primitive/medulloblastoma (9)	0-14	1,232	80.7%	69.8%	61.8%	56.9%
	0-19	1,358	81.6%	70.4%	61.7%	57.0%
	20-44	407	87.0%	79.7%	66.0%	55.1%
	45-54	53	80.9%	64.5%	55.7%	34.5%
	55-64	26	69.2%	nd	nd	nd
	65-74	nd	nd	nd	nd	nd
	75+	nd	nd	nd	nd	nd
Lymphoma (63)	0-14	37	86.3%	82.8%	77.3%	77.3%
	0-19	59	82.7%	78.6%	75.6%	65.1%
	20-44	887	37.2%	31.4%	25.8%	19.8%
	45-54	574	57.9%	48.9%	39.3%	29.0%
	55-64	615	61.2%	50.6%	37.3%	27.1%
	65-74	689	48.2%	37.7%	21.1%	9.3%
	75+	597	33.8%	23.1%	12.1%	9.7%
Total: all brain and CNS	0-14	5,596	85.6%	77.9%	71.9%	67.8%
	0-19	6,839	86.6%	78.8%	72.5%	68.6%
	20-44	10,472	82.6%	70.8%	56.6%	45.0%
	45-54	7,486	65.2%	43.7%	31.2%	23.4%
	55-64	8,125	49.6%	27.4%	17.4%	12.6%
	65-74	7,555	31.2%	16.3%	9.8%	6.9%
	75+	7,215	16.5%	8.8%	5.4%	4.0%