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Analysis of patients with supratentorial primitive neuro-ectodermal tumours entered into the SIOP/UKCCSG PNET 3 study

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ABSTRACT

The SIOP PNET 3 study was designed to determine whether 10 weeks of moderately intensive chemotherapy given after surgery and before radiotherapy (RT) would improve the outcome for patients with primitive neuroectodermal tumours (PNETs) compared with RT alone.

Patients with a histological diagnosis of supratentorial PNET (StPNET) and no radiological evidence of metastatic disease were initially eligible for randomisation to either chemotherapy followed by craniospinal RT 35 Gy in 21 fractions with a boost of 20 Gy in 12 fractions to the primary site, or RT alone. In respect of the increasing recognition that StPNET were high-risk tumours, randomisation for this group closed in November 1999. This analysis includes both randomised and non-randomised patients with StPNET entered into the study database.

Sixty-eight patients aged 2.9–16.6 years (median 6.5 years) were included in the analysis (chemotherapy + RT: 44, RT alone: 24). Fifty-four patients (79%) had a non-pineal and 14 (21%) a pineal site. At a median follow-up of 7.4 years, for all patients overall survival (OS) at 3 and 5 years was 54.4% and 48.3%, respectively. Event-free survival (EFS) at 3 and 5 years was 50.0% and 47.0%, respectively. There was no statistically significant difference in OS or EFS according to treatment received. OS ($P = 0.05$) and EFS ($P = 0.03$) were significantly better for patients with pineal primary sites. EFS for pineal tumours were 92.9% at 3 years and 71.4% at 5 years and for non-pineal primaries 40.7% at 3 years and 40.7% at 5 years. This study confirmed the relatively good survival for non-metastatic pineal PNETs but poor survival of non-pineal StPNETs. There was no evidence that pre-radiation chemotherapy improved outlook. Future treatment programs should be directed at the particular natural history of these tumours, to further define prognostic factors and to explore further biological characteristics.

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1. Introduction

Primitive neuroectodermal tumours (PNETs) are a group of malignant embryonal tumours of unknown aetiology accounting for approximately 20% of central nervous system (CNS) neoplasms in childhood. A histopathological classification of CNS PNETs was proposed by Rorke in 1983,[1] in recognition of the morphological and immunohistochemical characteristics shared by cerebellar PNETs (medulloblastomas) and supratentorial PNETs (StPNETs). These tumours also share common clinical features such as a propensity to leptomeningeal dissemination via the CSF pathways and sensitivity to both radiotherapy (RT) and chemotherapy. StPNETs comprise approximately 2–3% of CNS tumours in childhood.[2,3] Most arise in the cerebral hemispheres with a minority occurring in the pineal region (pineoblastomas).

Until the late 1980s, standard management of both medulloblastoma and StPNETs was maximum surgical resection followed by craniospinal RT (CSRT) to a dose of 35–36 Gy with a 'boost' of around 20 Gy to the primary tumour site. It is clear that using this so-called conventional treatment, StPNETs have a worse prognosis than medulloblastoma with various series reporting a 20–40% survival.[4–6] Very young patients appear to have a particularly poor prognosis possibly as a result of underutilization of adequate doses of RT, a higher rate of metastatic disease or adverse biological features.

There have been no large group-wide studies specifically for StPNET; instead they are generally treated with protocols designed for children with high-risk medulloblastoma. Similarly, prognostic factors for StPNETs are poorly defined although the larger series of patients with StPNETs such as those from the CCG-921[7] and the HIT 91[6] studies show an improved survival for pineal compared with non-pineal StPNETs.

Over the last 30 years the International Society for Paediatric Oncology (SIOP) has conducted a series of randomised controlled trials for medulloblastoma/PNET particularly addressing the role of adjuvant chemotherapy. There are theoretical advantages for giving chemotherapy before RT. The time between surgery and RT is when the tumour has its maximal blood supply and when the blood/brain barrier is maximally disrupted. The delivery of intensive chemotherapy may be more difficult after CSRT because of myelosuppression.

The central question for the SIOP PNET 3 study (from April 1992 to August 2000) was whether the use of intensive pre-RT chemotherapy would improve the outcome for patients with non-metastatic medulloblastoma although those with StPNET were eligible for entry and randomisation into the study.

The results of PNET-3 study for both M0–1 and M2–3 medulloblastoma have been reported.[8,9] This paper reports the results of an analysis of patients with StPNETs entered into the study including the assessment of prognostic factors on survival.

2. Patients and methods

2.1. Selection criteria

Patients eligible for randomisation were those aged 3 and 16 years inclusive with a histologically proven institutional diagnosis of StPNET. Patients should have had no radiological evidence of metastases. As for patients with medulloblastoma, it was recommended that StPNET patients with radiological evidence of leptomeningeal metastases at diagnosis (M2–3) should receive pre-RT chemotherapy.

In respect of the increasing recognition that StPNET were high-risk tumours, randomisation for this group closed in November 1999. Ethical approval for the study was acceptable at contemporaneous standards of the early 1990s.

2.2. Pre-treatment investigations

Patients should have had a spinal MR or myelogram before, or within two weeks after surgery, and a cranial CT or MR scan within 72 h after surgery. The study design did not include central radiological review and tumour size was assessed from institutional reports of the pre-operative imaging.

CSF sampling although recommended was not mandatory, and was inconsistently carried out throughout the study.

2.3. Surgical treatment

The extent of resection was assessed on the basis of institutional reports of post-operative imaging for 59 (87%) patients and by the neurosurgical assessment when an imaging report was not available for 9 (13%) patients and was classified as being either a total, or less than total resection.

2.4. Trial randomisation

Patients with non-metastatic tumours (M0–1) were randomised to treatment with either chemotherapy followed by RT, or RT alone. Randomization was stratified on the basis of extent of tumour resection, treating centre and age grouping (3–7, 8–11 and 12–16 years).

2.5. Chemotherapy protocol

Chemotherapy was intended to commence within 28 days of surgery and consisted of four cycles of treatment at three-weekly intervals using alternating cycles of:

Vincristine 1.5 mg/m^2, days 1, 8, 15.
Etoposide 100 mg/m^2, days 1, 2, 3.
Carboplatin 500 mg/m^2, days 1, 2.

and

Vincristine 1.5 mg/m^2, days 1, 8, 15 (day 1 only for final course).
Etoposide 100 mg/m^2, days 1, 2, 3.
Cyclophosphamide 1.5 g/m^2, day 1.

Count recovery (neutrophils $> 1.0 \times 10^9$/L, platelets $> 100 \times 10^9$/L) should have occurred before each cycle of chemotherapy.

2.6. Radiotherapy protocol

RT commenced with CSRT and was given in daily fractions, five days per week. The CSRT dose was 35 Gy in 21 daily

fractions of 1.67 Gy and was followed by RT to the primary tumour, 20 Gy in 12 fractions of 1.67 Gy (55 Gy total dose to primary tumour).

For patients treated by RT alone, it was intended that RT should commence within 4 weeks of surgery. For patients treated by chemotherapy, RT should have started as soon as possible after the last course of chemotherapy, following count recovery.

A full description of RT used for the patients in this study including RT quality control and an analysis of RT parameters in relation to outcome will be the subject of a future report.

2.7. *Central pathology review*

Central pathological review was undertaken on 50 tumours by two neuropathologists (D.E. and J.I.), using the World Health Organisation (WHO) classification of CNS tumours.[10]

2.8. *Statistical methods*

The analysis was performed in February 2004. Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method.[11] Patients alive were censored at date of last follow up. Survival curves were produced and log-rank tests performed to compare OS and EFS according to various prognostic factors. Confidence intervals for OS and EFS were calculated using Greenwood's formula.

All prognostic variables observed were tested individually in a Cox proportional hazards model using the change in log likelihood from the null model.[12] Those shown to be significant were entered into a multivariate model in a stepwise procedure[13] taking a P value of 0.05 to enter and 0.05 to be removed.

3. Results

Of the 511 on the PNET 3 database, 78 patients were registered with StPNETs of which 68 patients were considered eligible for analysis. Ten patients were ineligible for analysis for the following reasons: institutional diagnosis other than PNET (7), no histological diagnosis of PNET (1), consent for data collection withdrawn (1), and post-operative death (1). Of the 68 patients, 61 were from UK centres, four from Spain and one each from Norway, Switzerland and the Netherlands.

3.1. *Patient details*

As shown in Table 1, there were 39 (57%) males and 29 (43%) females, aged 2.9–16.6 years (median 6.5 years). 54 patients (79%) had a non-pineal and 14 (21%) a pineal site. 31 patients (46%) had a complete resection and 28 (41%) an incomplete resection. In 8 (12%) cases, including 5 of the 14 patients with pineal tumours, the tumour was considered inoperable with the extent of resection being unknown for one patient. A pre-operative diagnostic imaging report was available for 47 patients. The maximal tumour diameter was $\leqslant$5 cm in 25 (53%) patients and >5 cm in 22 (47%). 14 (21%) of the total of 68 patients had no evidence of metastatic disease (M0) at diagnosis either on CSF analysis or spinal imaging. Diagnostic lumbar puncture was not always performed. In this respect, 14 (21%) patients who were completely staged had M0 disease. 39 patients (57%) are classified as having M 0/1 disease, where CSF was not analysed but where there was no radiological evidence of cranial or spinal metastases. Two patients had confirmed M1 status, 1 M2 disease and 7 (10%) M3 disease. One patient had bony metastases (M4) and in 4 cases the M-status was unknown.

Table 1 – Patient demographics, tumour site and extent of resection

	Chemotherapy + RT (%)	RT alone (%)	Total (%)
Number	44 (64.7)	24 (35.2)	68
Gender			
Male	26 (38.2)	13 (19.1)	39 (57.4)
Female	18 (26.5)	11 (16.2)	29 (42.7)
Age group/years			
3–7	33 (48.5)	11 (16.2)	44 (64.7)
8–11	6 (8.8)	7 (10.3)	13 (19.1)
12–16	5 (7.4)	6 (8.8)	11 (16.2)
Median age at diagnosis (years)	6.0	8.6	7.3
Age range at diagnosis (years)	2.9–16.6	3.5–15.0	2.9–16.6
Site			
Non-pineal	34 (50.0)	20 (29.4)	54 (79.4)
Pineal total	10 (14.7)	4 (5.9)	14 (20.6)
Extent of resection			
Total	21 (30.9)	10 (14.7)	31 (45.6)
<Total	15 (22.1)	13 (19.1)	28 (41.2)
Inoperable	7 (10.3)	1 (1.5)	8 (11.8)
Unknown	1 (1.5)	0	1 (1.5)
M-status			
M0	10	4	14
M0/1	22	17	39
M1	2	0	2
M2	1	0	1
M3	5	2	7
M4	0	1	1
Unknown	4	0	4
Tumour size			
$\leqslant$5 cm	15	10	25
>5 cm	15	7	22
Unknown	14	7	21

Table 2 shows the location for non-pineal StPNETs based on imaging at diagnosis confirming that StPNETs may occur throughout the supratentorial region of the brain, with most in either or both of the frontal or parietal lobes.

3.2. *Central pathology review*

Fifty (74%) cases were subject to central histological review. A diagnosis of StPNET was confirmed for 44 (88%) of these. Of the 6 patients with a review diagnosis other than StPNET, 2 had a diagnosis of atypical teratoid/rhabdoid tumour, 2 of anaplastic astrocytoma and 1 each of anaplastic oligodendroglioma and anaplastic ependymoma. All 6 were in a supratentorial location.

Table 2 – Location of non-pineal StPNETs

Subsite	Number
Frontal	11
Parietal	10
Temporal	4
Temporo-parietal	5
Parieto-occipital	6
Fronto-parietal	9
Third ventricular	1
Intraventricular	1
Basal ganglia	1
Suprasellar	1
Fronto-temporal	2
Thalamus	1
Not known	2
Total	54

3.3. *Treatment*

Of 68 eligible patients, only 13 (6 pre-RT chemotherapy, 7 RT alone) were randomised, too few for a meaningful comparison of the effect of chemotherapy. Of the non-randomised patients, 38 (69%) received chemotherapy followed by RT, and 17 (31%) RT alone (Table 1). There was no statistically significant difference in treatment received according to extent of resection or M-status.

3.4. *Survival*

At a median follow-up of 7.4 years (range 0.2–10.8 years), 36 patients have died and 32 patients were still alive at last follow-up. For all patients, the 3-year OS was 54.4% (95% confidence interval [CI]: 42.6–66.2%) and the 5-year OS was 48.3% (95% CI: 36.4–60.2%) (Fig. 1). The 3-year EFS was 50.0% (95% CI: 38.1–61.9%) and the 5-year EFS was 47.0% (95% CI: 35.1–58.9) (Fig. 1).

For the 44 patients with a diagnosis of StPNET confirmed on central histological review, the 3-year and 5-year OS was 61.4% (95% CI: 47.0–75.8) and 54.5% (95% CI: 9.7–69.2), respectively, and the 3-year and 5-year EFS was 56.8% (95% CI: 42.2–71.5) and 52.3% (95% CI: 37.5–67.0), respectively. The differences between OS and EFS for these patients are not statistically significant as for the whole cohort of 68 patients.

3.5. *Survival according to treatment received*

For 44 patients receiving pre-RT chemotherapy, 3-year and 5-year OS were 52.3% (95% CI: 37.5–67.0) and 45.0% (95% CI: 30.2–59.8) and for 24 patients treated by RT alone, 58.3% (95% CI: 38.6–78.1) and 54.2% (95% CI: 34.2–74.1), respectively. The 3-year and 5-year EFS for those treated by pre-RT chemotherapy patients were 50.0% (95% CI: 35.2–64.8) and 45.2% (95% CI: 30.5–60.0), respectively, and 50.0% (95% CI: 30.0–70.0) for RT alone (Fig. 2). There was thus no statistically significant difference in OS or EFS according to treatment received.

3.6. *Survival according to primary site*

Details of the 14 patients with pineal disease including treatment received, metastatic status, extent of resection and survival are shown in Table 3. OS ($P = 0.05$) and EFS ($P = 0.03$) were statistically significantly better for patients with pineal primary sites than for those with non-pineal sites. The 3-year and 5-year OS for pineal tumours were 92.9% (95% CI: 79.4–100) and 71.4% (95% CI: 47.8–95.1), respectively, whereas the 3-year and 5-year OS for non-pineal tumours were 44.4% (95% CI: 31.2–57.7) and 42.5% (95% CI: 29.3–55.7), respectively. The 3-year and 5-year EFS for pineal tumours (Fig. 3) were 92.9% (95% CI: 79.4–100) and 71.4% (95% CI: 47.8–95.1), respectively, whereas the 3-year and 5-year EFS for non-pineal tumours were 40.7% (95% CI: 27.6–53.8) and 40.7% (95% CI: 27.6–53.8), respectively. The apparent survival advantage for patients with pineal tumours only applied to those with M0 or M0/1disease of which 7 of 8 patients are alive and disease free. On the other hand, of the 6 patients with metastatic pineal tumours there are only two survivors, one with M1 and one with M3 disease.

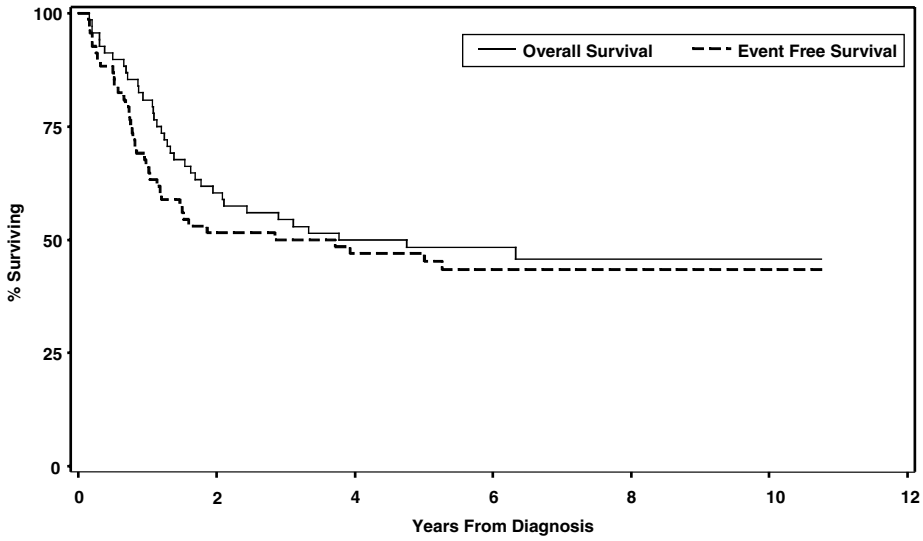

Fig. 1 – Overall and event-free survival – all patients.

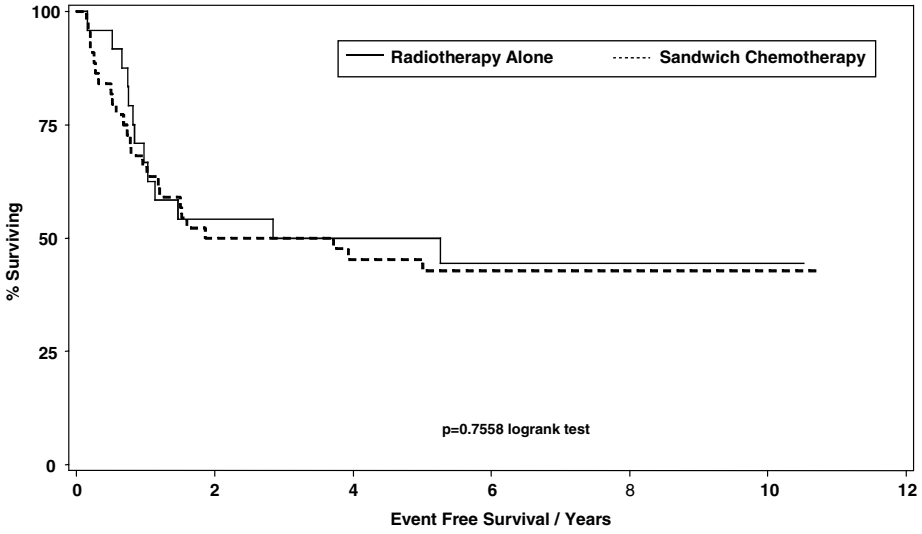

Fig. 2 – Event-free survival according to treatment received.

Table 3 – Details of patients with pineal PNETs

Patient	Treatment	M-status	Extent of resection	Status
1	Sandwich chemotherapy	M0/1	Inoperable	Alive
2	Sandwich chemotherapy	M0	Inoperable	Alive
3	Sandwich chemotherapy	M0/1	Inoperable	Alive
4	Sandwich chemotherapy	M3	Less than total	Alive
5	Sandwich chemotherapy	M0/1	Less than total	Dead
6	Sandwich chemotherapy	M0	Total	Alive
7	Sandwich chemotherapy	M3	Less than total	Dead
8	Sandwich chemotherapy	M0/1	Total	Alive
9	Radiotherapy alone	M3	Inoperable	Dead
10	Sandwich chemotherapy	M3	Less than total	Dead
11	Radiotherapy alone	M0/1	Total	Alive
12	Radiotherapy alone	M0	Less than total	Alive
13	Sandwich chemotherapy	M1	Inoperable	Alive
14	Radiotherapy alone	M3	Less than total	Dead

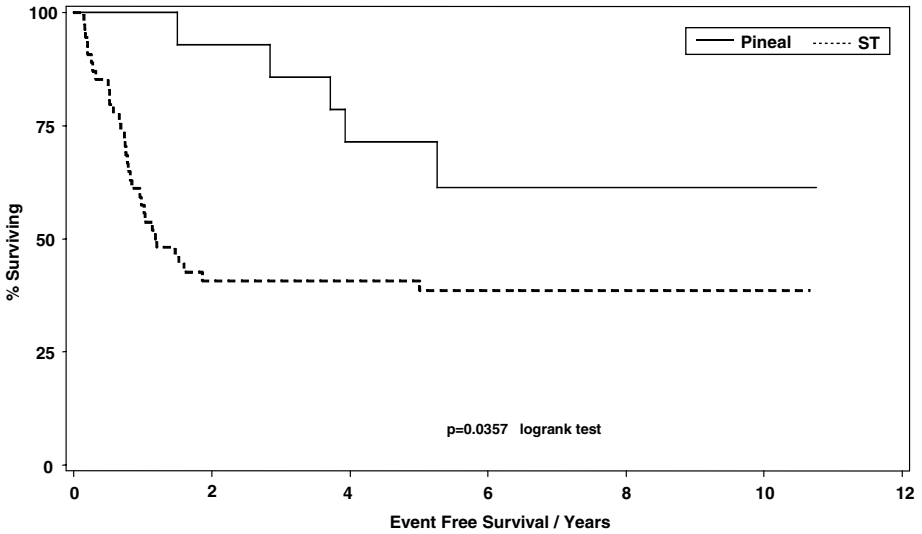

Fig. 3 – Event-free survival according to primary tumour site.

3.7. Survival according to metastatic status

Data on M-status was available for 64 patients who were grouped by Chang stages M0, M0/1 or M1+ (M1, M2, M3, M4). Patients with confirmed M0 status had a better OS and EFS (5-year OS and EFS, 64.3%) as compared with those with M0/1 status (5 year OS, 48.7%, EFS 46.2%) or M1+ disease (5-year OS, 36.4%, EFS 36.4%). For all patients, these differences in OS and EFS were, however, not statistically significantly different. As described above, four of the six patients with metastatic pineal disease died.

3.8. Survival according to tumour size

Data on tumour size was available for 47/68 (69.1%) patients. Those with a tumour size >5 cm had a significantly worse OS ($P = 0.01$) and EFS ($P = 0.03$) compared to those with a tumour size of $\leqslant$5 cm. An analysis of outcome related to tumour size limited to patients with non-pineal primaries suggested that non-pineal patients with large tumours had poorer overall survival than non-pineal patients with smaller tumours. The difference was not statistically significant. Data in respect to tumour size must, however, be treated with caution as central radiological review was not undertaken and there was no standard radiological technique used in this assessment.

3.9. Multivariate analysis

Results from the univariate Cox proportional hazards models for OS (Table 4) and EFS show similar results. Tumour size and site were found to have a statistically significant effect on overall survival. However, in a multivariate Cox model, site was no longer statistically significant in the presence of tumour size (Table 5a and b). Although site is not statistically significant in the multivariate model, as shown in Table 5a, there is an increased risk of death for those with supratentorial site compared to pineal site (HR = 1.74, 95% CI: 0.63–4.77) and an even greater increased risk for those with tumour size >5 cm (HR = 2.63, 95% CI: 0.93–7.45) or missing data for tumour size (HR = 5.80, 95% CI: 2.24–14.96). This is also true for EFS where in the multivariate model there is an increased risk of an event for those with supratentorial site compared to pineal site (HR = 2.06, 95% CI: 0.76–5.59) and for those with tumour size >5 cm (HR = 2.06, 95% CI: 0.77–5.51) or missing data for tumour size (HR = 5.45, 95% CI: 2.22–13.37).

3.10. Survival according to other factors

There was no statistically significant difference in OS or EFS according to gender or age grouping, although patients aged 12–16 generally had better OS and EFS than patients aged 3–11 and it is possible that with a larger number of patients this may have been statistically significant. In addition, there was no statistically significant difference in OS or EFS for patients who had a complete resection compared with those who had an incomplete resection. This observation also applies when metastatic patients are excluded.

Table 4 – Univariate Cox models for overall survival

Variable	Parameter Estimate	Standard Error	χ^2	P	Hazard ratio
Treatment					
Pre-RT chemotherapy	0.225	0.354	0.40	0.525	1.25
RT alone	0				1.00
Sex					
Male	0.082	0.338	0.06	0.892	1.09
Female	0				1.00
Age					
3–7 years	1.084	0.610	3.15	0.076	2.96
8–11 years	1.014	0.691	2.15	0.142	2.76
12–16 years	0				1.00
Site					
ST	0.902	0.484	3.47	0.062	2.46
Pineal	0				1.00
Extent of tumour resection					
Inoperable	0.168	0.517	0.11	0.745	1.18
<Total	0.151	0.360	0.18	0.675	1.16
Total	0				1.00
Tumour size					
Missing	1.866	0.476	15.40	<0.001	6.47
>5 cm	1.192	0.502	5.65	0.018	3.29
<5 cm	0				1.00
Residual tumour					
Missing	0.487	0.450	1.17	0.279	1.63
No	0.141	0.392	0.13	0.719	1.15
Yes	0				1.00
M-status					
M1/2/3/4	0.819	0.540	2.30	0.130	2.27
M0/1	0.450	0.500	0.81	0.368	1.57
M0	0				1.00

Table 5 – Multivariate Cox models

Variable	Parameter estimate	Standard error	χ^2	P	Hazard ratio
(a) Overall survival					
Site					
ST	0.551	0.516	1.14	0.285	1.74
Pineal	0				1.00
Tumour size					
Missing	1.757	0.484	13.15	<0.001	5.80
>5 cm	0.967	0.531	3.31	0.069	2.63
<5 cm	0				1.00
(b) Event-free survival					
Site					
ST	0.721	0.510	2.00	0.158	2.06
Pineal	0				1.00
Tumour size					
Missing	1.695	0.458	13.71	<0.001	5.45
>5 cm	0.722	0.502	2.07	0.151	2.06
<5 cm	0				1.00

Table 6 – Maximum toxicity grade experienced for each of four courses of chemotherapy (WHO Grading System)

	Grade					Unknown
	0	1	2	3	4	
Anaemia	0	1	7	14[a]	21[b]	1
Neutropaenia	1	0	2	1[c]	39[d]	1
Thrombocytopaenia	2	0	1	4[e]	36[f]	1
Gastro-intestinal	7	9	11	7	7	3
Renal	30	8	3	0	1	2

a 8.0–10.4 g/dL.
b <8.0 g/dL.
c $0.2–0.5 \times 10^9$/L.
d $<0.2 \times 10^9$/L.
e $25–49 \times 10^9$/L.
f $<25 \times 10^9$/L.

3.11. *Chemotherapy*

Chemotherapy was generally well tolerated. Of the 44 patents receiving pre-RT chemotherapy, 35 received at least the four courses as recommended in the protocol, with three of these patients receiving more than four courses. Only three patients received one or two courses. The median duration of chemotherapy for patients receiving all four courses ($n = 35$) was 75 days (range = 56–94 days). For all courses, the majority (27/44) received 100% of the recommended doses and there is no significant difference in survival for patients not receiving the full dose of chemotherapy.

Toxicity of the chemotherapy is given in Table 6, which shows the maximum toxicity experienced for each course of treatment. The WHO system, generally accepted when this study was designed, was used to grade toxicity.

3.12. *Pattern of relapse*

Of the 35 patients who relapsed, the majority (82.9%) had a relapse that included the local site. 24 (68.6%) patients relapsed only locally. Five patients (14.2%) had a combined local and distant relapse (3 local and brain metastases, 1 local and spinal metastases, 1 local and both brain and spinal metastases). Six patients (17.1%) relapsed only distally (2 spinal disease, 2 metastatic brain disease, 2 both brain and spinal metastatic disease). It is of note, however, that some patients did not have full neuraxis imaging at the time of relapse and in this respect the number and proportion of metastatic relapses may have been under-reported. Only 2 patients were alive following relapse. Of the 33 patients who relapsed and died, 29 died within a year of diagnosis.

4. Discussion

This series of 68 patients with StPNETs is the largest yet reported. Other comparatively large series come from the German HIT 88/89 and 91 trials[6] and from the CCG-921 study[7] with 64 and 55 patients, respectively. We have reported the outcome for the whole group rather than those with concordant histology on central review, as this reflects clinical reality and at the time this study was being undertaken it was not possible to obtain central pathology review on all patients in this international study. It is of note that the analysis of the CCG-921 study included patients with diagnoses other than StPNET on central review[7] and that in the report of the HIT 88/89 and 91 trials only 76% of patients had central pathology review. We do, however, feel that central pathology review is mandatory for current or future studies.

In the HIT 88/89 study, patients were treated with pre-RT chemotherapy (ifosfamide, etoposide, methotrexate, cisplatin and cytarabine) whereas in the HIT 91 studies, patients were randomised between this therapy and immediate RT followed by eight courses of 'maintenance' chemotherapy with cisplatin, CCNU and vincristine. 3-year progression-free survival (PFS) was 39%. In the CCG-921 study for high-risk PNETs, patients were randomised to receive CSRT followed by eight cycles of CCNU, vincristine and prednisolone or two cycles of 8-in-1 chemotherapy followed by CSRT and then eight further cycles of 8-in-1. 3-year PFS was 45%. These survival figures and the 5-year EFS of 47% from the present study confirm the relatively poor outlook for StPNETs. However, because of the relatively small size of these studies, prognostic factors for StPNETs are unclear.

This study included far too few randomised patients to fully assess the impact of chemotherapy on outcome. However, considering the total population of patients with StPNET in this study, there was no apparent benefit for the fairly intensive pre-RT chemotherapy as compared to RT alone. This is in contrast to the improved EFS for patients with standard risk medulloblastoma treated on the PNET 3 trial with the same chemotherapy.[8] In both HIT 91 and CCG-921, neither chemotherapy arm in each study showed a benefit over the other arm. The PNET 3 study was not designed to determine the response rate of StPNETs to chemotherapy, but responses were observed in this study as in others such as from the pilot HIT 88/89 study.[5] Despite the incorporation of chemotherapy into all group-wide protocols for StPNETs, there remains insufficient evidence to demonstrate that adjuvant chemotherapy has a role in increasing survival.

Other studies have investigated myeloablative chemotherapy for both pineal and non-pineal StPNETs.[14,15] For example, Gururangan evaluated the usefulness of a treatment regimen that included high-dose chemotherapy with stem-cell rescue in patients with newly diagnosed pineoblastomas.[15] Six children and 6 adults (four with metastatic disease) were initially treated with surgery and induction chemotherapy. All but 2 patients underwent radiotherapy. At the time of reporting, 9 patients were alive and recurrence-free at a median of 62 months from diagnosis, including 3 patients with metastatic disease and 2 infants who did not receive radiotherapy. The 4-year PFS and OS were 69% and 71%, respectively.

The precise reasons for the low number of randomised patients with StPNET in the PNET 3 study are unclear. The study was perceived as being principally for patients with medulloblastoma. It is also likely that during the study it became increasingly clear that patients with StPNET had a worse prognosis than patients with medulloblastoma, and some clinicians may have thus been unwilling to randomise patients. This was formally recognised by the study committee in 1999 when randomisation was closed for patients with StPNET. In

retrospect, it appears inappropriate that patients with StPNET were included in the randomised component of the PNET 3 trial as the study is underpowered to answer the primary question for this group of patients. In the late 1980s, however, when this study was conceived, the recently introduced concept of PNET to include both medulloblastoma and StPNET had gained acceptance and it was assumed that the behaviour of PNETs at different sites would be similar.

Although the concept of PNETs has been generally accepted and is now included in the WHO classification of CNS tumours,[10] there is increasing evidence of differences in the molecular characterization of medulloblastoma and StPNETs. A recent gene expression study strongly suggests that StPNETs are molecularly distinct from medulloblastomas.[16] Further evidence from comparative genomic hybridisation studies has shown different profiles in StPNETs and medulloblastomas. Russo and colleagues noted that whereas medulloblastomas were most likely to exhibit gain of 17q, StPNETs were most likely to have loss of 14q or 19q, but not show gain of 17q 2.[17] Similarly, Nicholson et al. observed 3 StPNETs with loss of 3p in the absence of any imbalance involving chromosome 17.[18] It is probable that achieving significant advances in the diagnosis, prognosis and treatment of StPNETs will rely on extensive molecular characterisation of these tumours.

The present study and others have shown improved survival for pineal PNETs as compared to non-pineal StPNETs. In this study the 5-year EFS for pineal tumours was 71% as compared to 41% for non-pineal tumours. A significantly higher survival for pineal tumours was also noted in CCG-921[7] in which pineal PNET site was an independent prognostic factor with a 3-year PFS of 61% as compared to 33% for non-pineal tumours. A similar but statistically non-significant trend was seen in the HIT 88/89 and 91 series where the 3 year PFS for pineal tumours was 64% and for non-pineal PNETs was 34%.[6]

Suggested reasons for this include earlier presentation and smaller size at diagnosis due to pineal tumours presenting with CSF obstruction, or possibly biological differences including differences in response to treatment. In the present study, however, the prognostic significance of pineal site was lost in a multivariate analysis, although the importance of pineal site as an independent prognostic factor cannot be excluded, as only a relatively small number of pineal cases were included in this analysis. In this study, relapses of patients with non-pineal PNETs (nearly all within 2 years of diagnosis) appeared to be earlier that those in patients with pineal PNETs, in whom relapses occurred up to 5 years after diagnosis. Patient numbers are too small for a meaningful statistical analysis but this interesting observation should be investigated in future larger trials. Furthermore, the apparent survival advantage for patients with pineal tumours only applied to those with M0 or M0/1 disease of which 7 of 8 patients are alive and disease-free in contrast to the 6 patients with metastatic disease of whom there are only 2 survivors.

The effect of tumour size was shown to be the only statistically significant factor in a multivariate analysis. This observation requires investigation in future studies which should include, unlike in this study, central review of diagnostic MRI scans.

Other factors including age, presence of metastatic disease, extent of resection and presence of residual tumour on postoperative imaging were not shown to be of prognostic significance. It is of note that despite the predominant pattern of relapse being at the primary tumour site, that the degree of resection and the presence of residual disease has not been clearly shown to be a prognostic factor in the present study nor in the HIT study referred to above. In the CCG-921 trial, however, there was a trend toward better outcome for tumours with less than 1.5 cm^2 of residual disease, but this difference did not reach statistical significance, possibly because of the small the number of centrally reviewed patients.[19] In addition, this paper reported that larger pre-operative tumours were more likely to be associated with greater that 1.5 cm^2 residual tumour. A paucity of prognostic factors was also noted in the HIT study where the only statistically significant factor on univariate analysis was the presence of a major RT violation.

The predominant local pattern of relapse noted in this study is consistent with that reported by Hong et al. in an analysis of the patterns of failure for StPNETs treated on the CCG-921 study.[20] This pattern of relapse would indicate that local control is one of the major challenges in the treatment of StPNETs. Planning RT for StPNET presents several technical issues that may contribute to local failure. There may be concern about the long-term effects of irradiating a large amount of supratentorial brain particularly for younger children, resulting in the use of 'tight' margins. Planning technology and imaging have improved, and in the early years of the study the radiological methods used for defining the target volume may have been suboptimal by current standards. The question of local tumour control is being addressed in the current UKCCSG study that is investigating hyperfractionated accelerated RT (HART)[21] followed by eight courses of cisplatin, CCNU and vincristine.

In conclusion, this study has shown a relatively good outlook for non-metastatic pineal PNETs and confirms the relatively poor survival of non-pineal StPNETs. There is a suggestion that tumour size may be an important prognostic factor. There was no evidence that fairly intensive pre-radiation chemotherapy improved outlook. Given the clinical and biological differences between StPNETs and medulloblastoma it now seems prudent to undertake studies specifically designed for StPNETs with treatment directed at the particular natural history of these tumours, to further define prognostic factors and to explore further biological characteristics.

Conflict of interest statement

None declared.

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