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Incidence and survival of children and young people with central nervous system embryonal tumours in the North of England, 1990-2013

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Abstract

Background: Medulloblastoma and primitive neuroectodermal tumours (PNET) are the most common central nervous system (CNS) embryonal tumours diagnosed in childhood. Survival outcomes are worse for children diagnosed with CNS PNET compared to medulloblastoma. Less is known about survival outcomes in teenagers and young adults (TYA).

Methods: Data were extracted from two population-based cancer registries of children and young people (0-24 years) in the north of England for all diagnoses of medulloblastoma and CNS PNET between 1990 and 2013. Incidence and survival trends were analysed using Poisson and Cox regression.

Results: Between 1990 and 2013, 197 medulloblastomas and 58 CNS PNET were diagnosed; age standardised incidence rates of 3.8 and 1.5 per million, respectively. Medulloblastoma incidence decreased over time while there was no significant change in trend for CNS PNET. The overall 5 year survival rate was 54%. The risk of death was 2.4 times higher (95%CI 1.6, 3.7) for patients with CNS PNET compared to medulloblastoma, after adjustment for patient characteristics. There was a 39% reduction (95%CI 0.43, 0.87) in the risk of death for patients diagnosed between 2000 and 2013 compared to 1990-1999. Risk of death did not differ for TYA (15-24 years) compared to children aged 5-9 years.

Conclusions: Medulloblastoma incidence decreased over time and differences in survival between medulloblastoma and PNET emerged within the first year post diagnosis leading to poorer outcomes for children and young adults diagnosed with PNET, however a significant improvement in survival over time was observed.

Highlights

- Little is known about incidence and survival outcomes in teenagers and young adults (TYA) with CNS embryonal tumours
- Incidence trends decreased over time for medulloblastoma, however no significant trend was observed for CNS PNET over time
- Differences in survival between medulloblastoma and CNS PNET emerged within the first year post diagnosis
- There was an improvement in survival over time for children and TYA with medulloblastoma and CNS PNET
- There were no differences in survival between TYA compared to children aged 5-9 years

Key words

Medulloblastoma, CNS PNET, CNS embryonal, children, teenager and young adult

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Introduction

Central nervous system (CNS) tumours are the second most common site of neoplasms diagnosed in children, accounting for approximately one quarter of all childhood cancers (0-14 years), (1) and 14% of tumours diagnosed in teenagers and young adults (TYA) (15-24 years) (2). They are the most common cause of cancer related death in children and TYA (1, 2).

CNS embryonal tumours are the second most frequent CNS subgroup of tumours in childhood, (3) which are further classified into one of four groups based on morphology and topography according to the International Classification of Cancer in Children version 3 (ICCC-3) (4): medulloblastoma, primitive neuroectodermal tumours (CNS PNET), medulloepitheliomas and atypical teratoid/rhabdoid tumours (ATRT). Medulloblastomas are the most common embryonal tumours (3, 5). CNS PNETs are rare; in England between 1995 and 2003 there were an estimated average of 15 new cases per year in children and 5 per year in TYA, compared with 44 and 7 cases of medulloblastoma in children and TYA respectively (6).

In recent years, molecular testing of CNS tumours has evolved. Medulloblastomas are considered to comprise at least four distinct diseases that differ according to their demographic characteristics, histology, genetics and clinical outcomes (7-9). The CNS PNET subgroup refers to a heterogeneous group of tumours that show aggressive clinical behaviour. Specific histotypes with distinct molecular features have recently been identified such as embryonal tumour with abundant neuropil and true rosettes (ETANTR) (10, 11). Moreover, a significant proportion have molecular phenotypes more characteristic of other tumour types such as ependymomas and high grade gliomas, suggesting that histological appearance alone may be inadequate to accurately classify many of these tumours (12-14). However these distinctions are not yet clarified in either the 2007 World Health Organisation

classification of CNS tumours or the ICCC-3 and historical cancer registration data comprise very little, if any, information on molecular status.

Population- based studies which have analysed survival rates separately for medulloblastoma and CNS PNET have shown that children diagnosed with medulloblastoma have better survival outcomes than those with CNS PNET (5-year survival rates range between 58-69% for medulloblastoma vs. 27-47% for CNS PNET) (3, 15-18). The incidence of childhood CNS embryonal tumours increased in Europe between 1978 and 1997 (19). Analysis by subgroup in children in Germany found that incidence trends for medulloblastoma in children have remained stable between 1991 and 2012 while over the same period the PNET rate decreased mainly due to improved diagnostic tools and classification of tumours (18).

Previous studies of incidence and survival of CNS embryonal tumours have generally been limited to children only. The aim of this study was to describe patterns and trends in incidence and survival of children and young people, aged 0-24 years, diagnosed with CNS embryonal tumours in the North of England focusing specifically on medulloblastomas and CNS PNET adjusting survival for patient case-mix including treatment.

Patients and methods

This study used data from two geographically adjacent population based tumour registers in the north of England; the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) and the Northern Region Young Person's Malignant Disease Register (NRYPMDR) (Figure 1). YSRCCYP collects information on children and young people aged 0-29 years at diagnosis whilst resident in the Yorkshire area (0-29 year population of 2 million in 2011) (20). Case ascertainment was complete for all patients aged under 30 years resident in the former Yorkshire Health authority from 1990 onwards; patients resident in the South Yorkshire Strategic Health Authority part of the region were included in the register

between 1998 and 2013 for children (0-14 years) and between 1998 and 2009 for teenagers and young adults (15-29 years). The NRYPMDR covers the counties of Northumberland, Tyne and Wear, Durham, Teesside and Cumbria (excluding Barrow-in-Furness) (0-24 year population of 0.9 million in 2011) and has recorded information on all cases of cancers in the region diagnosed in 0-24 year olds since 1968 (21). For both registers cases are identified through multiple sources including: hospital records, neuropathology reports, hospital admissions, other regional and national cancer registries (20, 21). Patients are regularly followed up to determine current status.

All tumours were classified into a histological group according to ICCC-3 (4). The group of embryonal tumours (ICCC-3 IIIc) can be further broken down into one of four subgroups; medulloblastoma, CNS PNET, medulloepitheliomas and Atypical teratoid/rhabdoid tumours (ATRT) (4). Medulloepitheliomas have recently been identified to be the same pathological entity as ETANTRs, many of which would have been previously classified as CNS PNETs. Therefore for this analysis medulloepitheliomas have been included in the CNS PNET group. ATRT are excluded from further analysis due to small numbers.

All diagnoses of CNS tumours between 1990 and 2013 in patients aged 0-24 years were extracted from the YSRCCYP and the NRYPMDR. Only first, primary tumours within each patient were analysed. We extracted information on each patient's age at diagnosis, gender, treatment received, date of diagnosis and date of death or last follow-up. All cases were followed up until death or a censor date of 31/12/2014. Deprivation was measured using the area-based Townsend index derived from the 2001 UK census based (22).

Information on the treatment modality each individual received was classified into one of six groups: surgery, radiotherapy and chemotherapy; surgery alone; surgery and radiotherapy; surgery and chemotherapy; adjuvant therapy without surgery (including radiotherapy and chemotherapy, radiotherapy alone or chemotherapy alone); and no treatment recorded. The

treatment patterns for medulloblastoma changed over the study period with the introduction of reduced dose radiation therapy and adjuvant chemotherapy in 1999 (23). We defined the period of diagnosis as either 1990-1999 or 2000-2013 to reflect changes in treatment over the study period.

Statistical analysis

Direct age standardised incidence rates (ASR) adjusted to the World standard population were calculated and reported per 1,000,000 person-years by gender and period of diagnosis (24). For incidence rate trends the age and sex adjusted average annual percent change (AAPC) was estimated by Poisson regression. Kaplan Meier 1, 2, 5 and 10 year survival estimates were calculated separately for medulloblastoma and CNS PNET. Cox proportional hazards models were used to model survival trends. Multivariable models included variables for diagnostic subgroup, age at diagnosis, gender, period of diagnosis, area deprivation and treatment. Tumour grade at diagnosis was not included in the model as all cases were classified as WHO grade IV (12). Additionally interaction terms between (a) diagnostic subgroup and period of diagnosis, (b) diagnostic subgroup and gender, and (c) diagnostic subgroup and age at diagnosis were included in the models to formally test if there were differences in survival patterns by diagnostic subgroup over time, by gender or by age groups. The proportional hazards assumption was checked for each variable using the Therneau and Grambsch test (25) within Stata (26). This assumption was met for all variables except treatment; we stratified the model across treatment categories and found the proportional hazards assumption to hold for all other variables.

Conditional 5 year survival was calculated separately for each diagnostic subgroup. Conditional survival is the probability of surviving an additional x years given that the person has already survived y years and is calculated by dividing the (x+y) year cumulative survival by the y year cumulative survival (27). For example, the 5 year conditional survival of

patients who had survived 1 year was estimated by dividing the 6 year cumulative survival by the 1 year cumulative survival. This measure shows how the survival probability changes with increasing duration of follow-up from the time of initial cancer diagnosis (27).

Incidence and survival rates by subgroup were compared with those published in the literature from population based cancer registries within the age range 0-24 years and covering time periods that overlapped with this study.

Results

Incidence

Between 1990 and 2013 there were 277 children and young people diagnosed with a CNS embryonal tumour; medulloblastomas were the most common type (n=197, 71%), followed by CNS PNET (n=58, 21%), and a further 22 (8%) patients were diagnosed with ATRT (this group was excluded from further analysis) (Table 1).

The overall ASRs for medulloblastoma and CNS PNET were 3.8 and 1.5 per 1,000,000 person-years respectively. Between 1990 and 2013 there was a statistically significant decreasing trend for medulloblastoma (AAPC= -2.3% (95%CI -4.4, -0.3)) and no significant change for CNS PNET (AAPC= -1.8% (95%CI -5.6, 2.0)) (figure 2).

Survival

Survival rates were considerably lower for CNS PNET compared to medulloblastoma; 5 year survival rates were 33% (95%CI (21, 46)) and 64% (95% CI (56, 70)), respectively (table 2). Unadjusted survival rates were better for cases diagnosed between 2000 and 2009 compared to those diagnosed between 1990 and 1999 for medulloblastoma only (table 2). For medulloblastoma there were no survival differences between children and TYA, however for CNS PNET TYA had slightly higher survival rates (Table 2).

The adjusted risk of death was 2.4 times higher for CNS PNET compared to medulloblastoma (HR=2.4, 95%CI (1.6, 3.7) table 3). Age was also significantly associated with survival with an increased risk of death in those aged 0-4 years compared to those aged 5-9 years at diagnosis, but there was no difference in survival for TYAs compared to 5-9 year olds. Survival improved over time, with a significant 37% reduction in the risk of death for patients diagnosed between 2000 and 2013 compared to 1990-1999 (HR=0.63, 95%CI (0.43, 0.92)). The risk of death increased by 30% for patients with a deprivation score on the 75th percentile compared to those on the 25th percentile (HR=1.3, 95%CI (1.0, 1.6)). There were no significant interactions between diagnostic subgroup and period of diagnosis (p=0.21), diagnostic subgroup and gender (p=0.84) or diagnostic subgroup and age (p=0.46).

For both diagnostic subgroups conditional survival increased for every additional year survived. Although the initial prognosis was worse for CNS PNET compared to medulloblastoma, for those who survived 3 years from diagnosis, the conditional 5-year survival rates were similar in both groups (85% for medulloblastoma and CNS PNET) (Figure 3).

International comparisons

Table 4 compares incidence and survival rates by diagnostic subgroup from our study with published population based studies including 5 in Europe and 1 from the USA. Medulloblastoma survival in 0-14 year olds in the North of England was slightly lower than in Germany over a very similar time period (63% and 69% respectively) but higher than that in Great Britain between 1991 and 2000 (58%). Our childhood CNS PNET survival rates were lower than those in Germany, France and Sweden but our CNS PNET group also included medulloepithelioma, recognised to have a particularly aggressive clinical course, which other studies included as a separate group.

Discussion

CNS tumours are the most common cause of cancer related death in children and TYA; 15% of children and 9% of TYA diagnosed with CNS tumours die within one year of diagnosis (28, 29), however little is known about how this varies by diagnostic subgroup. CNS embryonal tumours generally have poor prognosis and this study adds to the existing literature by describing trends in medulloblastoma and CNS PNET incidence and survival and includes teenagers and young adults aged 15- 24 years for whom comparatively little is known about disease epidemiology.

Over time the incidence trend for CNS embryonal tumours remained stable but there were differences by subtype with a significant decreasing incidence trend for medulloblastoma. We found that the 5 year overall survival rate for CNS embryonal tumours diagnosed aged 0-24 years was 54%. However, this masked clear differences according to diagnostic subtype with significantly poorer five-year survival rates seen for CNS PNET (33%) compared to medulloblastoma (64%) with differences emerging within the first year after diagnosis. The relative risk of death was 2.4 times higher for patients with CNS PNET compared to medulloblastoma, after adjustment for patient case-mix. Encouragingly, survival rates improved over time, driven by an increase for medulloblastoma. The risk of death was greatest in those aged 0-4 years, and there were no differences in survival between older children and TYA or by gender. Our conditional survival results showed that although CNS PNET prognosis was poor (one year survival rate 64%), for the small group of patients who survive three years from diagnosis the survival probabilities for the next 5 years were similar for medulloblastoma and CNS PNET.

CNS PNET are a heterogeneous group of tumours that can be difficult to classify and historically many CNS PNETs may have been misdiagnosed high grade gliomas with poor survival outcomes (13, 14). Improvements in molecular testing of CNS PNET will result in less misclassification of these tumours and is likely that this will impact of future incidence and survival estimates; indeed the observed decreasing trend in medulloblastoma incidence in this study may be due to improvements in classification over time.

Across Europe survival rates improved for children diagnosed with CNS tumours and in particular CNS embryonal tumours between 1995 and 2002 (30). Other studies have also shown a general improvement in survival for childhood CNS tumours over the last 20-30 years identifying improvements in CNS embryonal tumour survival specifically (3, 16, 19, 30, 31). TYA, aged 16-24 years, from Yorkshire showed a significant increase in survival from medulloblastoma and CNS PNET combined between 1990 and 2009 (32). As one of the few studies to consider children and TYA together over an extended time period and uniquely able to account for the effects of treatment modality, we observed an improvement in survival rates over time, with better survival in patients diagnosed after 2000 compared to those diagnosed in the 1990s. This statistically significant difference was only evident after adjustment for treatment. This finding reflects the timing of the changes in treatment patterns with the introduction of reduced dose radiation therapy and adjuvant chemotherapy (23).

We compared our survival rates to those from other international studies and found childhood medulloblastoma rates are similar to those in France (16) and Sweden (15) but are slightly lower than those in Germany (18). It is difficult to directly compare our CNS PNET rates as we included medulloepithelioma in our grouping which have particularly poor outcomes. International comparisons of CNS PNET are difficult due to differences in diagnostic procedures. No studies looked specifically at these subgroups in 15-24 years olds. Data from the US between 2001 and 2006 have shown that survival rates for medulloblastoma and CNS PNET were similar in children aged 1-9 years and adolescents

aged 10-19 years (17). In our study we did not find a difference in survival between the TYA age group and children aged 5-9 years. We did however observe a doubling of the risk of death for those aged under 5 years, consistent with other studies (3, 5, 15-19, 31) due to treatment strategies for infants and young children that defer or avoid radiation (7).

Notable strengths of our study include detailed data on patient characteristics particularly treatment received allowing us to adjust for patient case-mix. The main limitation of this study is the lack of information on molecular status of the tumours. Although distinct subgroups of medulloblastoma and CNS PNET have been established (7-13), these subgroups are not as yet classified as separate entities according to WHO or the ICCC-3. The recent progress in classification should lead to new biomarkers that can be used in clinical practice to improve risk stratification and adapt existing and new treatments to each patient (33, 34).

In conclusion, we found a decreasing incidence trend for medulloblastoma and differences in survival between medulloblastoma and CNS PNET which appeared within the first year post diagnosis leading to poorer outcomes for children and young adults diagnosed with CNS PNET. The risk of death was lower for patients diagnosed after 2000, and was highest in infants and young children, although there were no survival differences for TYA compared to children aged 5-9 years or by gender.

Conflict of Interest Statement

None declared

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Table and figure title and footnotes

Table 1: Patient characteristics and age standardised incidence rates (ASR)

	Medulloblastoma		CNS PNET		All CNS embryonal tumours*	
Characteristic	**n (%)**	**ASR (95%CI)**	**n (%)**	**ASR (95%CI)**	**n (%)**	**ASR (95%CI)**
Total	197	3.8 (3.3, 4.3)	58	1.5 (1.2, 1.9)	277	5.3 (4.7, 6.0)
Gender						
Male	119 (60%)	4.5 (3.7, 5.3)	36 (62%)	1.9 (1.4, 2.4)	169 (61%)	6.4 (5.4, 7.4)
Female	78 (40%)	3.1 (2.4, 3.8)	22 (38%)	1.2 (0.8, 1.6)	108 (39%)	4.3 (3.5, 5.1)
Male:Female ratio	1.5		1.6		1.6	
Age group						
0-4 years	65 (33%)	-	20 (35%)	-	99 (36%)	-
5-9 years	79(40%)	-	15 (26%)	-	98 (35%)	-
10-14 years	36 (18%)	-	8 (14%)	-	47 (17%)	-
15-19 years	12 (6%)	-	8 (14%)	-	21 (8%)	-
20-24 years	5 (3%)	-	7 (12%)	-	12 (4%)	-
Period of diagnosis						
1990-1999	88 (45%)	4.3 (3.4, 5.2)	28 (48%)	1.4 (0.9, 1.9)	117 (42%)	5.6 (4.6, 6.7)
2000-2013	109 (55%)	3.5 (2.8, 4.1)	30 (52%)	1.7 (1.2, 2.1)	160 (58%)	5.1 (4.3, 6.0)
Treatment						
Surgery, radiotherapy and chemotherapy	104 (53%)		20 (34%)		130 (47%)	
Surgery alone	19 (10%)		12 (21%)		35 (13%)	
Surgery and radiotherapy	19 (10%)		5 (9%)		24 (9%)	
Surgery and chemotherapy	36 (18%)		12 (21%)		58 (21%)	
Other treatment	11 (6%)		6 (10%)		18 (7%)	
No treatment recorded	8 (4%)		3 (5%)		12 (4%)	

Footnote: ASR = Directly age standardised incidence rate, adjusted to World standard population, per 1,000,000 population
* All CNS Embryonal includes medulloblastoma (n=197), CNS PNET (n=58) and Atypical tertoid/rhabdoid tumours (n=22)

Table 2: One, two, five and ten year Kaplan-Meier overall survival estimates by diagnostic sub group, period of diagnosis and age group.

	% survival (95% CI)			
Diagnostic subgroup	**1 year**	**2 year**	**5 year**	**10 year**
All Embryonal				
All years	76 (71, 81)	63 (57, 68)	54 (48, 60)	45 (39, 52)
1990-1999	73 (64, 80)	59 (50, 67)	50 (40, 58)	41 (32, 50)
2000-2013	79 (72, 85)	66 (58, 72)	58 (49, 65)	49 (40, 57)
Age group				
0-14 years	74 (68, 79)	62 (55, 68)	54 (47, 60)	46 (39, 52)
15-24 years	91 (74, 97)	69 (50, 82)	59 (40, 74)	42 (22, 61)
Medulloblastoma				
All years	83 (77, 87)	72 (65, 78)	64 (56, 70)	55 (47, 62)
1990-1999	77 (67, 85)	64 (53, 73)	55 (44, 64)	47 (63, 57)
2000-2013	87 (79, 92)	78 (69, 85)	71 (61, 79)	61 (50, 70)
Age group				
0-14 years	82 (76, 87)	71 (64, 77)	63 (55, 70)	54 (46, 61)
15-24 years	88 (61, 97)	76 (49, 90)	70 (41, 86)	56 (23, 79)
CNS PNET				
All years	64 (50, 75)	46 (33, 58)	33 (21, 46)	23 (12, 35)
1990-1999	57 (37, 73)	46 (28, 63)	36 (19, 53)	25 (11, 42)
2000-2013	70 (50, 83)	46 (27, 62)	30 (15, 48)	15 (2, 43)
Age group				
0-14 years	53 (38, 67)	39 (25, 53)	27 (15, 41)	19 (8, 34)
15-24 years	93 (61, 99)	66 (36, 84)	51 (24, 73)	34 (11, 59)

Footnote: PNET = Primitive neuroectodermal tumour

Table 3: Multivariable Cox regression model results

Characteristic	Adjusted HR†	95%CI
Diagnostic subgroup		
Medulloblastoma	1	-
CNS PNET	2.4	(1.6, 3.7)
Gender		
Male	1	-
Female	1.1	(0.8, 1.6)
Age group		
0-4 years	2.1	(1.3, 3.3)
5-9 years	1	-
10-14 years	1.3	(0.8, 2.2)
15-19 years	0.7	(0.3, 1.7)
20-24 years	1.3	(0.6, 3.2)
Period of diagnosis		
1990-1999	1	-
2000-2013	0.63	(0.43, 0.92)
Townsend deprivation	1.05	(1.0, 1.1)

Footnote: HR = hazard ratio and 95% confidence interval (CI)
† Model adjusted for all variables in table and treatment

Table 4: Comparison of incidence and survival estimates with published literature

Study	Region	Diagnosis period	Age range	Diagnostic subgroup	Incidence ASR	Survival 1 year (%)	Survival 5 year (%)
This publication	North of England	1990-2013	0-24 years	Medulloblastoma	3.8	83	64
				CNS PNET†	1.5	64	33
			0-14 years	Medulloblastoma	5.5	82	63
				CNS PNET†	2.0	53	27
			15-24 years	Medulloblastoma	0.7	88	70
				CNS PNET†	0.7	93	51
Tulla et al, 2015 (18)	Germany	1991-2012	0-14 years	Medulloblastoma	5.4	-	69
				CNS PNET	1.3	-	38
Desandes et al, 2014 (16)	France	2000-2008	0-14 years	Medulloblastoma	5.4	87	65
				CNS PNET	1.1	58	34
Smoll, 2012 (17)	US (SEER)	2001-2006	<1 year	Medulloblastoma	-	52	42
			1-9 years	Medulloblastoma	-	90	72
			10-19 years	Medulloblastoma	-	92	69
			<1 year	CNS PNET	-	31	14
			1-9 years	CNS PNET	-	88	64
			10-19 years	CNS PNET	-	94	57
Lannering et al, 2009 (15)	Sweden	1984-2005	0-14 years	Medulloblastoma	6.4	-	63
				CNS PNET	1.6	-	47
Arora et al, 2008 (6)	England	1995-2003	0-14 years	Medulloblastoma	4.9	-	-
				CNS PNET	1.7	-	-
			15-24 years	Medulloblastoma	1.1	-	-
				CNS PNET	0.8	-	-
Stiller, 2007 (3)	Great Britain	1991-2000	0-14 years	Medulloblastoma	4.8	81	58
				CNS PNET	1.6	56	27

ASR = Directly age standardised incidence rate, adjusted to World standard population, per 1,000,000 population
† In our study CNS PNET includes medulloepithelioma

Figure 1: Map of the combined geographic region covered by the Yorkshire Specialist Register of Cancer in Children and Young People and the Northern Region Young Person's Malignant Disease Register

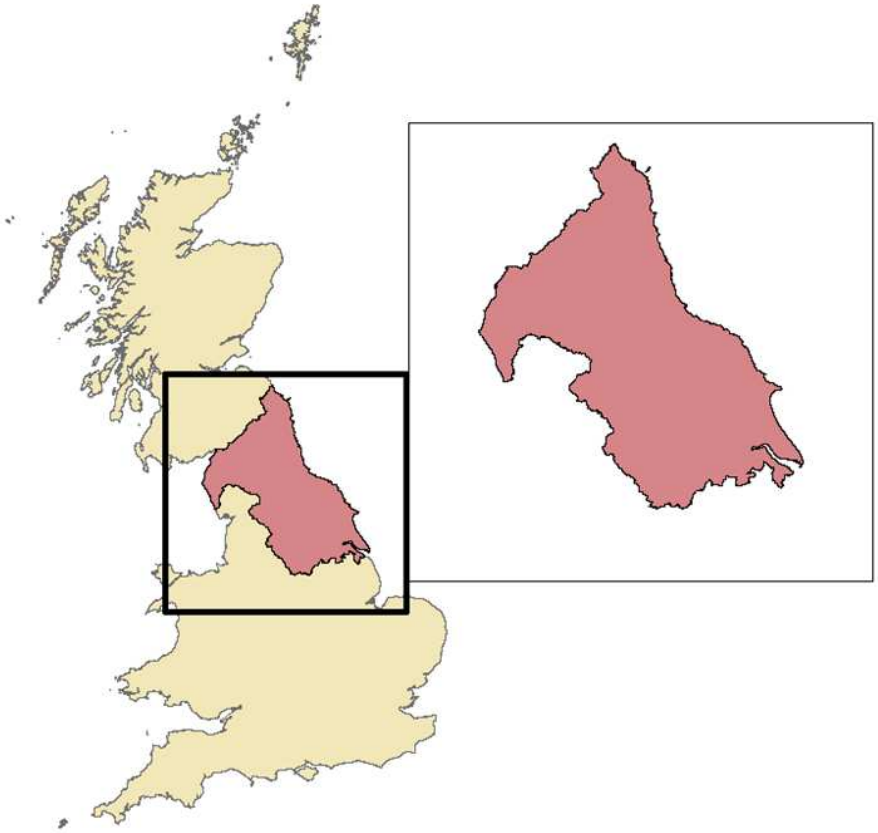
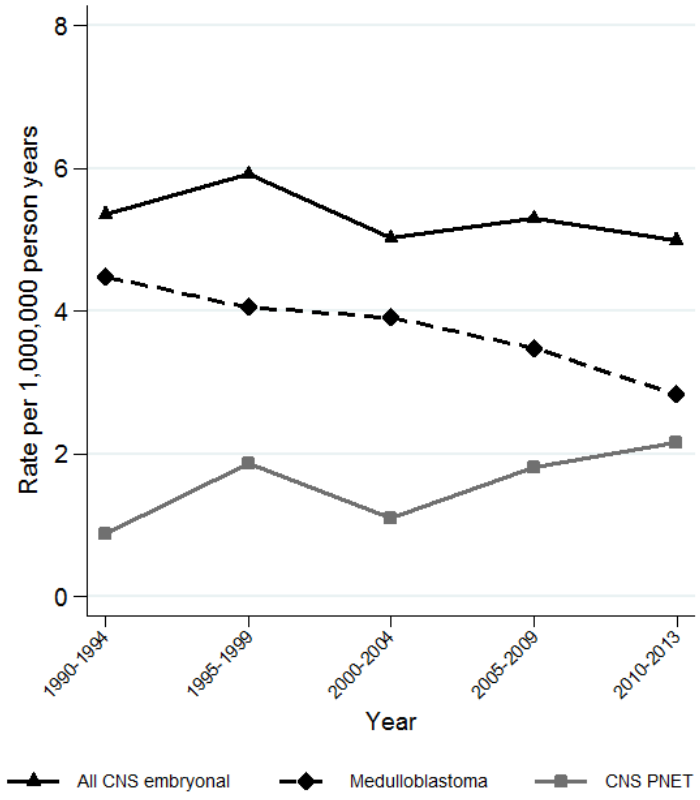
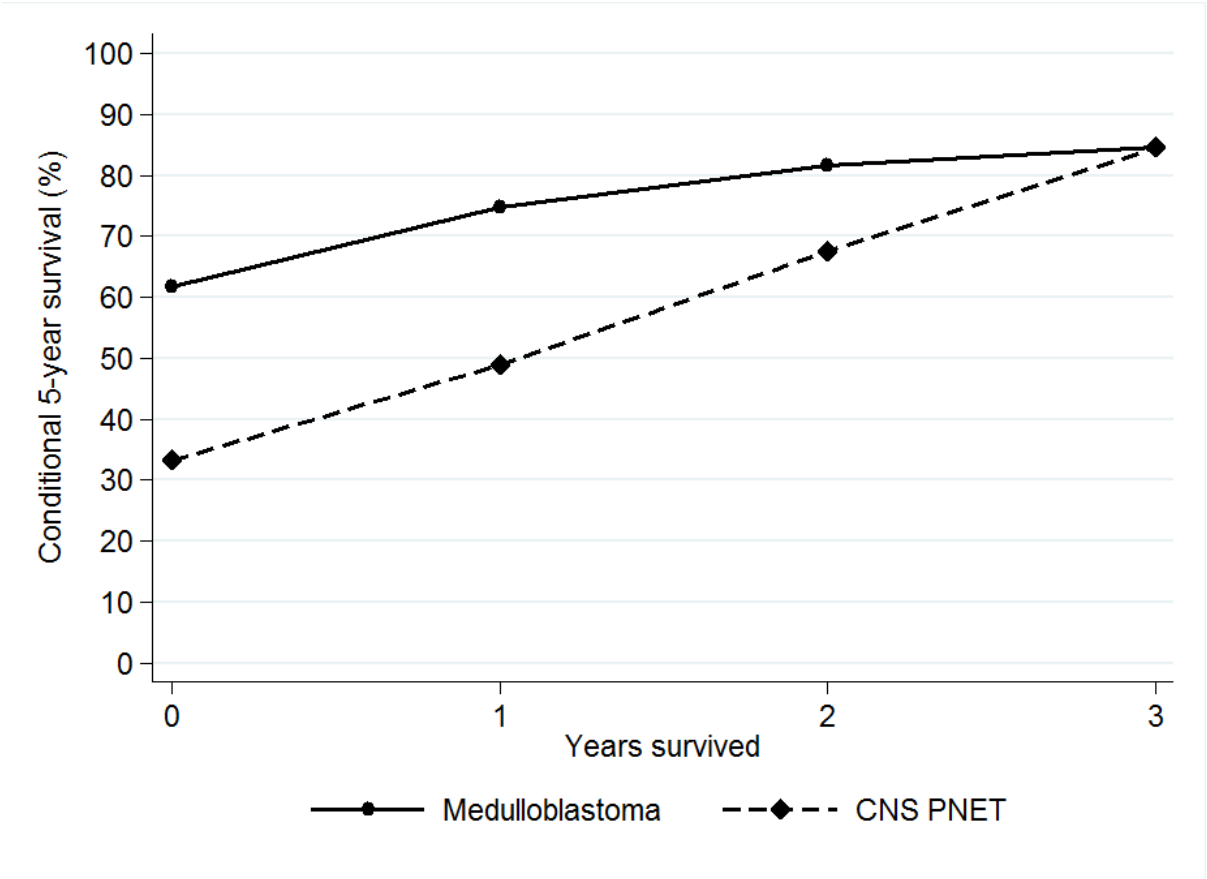


Figure 2: Trends in directly age-standardised (world population, per 1,000,000 person-years) incidence rates for Medulloblastoma and CNS PNET in the north of England aged 0-24 years, 1990-2013



Footnote: PNET = Primitive neuroectodermal tumour

Figure 3: Conditional 5- year survival at 1, 2 and 3 years after diagnosis, by diagnostic subgroup, CNS embryonal tumours diagnosed in the north of England aged 0-24 years, 1990-2013



Footnote: PNET = Primitive neuroectodermal tumour