PERGAMON

European Journal of Cancer 39 (2003) 2355–2363

European Journal of Cancer

www.ejconline.com

Cause of death and long-term survival in patients with neuro-epithelial brain tumours: a population-based study

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Received 17 December 2002; received in revised form 19 March 2003; accepted 23 March 2003

Abstract

Long-term survivors of neuro-epithelial brain tumours have a higher death rate compared with the general population and the aims of this study were to investigate the causes of death and analyse long-term survival using population-based material. A total of 6209 patients were registered in the period of 1970–1993 with a primary intracranial neuro-epithelial tumour in the The Norwegian Cancer Registry. In a pilot study, a high level of agreement with regard to the cause of death was found between clinical data and the registered cause of death. Underlying causes of death in the whole population were therefore analysed. Most deaths were caused by the primary neuro-epithelial brain tumour within 10 years of diagnosis. Although the numbers were small, the proportion of patients dying from other cancers, vascular disease, infections and accidents continued to rise with time. Survival was computed using the Kaplan–Meier method. For children, survival at 5, 10 and 15 years significantly improved from the time period of 1970–1981 to 1982–1993 (47.9, 43.6 and 43.3% versus 63.8, 59.8 and 59.8%, respectively, $P < 0.0001$). Similar improvements in survival at 5, 10 and 15 years were observed for young adults aged 15–49 years (32.7, 21.3 and 16.5% versus 50.1, 37.5 and 33.1%, for the same time periods, $P < 0.0001$). No such improvement for those aged 50 years and over was observed (corresponding figures of 6.6, 3.8 and 2.8% versus 7.7, 4.8 and 3.4%). Prognosis for those with childhood medulloblastomas improved significantly, as did the prognosis of younger adults with low-grade gliomas and unbiopsied/ unclassifiable grade gliomas.

Keywords: Long-term survival; Brain tumour; Cause of death; Adults; Children

1. Introduction

In addition to the considerable early mortality among brain tumour patients, premature late deaths are a concern for both children [1] and adults [2,3]. Although the conditional probability of further survival, given that a patient has survived so far, increases with the length of time since diagnosis [4], long-term survivors experience an excess of deaths compared with the general population [5,6]. Patients with central nervous system (CNS) tumours have especially been shown to have poor overall survival [6–8] and have the highest rate of recurrent disease [6]. In studies describing patients up to 20–25 years of age after initial diagnosis, it has been shown that deaths from other diseases, accidents and second cancers contribute to the late mortality after treatment of brain tumours [5,6,8].

The prognosis for adults with primary malignant brain tumours is generally worse than the prognosis for children [4,9] and depends on factors such as age, performance status and tumour histology [9–11]. Less than 30% of adult patients survive 5 years after diagnosis of a primary malignant brain tumour [4,9,12] and premature late deaths are common among these long-term survivors, although the mortality rate decreases with time [4].

It has been uncertain whether improvements in imaging, surgery, chemotherapy and radiotherapeutic techniques have significantly improved overall long-term survival after childhood and adult brain tumours [13–15]. The significant decrease in mortality observed for lymphomas and leukaemias has not been evident to the same extent as for CNS tumours [5]. European data have lately indicated a slightly improved survival prob-

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doi:10.1016/S0959-8049(03)00603-8

ability [14] and survival of medulloblastoma has improved in recent years [7,9]. In addition, in studies of the Surveillance, Epidemiology and End-Results (SEER) data in the United States of America (USA), survival rates of patients with medulloblastoma, astrocytoma and oligodendroglioma have shown improvement [9], but long-term results are uncertain. In a pilot study, we examined the cause of death and the reliability of mortality registration in patients surviving five years or longer after diagnosis in a large Norwegian radiation oncology centre. We next sought to establish the cause of death of all Norwegian patients diagnosed with a neuro-epithelial brain tumour during the 24-year period of 1970–1993. We also compared long-term survival among patients diagnosed during 1970–1981 with that for the period of 1982–1993.

2. Patients and methods

2.1. Pilot study of the cause of death

The Norwegian system for health and demographic statistics is centralised in Statistics Norway (SN) and the mortality of all inhabitants is registered on the basis of death certificates, autopsy reports and information from the Norwegian Cancer Registry. The present project was initiated with a pilot study to investigate the accuracy of diagnosis of the underlying cause of death as recorded by SN. This was performed using data on long-term survivors treated at the Norwegian Radium Hospital (NRH), the largest radiation oncology unit in Norway. Between 1 January 1970 and 31 December 1993, a total of 1599 patients (171 children, 1428 adults) were treated at the NRH for intracranial astrocytic or oligodendroglial tumours, mixed gliomas, ependymal tumours, embryonal tumours, pineal parenchymal or germ-cell tumours. Among the 546 (34%) patients who survived 5 years, there were a total of 255 subsequent deaths. These patients were selected for further investigation of the cause of death. Hospital records including surgical pathology and autopsy records were reviewed. Documents from each patient's local hospital, general practitioner (GP) and nursery home were also retrieved. On the basis of this information, we sought to establish the conditions which led directly to death, as well as the antecedent conditions giving rise to this final cause. This was possible for 251 of the 255 patients. The World Health Organization (WHO) guidelines and codes for mortality and morbidity were used [16], as were the standard registration algorithms according to the International Classification of Diseases versions 8, 9 and 10 for the appropriate time periods. The analysis was carried out in a blinded manner and a concordance rate exceeding 95% was found (see Section 3). On the basis of this high level of concordance in the pilot study, the causes of death registered by SN were subsequently used for the whole population-based set of patient data.

2.2. The Norwegian Cancer Registry

The Norwegian Cancer Registry, founded in 1951, receives data on all cases of malignant neoplasms together with benign tumours of the CNS. The mandatory reporting is based on three sources of information: (1) copies of all pathology and autopsy reports from all laboratories in the country, (2) registration forms filled in by clinicians giving the localisation, extent of disease and treatment and (3) copies of all death certificates that mention neoplastic disease. The Norwegian population of 4.4 million in 1998 is well defined and stable with regard to migration. Each individual is uniquely identified by their date of birth together with a five-digit number to ensure that cases are not registered twice or lost to follow-up. If the registry receives a report from a pathology laboratory but has no clinical form, the clinician is contacted. In addition, if information on a death certificate is not in accordance with the files of the Cancer Registry this is investigated further. If patients are reoperated upon or have surgery several years after initially being diagnosed by radiological methods alone, the database is continuously updated according to the additional histological reports that are submitted. Throughout the study period, tumour location was classified according to the seventh revision of the International Classification of Diseases [17]. Histological groups according to WHO for the appropriate time-periods are presented according to the integration of classification systems [18] which have been published in order to standardise registration and reporting. Date of diagnosis was defined as the date of the primary radiological tumour diagnosis. Age was defined as age at the time of initial tumour diagnosis. Results of quality control indicated that the data from the Norwegian Cancer Registry were valid for a thorough population-based study of CNS neoplasms [19].

2.3. Patients, population-based material

Between 1 January 1970 and 31 December 1993, a total of 10 561 patients in Norway were diagnosed as having primary intracranial brain tumours. The following groups were excluded: meningeal tumours (2001 cases), pituitary tumours (1001 cases), craniopharyngioma (90 cases), and optic and other cranial nerves (513 cases). Lymphomas (80 cases), vascular and mesenchymal tumours and rare tumours not of glial or germ-cell origin (296 cases) were also excluded, leaving a total of 6580 patients with astrocytic and oligodendroglial tumours, mixed gliomas and ependymal tumours together with embryonal tumours, pineal parenchymal and germ-cell tumours. Patients with uncer-

tain radiological diagnosis were also excluded (317 cases), as were patients diagnosed incidentally at autopsy (54 cases), leaving 6209 patients available for analysis. Radiological findings were the basis for diagnosis in 1396 patients, while 4813 patients (77.5%) had histological confirmation. Surgery was performed at one of the five neurosurgical departments in Norway and histological examination was done in the corresponding pathology unit. Histology reports were available on microfilm, but review of slides and tissue blocks was not possible. Patients were followed until death, emigration, or status on the 31 December 1998. 5 patients were lost during follow-up as they had emigrated. Cause of death was not available for 4 patients as they had died abroad. 624 patients were children ($\leqslant$14 years) at diagnosis.

2.4. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 10.1.0 statistical program [20] was used for the data analysis. Computation of survival probabilities was done using the Kaplan–Meier method. Equality of survival was tested by the log-rank method. Testing for a statistically significant tendency of difference in the proportion of patients found to have died from a brain tumour, with and without autopsy results, was done using the Fisher's exact test for children and the Chi-squared test for adults. A Confidence Interval (CI) of 95% was chosen and a P value of <0.05 was considered to be statistically significant.

3. Results

3.1. Pilot study of the cause of death

The cause of death was established for 251 of the 255 patients who were treated at the NRH and died 5 or more years later. Records covering the time period immediately before death were not available for 4 patients. 33 patients died at home, 64 in nursing homes and 158 in hospital. The underlying cause stated by SN was confirmed by the hospital diagnosis for 239 patients out of 251 (95.2%; CI 92.6–97.4%).

Registration by SN of the cause of death as due to a brain tumour was not confirmed by the hospital diagnosis of the underlying cause of death for 11 patients, for whom the hospital diagnosis was late radiation effects with no evidence of recurrence (6 patients), possible treatment-induced malignancy (2 patients), death due to intestinal haemorrhage (1 patient), ischaemic heart disease (1 patient) and pneumonia (1 patient). A hospital diagnosis of brain tumour as the underlying cause of death was established for 1 patient registered by SN as having died from pneumonia.

3.2. Norwegian population-based material

The underlying causes of death among children are given in Table 1. The vast majority of deaths (299/311, 96.1%) were caused by the primary neuro-epithelial brain tumour and 91.6% (273/298) of deaths occurred within 5 years of diagnosis. Only 4/299 deaths from primary brain tumour (1.3%) occurred later than 10 years after the diagnosis. 3 children died from accidental causes (1 transport accident, 1 alcohol intoxication and 1 drowning). 2 children died from other cancers. One of these developed acute myelogenous leukaemia 2 years after chemotherapy and CNS axis radiotherapy for medulloblastoma. The other, a patient with tuberous sclerosis treated for astrocytoma when he was 14 years old, developed renal-cell carcinoma at 24 years of age; the conclusion at autopsy was a possible association with the tuberous sclerosis, as has been previously described in Ref. [21]. 2 children died from pneumonia, 1 from cachexia, 1 from cerebrovascular disease without a reported recurrence of the brain tumour and 1 due to poorly controlled epilepsy. In 1 patient, autopsy confirmed bacterial endocarditis 2 months after surgery for pinealoma.

For adult patients, the corresponding results are shown in Table 2. Initial failure to control the tumour or relapse was the underlying cause of death in 4723/4997 (94.5%) patients. In adult patients who survived more than 5 years after diagnosis, mortality due to the brain tumour gradually tapered to 76.6% of deaths up to 15 years and 64.0% up to 20 years, although the absolute number of adult patients who survived for that long was low. The proportion of patients dying from other cancers increased up to 15 years and the proportions of patients dying from ischaemic heart disease,

Table 1
Underlying cause of death in children with histologically-confirmed neuro-epithelial brain tumours diagnosed between 1 January 1970 and 31 December 1993

	Years after diagnosis						Total
	0–4 *n*	5–9 *n*	10–14 *n*	15–19 *n*	20–24 *n*	25–29 *n*	*n* (%)
Brain tumour	273	22	1	2	1		299 (96.1)
Accidents	1	1		1			3 (1.0)
Other cancer	1		1				2 (0.6)
Infections	2						2 (0.6)
Cerebrovascular disease	1						1 (0.3)
Cachexia	1						1 (0.3)
Epilepsy		1					1 (0.3)
Surgical complications	1						1 (0.3)
RT complications						1	1 (0.3)
Total	280	24	2	3	1	1	311 (100)

RT, radiotherapy.

Table 2
Underlying cause of death for adults (aged ⩾15 years) in Norway with histologically-confirmed neuro-epithelial brain tumours diagnosed between 1 January 1970 and 31 December 1993

	Years after diagnosis						Total *n* (%)
	0–4 *n* (%)	5–9 *n* (%)	10–14 *n* (%)	15–19 *n* (%)	20–24 *n*	25–29 *n*	
Brain tumour	4366 (95.5)	265 (89.8)	72 (76.6)	16 (64)	4		4723 (94.5)
Other cancer	63 (1.4)	6 (2.0)	7 (7.4)	1 (4)			77 (1.5)
Ischaemic heart disease	38 (0.8)	4 (1.4)	7 (7.4)	4 (16)		2	55 (1.1)
Cerebrovascular disease	35 (0.8)	6 (2.0)	5 (5.3)	3 (12)			49 (1.0)
Infections	28 (0.6)	3 (1.0)	2 (2.1)	1 (4)			34 (0.7)
Intestinal haemorrhage	9 (0.2)				1		10 (0.2)
Accidents	8 (0.2)	3 (1.0)			2		13 (0.3)
Other causes	26 (0.6)	8 (2.7)	1 (1.1)		1		36 (0.7)
Total	4573 (100)	295 (100)	94 (100)	25 (100)	8	2	4997 (100)

cerebrovascular disease and infections also continued to rise with time, although the numbers were small.

Autopsy was performed in 851/5308 patients (16.0%). The underlying cause of death, for these patients (83 children, 768 adults) as established at autopsy, is given in Table 3. The autopsy rate decreased from 25.0% (776 autopsies/3104 deaths) in the period from 1 January 1970–30 June 1984 to 3.4% (75 autopsies /2204 deaths) in the period 1 July 1984–31 December 1998. Fourteen of the autopsies were performed in patients who had survived more than 5 years. For children who survived less than 5 years, the percentage found to have died from brain tumours was not significantly lower in the autopsied group than in the group where autopsy was not performed: 76/80 (95.0%; CI 87.0–98.4%) versus 197/200, (98.5%; CI 95.3–99.6%), respectively ($P = 0.11$). For adults who survived less than 5 years, the percentage of patients found to have died from brain tumour was significantly lower in the autopsied group than in the group where this had not been done: 686/757 (90.6%; CI 88.3–92.6%) versus 3680/3816 (96.4%; CI 95.8–97.0%), respectively ($P < 0.001$).

Table 3
Underlying cause of death as established by autopsy between 1 January 1970 and 31 December 1998 in patients with histologically-confirmed neuro-epithelial brain tumours[a]

	Total *n*	(%)
Brain tumour	775	(91.1)
Cerebrovascular disease	25	(2.9)
Other cancer	16	(1.9)
Ischaemic heart disease	13	(1.5)
Infections	12	(1.4)
Surgical complications	4	(0.5)
Accidents	3	(0.4)
RT complications	2	(0.2)
Intestinal haemorrhage	1	(0.1)
Total	851	(100)

RT, radiotherapy.
[a] Patients diagnosed incidentally at autopsy (54 cases) were excluded.

A total of 383/4813 (8.0%) patients died within 30 days after surgery. Surgical complications were assigned as the underlying cause of death for only 1 patient, so perioperative and postoperative deaths are possibly often ascribed to the brain tumour.

3.3. Survival

Tumour type for the children and adults in the population-based patient data-set are given in Table 4. Median ages of the children and adult groups were 7 years (range 0–14 years) and 58 years (range 15–93 years), respectively. Radiological methods were the basis for diagnosis for 1396 patients, while 4813 patients (77.5%) had a histological confirmation. Low-grade glioma and medulloblastoma/primitive neuroectodermal tumour (PNET) were the most common childhood tumours, comprising 67.6% of the total number of tumours. Glioblastoma was the most common tumour in adults followed by unbiopsied/unclassifiable grade gliomas and low-grade glioma, together comprising 92.7% of the total.

Table 4
Distribution according to the histology of neuro-epithelial brain tumours diagnosed in Norwegian children and adults between 1 January 1970 and 31 December 1993

Histology	Children *n* (%)	Adults *n* (%)
Low grade glioma	314 (50.3)	1178 (21.1)
Anaplastic glioma	16 (2.6)	267 (4.8)
Glioblastoma	50 (8.0)	2581 (46.2)
Ependymoma	37 (5.9)	54 (1.0)
Germ-cell tumours	11 (1.8)	22 (0.4)
Medulloblastoma/PNET	108 (17.3)	49 (0.9)
Glioma unbiopsied/unclassifiable grade	78 (12.5)	1418 (25.4)
Others	10 (1.6)	16 (0.3)
Total	624 (100)	5585 (100)

PNET, primitive neuroectodermal tumour.

Table 5
Overall survival compared with cause-specific brain tumour survival rates for children ($n=624$) and adults ($n=5585$) diagnosed with neuro-epithelial brain tumours in the period of 1 January 1970 to 31 December 1993

	Survival years				
	5	10	15	20	25
Children ($n=624$)					
Overall survival (%)	55.1	50.7	50.2	48.8	48.2
Cause-specific survival (%)	55.9	51.8	51.5	50.5	49.9
Adults ($n=5585$)					
Overall survival (%)	18.1	12.0	9.0	7.5	6.6
Cause-specific survival (%)	19.4	13.4	10.7	9.6	9.0

By 31 December 1998, 896 patients were alive (14.4%) and 5308 had died. Overall survival rates compared with disease-specific survival rates for children ($n=624$) and adults ($n=5585$) at 5, 10, 15, 20 and 25 years are given in Table 5. For childhood neuro-epithelial brain tumours, the difference between overall and disease-specific survival did not exceed 2% during the 25-year observation period. Neither did the difference between overall and disease-specific survival for adult neuro-epithelial brain tumour patients exceed 2% during the first 15 years of observation. In adult patients surviving beyond 15 years, the difference between overall and disease-specific survival increased slightly, but remained below 3% at 25 years.

Disease-specific survival of children (total $n=624$) is shown in Fig. 1 for those diagnosed in period 1 (1 January 1970–31 December 1981; $n=307$) compared with those diagnosed in period 2 (1 January 1982–31 December 1993; $n=317$). The median age at diagnosis was 7 years (range 0–14 years) and 6 years (range 0–14 years) for periods 1 and 2, respectively. Survival at 5, 10 and 15 years was significantly improved from the period of 1970–1981 to the period of 1982–1993 (47.9, 43.6% and 43.3% versus 63.8, 59.8 and 59.8%, respectively, $P<0.0001$; Fig. 1). For children diagnosed from 1970 to 1981, median survival was 48.3 months (CI 17.1–79.6), while for those diagnosed from 1982 to 1993, median survival has not yet been reached ($P<0.0001$). Disease-specific survival of patients in the age group 15–49 years (total $n=1887$) is compared for periods 1 ($n=828$) and 2 ($n=1059$) in Fig. 2. The median age was 35 years (range 15–49 years) and 37 years (15–49 years) for periods 1 and 2, respectively. Survival at 5, 10 and 15 years in this group of younger adult patients was also significantly improved when comparing the first to the second time period (32.7, 21.3 and 16.5% versus 50.1, 37.5 and 33.1%, respectively, $P<0.0001$; Fig. 2). The median survival of patients diagnosed during period 1 was 24.0 months (CI 19.4–28.5) compared with 60.6 months (CI 48.1–73.1) during period 2 ($P<0.0001$). Disease-specific survival and median survival during the two time periods were also compared for patients aged 50 years and above ($n=3698$). In this group, median survivals for periods 1 ($n=1602$) and 2 ($n=2096$) were 4.9 months (CI 4.6–5.3) and 5.5 months (CI 5.1–5.9), respectively ($P=0.03$). The median age was 62 years (range 50–91 years) and 66 years (range 50–93 years) for periods 1 and 2, respectively. Survival at 5, 10 and 15 years was 6.6, 3.8, 2.8 and 7.7, 4.8, 3.4% for periods 1 and 2, respectively (Fig. 3).

Fifteen-year survival rates conditional on 5-year survival were for children 90.2 and 93.8% for periods 1 and 2, respectively. For patients aged 15–49 years, corresponding results were 50.3 and 66.1% and for patients aged 50 years or above survival rates were 42.0 and 43.9%.

In Table 6, disease-specific survival for the largest histological subgroups is compared for the two time periods. No significant improvement in 5-year survival

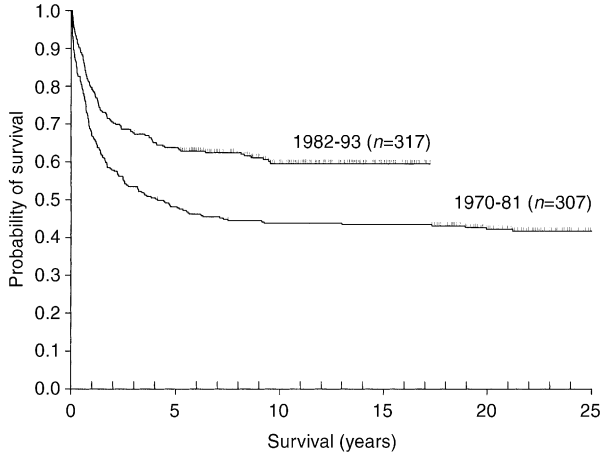

Fig. 1. Disease-specific survival of paediatric patients ($n=624$) with neuro-epithelial brain tumours diagnosed in time period 1 (1 January 1970–31 December 1981) and time period 2 (1 January 1982–31 December 1993).

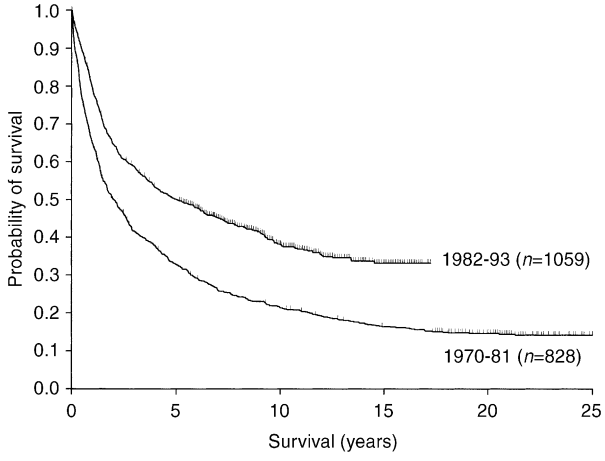

Fig. 2. Disease-specific survival of patients aged 15–49 years ($n=1887$) with neuro-epithelial brain tumours diagnosed in time period 1 (1 January 1970–31 December 1981) and time period 2 (1 January 1982–31 December 1993).

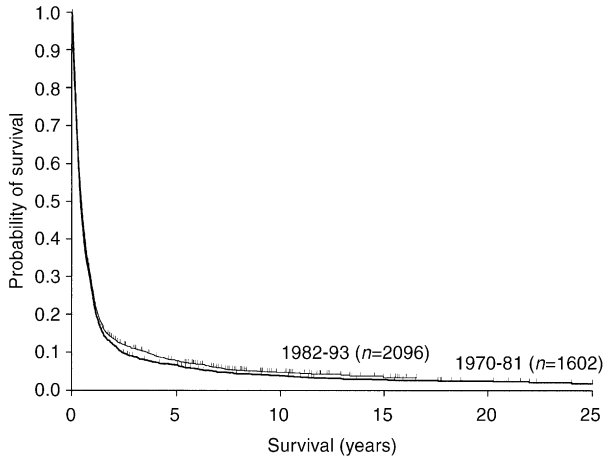

Fig. 3. Disease-specific survival of patients aged 50 years and above ($n = 3698$) with neuro-epithelial brain tumours diagnosed in time period 1 (1 January 1970–31 December 1981) and time period 2 (1 January 1982–31 December 1993).

for low-grade gliomas was seen in children, although for young adults with these tumours diagnosed during 1982–1993, the 10-year survival improved. The prognosis for childhood medulloblastoma improved, as did the prognosis for low-grade glioma and unbiopsied/unclassifiable grade gliomas in younger adults. No improvement was seen in survival for children or younger adults with high-grade gliomas.

4. Discussion

4.1. Cause of death

Our population-based data-set includes all registered patients in the Norwegian Cancer Registry with a diagnosis of a primary neuro-epithelial brain tumour during the 24 years of 1970–1993 and followed-up for at least 5 years after their diagnosis. Very few patients were lost to follow-up. We used the SN registration data on cause of death and found a confirmation rate exceeding 95%. The patients treated at NRH may, compared with the population-based data, represent selection biases associated with referral populations and populations recruited into clinical trials. The patients of the pilot study may therefore not have correctly reflected the main study population and patients who did not receive radiotherapy may have been under-represented. Death certificates also do not always correctly state the underlying cause of death [22,23]. In a study carried out in the USA, based on computer linkage of death records and hospital discharge records, the underlying causes of death and discharge diagnoses for 9724 patients were compared; the agreement between cause and closest medical record diagnosis was 72% [24]. Critical reviews comparing the information in hospital medical records with the cause of death stated on death certificates for men with prostate cancer have shown both high (87–90%) [25,26] and low (65–78%) [27,28] levels of agreement. For brain tumours, a confirmation rate of 87.4% has been reported [27]. The high confirmation rate found in this study is possibly due to the fact that the SN data is based on both death certificates, autopsy reports and information from the Norwegian Cancer Registry.

Among autopsied patients dying within 5 years from diagnosis, the underlying cause of death was from brain tumours for 95% of the children and for 90% of the adults. The rate among autopsied adult patients was significantly lower compared with the general rate of 95.4% for all adults dying within 5 years after their brain tumour diagnosis. The selection criteria for

Table 6
Five-year disease-specific survival in children (<15 years) and younger adults (15–49 years) with brain tumours treated during 1970–1981 compared with patients treated during 1982—1993[a]

	Children			Adults		
	1970–1981	1982–1993	*P* value	1970–1981	1982–1993	*P* value
Low-grade glioma	($n = 140$)	($n = 174$)		($n = 270$)	($n = 478$)	
5-year survival (%)	68.3	76.3	0.09	52.8	75.0	<0.001
High-grade glioma	($n = 38$)	($n = 28$)		($n = 367$)	($n = 402$)	
5-year survival (%)	23.7	17.8	0.9	16.3	14.2	0.49
Medulloblastoma/PNET	($n = 52$)	($n = 56$)		(n = 22)	($n = 25$)	
5-year survival (%)	34.6	55.1	0.03	52.3	48.8	0.87
Glioma, unbiopsied/unclassifiable	($n = 46$)	($n = 32$)		($n = 146$)	($n = 114$)	
5-year survival (%)	31.1	56.3	0.06	34.3	59.5	<0.001

WHO, World Health Organization; PNET, ?.

[a] Gliomas corresponding to WHO grades I and II are here classified as low-grade gliomas, while those corresponding to WHO grades III and IV are classified as high-grade gliomas. Tests of equality of survival were performed for the whole observation period.

autopsy of patients diagnosed with a brain tumour cannot be ascertained, but it is possible that patients perceived by clinicians to have an unexplained cause of death were over-represented among the autopsied brain tumour patients. The general autopsy rate has been declining worldwide for decades [29,30] and this report supports the scientific importance of continuing to perform autopsy as a means of medical audit, quality assurance and medical education.

4.2. Survival

Overall survival during the first 5 and 10 years after diagnosis in patients with malignant brain tumours is generally accepted as being close to disease-specific survival, due to the high lethality of these tumours, and is often used as the primary endpoint in studies [3,4,9,31]. In the population-based data-set examined here, we confirm that the difference between overall survival rates and disease-specific survival rates in children was less than 2% and in adult patients less than 3% during 25 years of observation.

No significant improvements in long-term survival of childhood brain tumour patients have been described for the last decades in large population-based studies [13,15]. Positive trends have been observed in EUROCARE data for both childhood [14] and adult [7] CNS tumours, but increases in survival have been modest. In our population-based study, disease-specific 5-, 10- and 15-year survival in childhood brain tumours improved by approximately 15% during the years 1982–1993 compared with the levels during 1970–1981. Disease-specific survival reached a plateau at approximately 60% after 15 years of observation. Very few children relapsed later than 10 years after diagnosis in either time period. Results are in accordance with survival rates observed in other parts of Northern Europe [14]. Medulloblastoma showed significantly improved survival in children. A trend of increased survival in low-grade glioma and unbiopsied/unclassifiable grade gliomas may also be indicated. The amount of children with unbiopsied/unclassifiable grade gliomas was lower in the last time period and the composition of this group may have changed over time with an increase in the biopsy rates.

A possible reason for improved survival in children could be the increased proportion of cases included in clinical trials, while this proportion is still low for adult patients. An additional reason could be the centralisation of management and paediatric neurosurgical training which have been shown to influence survival [32]. In adult patients aged 15–49 years, we also found an improvement of approximately 15% in disease-specific 5-, 10- and 15-year survivals, and the median survival more than doubled from 24 to 60 months. Although the survival curve in Fig. 2 has not yet reached a plateau, long-term disease-specific survival considerably improved for these younger brain tumour patients treated during 1982–1993 compared with 1970–1981. Increased diagnostic sensitivity following progress in brain imaging after the introduction of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in clinical practice may have shortened the pre-diagnostic period of indolent tumours, thus possibly explaining, at least part of, the improved prognosis [33,34]. While the poor prognosis associated with high-grade tumours remained unchanged, the histological subgroups of low-grade glioma and unbiopsied/unclassifiable grade gliomas showed significantly improved survival in younger adults. In contrast, we found no real improvement in median or long-term survival from 1970 onwards for patients aged 50 and over when diagnosed. The probability of having an anaplastic glioma or glioblastoma increases with the increasing age of the patients [9] and older patients derive less benefit from treatment [9,35] and have a worse outcome than younger patients for both high-grade [9] and low-grade [2,3] gliomas. Although statistically significant, the very modest improvement in the median disease-specific survival achieved for patients aged 50 years and over during the later time period may have little clinical significance. No improvement in disease-specific survival for high-grade gliomas was seen in any age group. Low grade gliomas in adult patients are usually strictly local tumours [36,37], so any improvement in the long-term survival of these patients probably reflects improvements in local therapy. Comparable fractionated megavoltage radiotherapy was used in the reported patient population during the entire study period, and the effect of radiotherapy on overall survival in low-grade glioma is uncertain [31,38], nor did the chemotherapy that was available in this study prolong survival [2]. The demonstrated significantly improved long-term survival exceeding 20% in these subgroups of adult patients may suggest progress that has been made in neuroimaging and neurosurgical treatments for adult low grade gliomas during the latter half of the study period.

In conclusion, the primary malignancy continues to be the main cause of death during the long-term follow-up of these brain tumour patients. A high level of agreement in the cause of death was found between the clinical data and the registered cause of death based on death certificates, autopsy reports and information from the National Cancer Registry. For adults, the percentage of patients found to have died from causes other than their brain tumour was significantly higher in the autopsied group than in the non-autopsied group.

An approximate 15% improvement in 5-, 10- and 15-year survival was found for both childhood neuro-epithelial brain tumours and for adults aged 15–49 years

during the two time periods studied, while only marginal improvements in prognosis were seen in patients aged 50 years and over.

Acknowledgements

This work was supported by a grant from the Norwegian Cancer Society.

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