# SUBFERTILITY AFTER CHEMOTHERAPY IN PNET BRAIN TUMOURS 34 YEAR EXPERIENCE FROM A SINGLE CENTRE (1980-2013)

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## BACKGROUND

- Primitive Neuroectodermal Tumour (PNET) paneuropean studies aimed to enhance cure.
- Chemotherapy (CT) (*vincristine, etoposide, carboplatin,cyclophosphamide*) added to craniospinal irradiation (CSI) in PNET3 led to a survival advantage and hence adopted as standard of care in PNET4 *(with "Packer" CT: vincristine, lomustine (CCNU), cisplatin).* However, this CT advantage was tempered by a reduced health-related quality of survival (HR-QOS) and a suggestion of evolving gonadotoxicity in the CT group at a 7-year followup *(Bull et al, 2007).*
- Alkylating agents, particularly cyclophosphamide and CCNU, cause a dose-dependent gonadotoxicity, from destruction of oocytes, follicular depletion, and associated ovarian cortical fibrosis and vessel damage.
- The platins, cisplatin and carboplatin, may be gonadotoxic to a lesser degree.

## OBJECTIVE

To assess long term prevalence of subfertility in survivors of surgically resected childhood PNETs according to gender and treatment, especially adjuvant CT.

## MATERIALS AND METHODS

- Retrospective longitudinal case note review.
- All patients with intracranial PNETs between 1.1.1980 and 31.12.2013 and followed for over 1year.
- Data on treatment, relapse, gonadotrophin levels, puberty and (in girls) estrogen/HRT replacement were collected from diagnosis.
- Time to, and cross-sectional rates of, subfertility (FSH>15 mIU/mL and/or HRT use) at last follow-up were compared between groups with and without CT.
- Non parametric statistics (SPSS v21); data shown as median, 1st & 3rd quartiles

## RESULTS

All patients registered in our joint centre (UCLH/GOSH) with search terms PNET/medulloblastoma/pineoblastoma from 1.1.1980 until 31.12.2013
**N=364**

Excluded (N=80)
- Follow-up ≤ 1y (N=78)
- Peripheral PNET (N=2)

Patients evaluated for analysis
**N=284**

With gonadotoxicity data
N=158 (55.6%)

Without gonadotoxicity data
N=126 (44.4%)

### Table 1. General characteristics
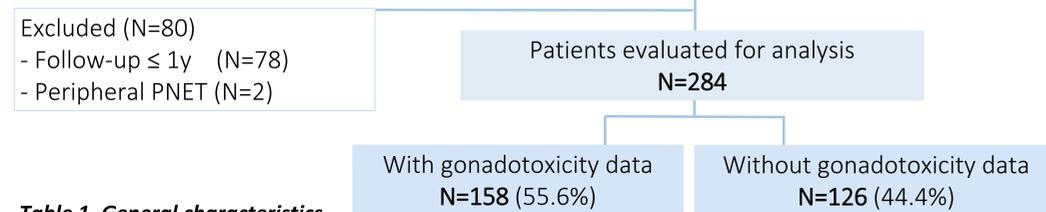
| Patients characteristics | With data | Without data | P value | All patients |
|---|---|---|---|---|
| Sex (Male:Female) | 94:64 (59.5%:40.5%) | 78:48 (61.9%:38.1%) | 0,715 | 172:112 (60.6%:39.4%) |
| Age at oncology diagnosis (y) | 6.51 (3.76;8.72) | 6.23 (3.33;9.26) | 0,547 | 6.33 (3.55;8.94) |
| - < 1 year (baby) | 4/158 (2.5%) | 9/126 (7.1%) | 0,086 | 13/284 (4.6%) |
| - < 3 years (infant) | 22/158 (13.9%) | 29/126 (23%) | 0,061 | 51/284 (18%) |
| Puberty timing | | | 0,550 | |
| - Normal | 56/82 (68.3%) | 4/5 (80%) | | 60/77 (77.9%) |
| - Precocious/Delayed puberty | 1:0 | 10:6 (62.5%:37.5%) | | 11:6 (64.7%:35.3%) |
| - Age at B2/G2 | 10.86 (9.47;11.86) | 10.20 (8.50;12.18) | 0,615 | 10.82 (9.42;11.87) |
| Age at last follow-up (y) | 16.19 (11.85;19.49) | 11.23 (7.43;14.61) | <0,001 | 13.97 (9.21;18.27) |
| Follow-up time since diagnosis (y) | 9.43 (5.00;12.93) | 2.83 (1.33;4.78) | <0,001 | 6.50 (2.55;11.43) |
| Follow-up time since EOT (y) | 2.00 (0.58;3.51) | 0.93 (0.73;1.41) | <0,001 | 6.84 (2.44;11.36) |
| Last status (dead:alive) | 45:81 (35.7%:64.3%) | 125:33 (79.1%:20.9%) | <0,001 | 170:114 (59.9%:40.1%) |
| **Disease characteristics** | | | | |
| Tumour location (infra:supratentorial) | 141:17 (89.2%:10.8%) | 107:19 (84.9%:15.1%) | 0,287 | 248:36 (87.3%:12.7%) |
| Exact tumour location | | | 0,034 | |
| - Posterior fossa | 131/149 (87.9%) | 99/122 (81.1%) | | 230/271 (84.9%) |
| - Pineal gland | 3/149 (2.0%) | 4/122 (3.3%) | | 7/271 (2.6%) |
| - Cerebral hemisphere | 14/149 (9.4%) | 13/122 (10.7%) | | 27/271 (10%) |
| - Ventricles | 0/149 (0%) | 3/122 (2.5%) | | 3/271 (1.1%) |
| - Multiple | 1/149 (0.7%) | 3/122 (2.5%) | | 4/271 (1.4%) |
| Tumour histology | | | 0,010 | |
| - Classic medulloblastoma | 126/158 (79.7%) | 118/126 (93.7%) | | 244/284 (85.9%) |
| - Desmoblastic MB | 15/158 (9.5%) | 4/126 (3.2%) | | 19/284 (6.7%) |
| - Anaplastic | 12/158 (7.6%) | 1/126 (0.8%) | | 13/284 (4.6%) |
| - Others | 5/158 (3.2%) | 3/126 (2.4%) | | 8/284 (2.8%) |
| Metastatic (yes:no) | 51:107 (32.3%:67.7%) | 17:109 (13.5%:86.5%) | <0,001 | 68:216 (23.9%:76.1%) |
| Recurrence (yes:no) | 50:108 (31.6%:68.4%) | 87:39 (69.0%:31.0%) | <0,001 | 137:147 (48.2%:51.8%) |
| Time to relapse (y) | 2.00 (0.58;3.51) | 0.93 (0.73;1.41) | 0,154 | 1.11 (0.66;2.86) |
| **Treatment characteristics** | | | | |
| Type of surgical intervention | | | <0,001 | |
| - Biopsy [< 10%] | 4/152 (2.6%) | 17/122 (13.9%) | | 21/274 (7.7%) |
| - Partial resection [10-50%] | 23/152 (15.1%) | 30/122 (24.6%) | | 53/274 (19.3%) |
| - Subtotal resection [51-90%] | 33/152 (21.7%) | 15/122 (12.3%) | | 48/274 (17.5%) |
| - Near-total resection [> 90%] | 5/152 (3.3%) | 6/122 (4.9%) | | 11/274 (4.0%) |
| - Total resection | 87/152 (57.2%) | 54/122 (44.3%) | | 141/274 (51.5%) |
| Residual volume <1.5 cm³ (yes:no) | 92:60 (60.5%:39.5%) | 60:62 (49.2%:50.8%) | 0,067 | 152:122 (55.5%:44.5%) |
| Non surgical treatment (yes:no) | | | <0,001 | |
| - None | 0/158 (0%) | 2/124 (1.6%) | | 2/282 (0.7%) |
| - RT alone | 68/158 (43.0%) | 70/124 (56.5%) | | 138/282 (48.9%) |
| - CT alone | 2/158 (1.3%) | 11/124 (8.9%) | | 13/282 (4.6%) |
| - RT+CT | 88/158 (55.7%) | 41/124 (33.1%) | | 129/282 (45.7%) |
| Radiotherapy (yes:no) | 155 /158 | 108/108 | 0,051 | |
| - High dose | 83/155 (53.5%) | 67/108 (62.0%) | | 150/263 (57.0%) |
| - Low dose | 65/155 (41.9%) | 40/108 (37.0%) | | 105/263 (39.9%) |
| - Focal beam | 7/155 (4.5%) | 1/108 (0.9%) | | 8/263 (3.0%) |
| - Low spade beam | 49/109 (31.0%:69.0%) | 59/67 (46.8%:53.2%) | 0,007 | 108/176 (38.0%:62.0%) |
| Chemotherapy (yes:no) | | | | |
| - 1st treatment | 89/68 (56.7%:43.3%) | 23/72 (24.2%:75.8%) | <0,001 | 112/140 (44.4%:55.6%) |
| - For relapse | 27/127 (17.5%:82.5%) | 38/83 (31.4%:68.6%) | 0,010 | 65/210 (23.6%:76.4%) |
| - Overall | 95/62 (60.5%:39.5%) | 73/48 (60.3%:39.7%) | 1,000 | 168/110 (60.4%:39.6%) |

### Table 2. Subfertility cohort (FSH>15 and/or HRT)
Females had more subfertility, were younger at diagnosis and required HRT more often than males

| | Male | Female | p | All |
|---|---|---|---|---|
| Subfertility | 11/94 (11.7%) | 26/64 (40.6%) | <0,001 | 37/158 (23.4%) |
| Age at subfertility diagnosis | 17.15 (13.22; 17.85) | 10.98 (8.02; 13.10) | <0,001 | 12.60 (9.80; 15.75) |
| HRT (yes:no) | 4:90 (4.3%:95.7%) | 13:51 (20.3%:79.7%) | 0,003 | 17:141 (10.8%:89.2%) |
| Time after diagnosis (y) | 4.75 (2.47; 9.07) | 3.02 (1.78; 4.83) | 0,095 | 3.15 (2.05; 6.43) |
| Time after end treatment (y) | 3.49 (1.29; 6.82) | 2.03 (0.86; 3.80) | 0,212 | 2.31 (1.08; 4.99) |
| Pubertal stage (pre:pubertal) | 3:36 (7.7%:92.3%) | 0:28 (0%:100%) | 0,191 | 3:64 (4.5%:95.5%) |

### Table 3. Factors influencing subfertility

| | Subfertility | Normal fertility | p |
|---|---|---|---|
| Sex (Male:Female) | 11:26 (29.7%:70.3%) | 83:38 (68.6%:31.4%) | <0,001 |
| Age - Infants (yes:no) | 5:32 (13.5%:86.5%) | 17:104 (14.0%:86%) | 1,000 |
| Tumour location (Infra:supratentorial) | 32:5 (86.5%:13.5%) | 109:12 (90.1%:9.9%) | 0,550 |
| Metastatic (yes:no) | 18:19 (48.6%:51.4%) | 33:88 (27.3%:72.7%) | 0,026 |
| Relapse (yes:no) | 12:25 (32.4%:67.6%) | 38:83 (31.4%:68.6%) | 1,000 |
| Surgery (major:minor) | 23:13 (63.9%:36.1%) | 69:47 (5.5%:40.5%) | 0,699 |
| RT (yes:no) | 37:0 (100%:0%) | 119:2 (98.3%:1.6%) | 0,013 |
| RT dose (low:high:focal) | 18:15:4 (48.6%:40.5%:10.8%) | 65:50:3 (55.1%:42.4%:2.5%) | 0,845 |
| RT low spade beam (yes:no) | 5:32 (13.5%:86.5%) | 44:77 (36.4%:63.6%) | 0,008 |
| Any CT at all (yes:no) | 30:7 (81.1%:18.9%) | 65:55 (54.2%:45.8%) | 0,004 |

### Table 4. Comparing RT to RT plus CT

| | RT only | RT + CT | p |
|---|---|---|---|
| Subfertility (yes:no) | 9:59 (13.2%:86.7%) | 28:60 (31.8%:68.2%) | 0,008 |



**Subfertility diagnosis along time**
$\chi^2(1) = 0.323$, $p = 0.570$
No CT
CT

Cumulative Proportion Survival — Time after end of treatment (years)
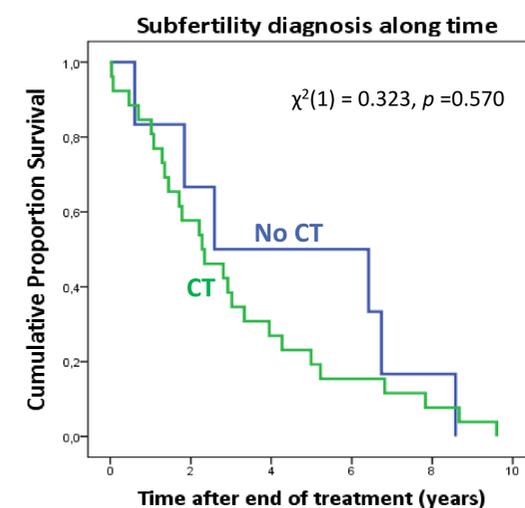
**Graph 1. Time to subfertility is decreased by CT**



**LH/FSH and sex steroid change in cases without subfertility**
Pubertal p<0,001 — FSH p<0,001 — LH p 0,007 — FSH>LH p 0,090 — Oestradiol p 0,655 — Testosterone p 0,0047
First evaluation — Last evaluation
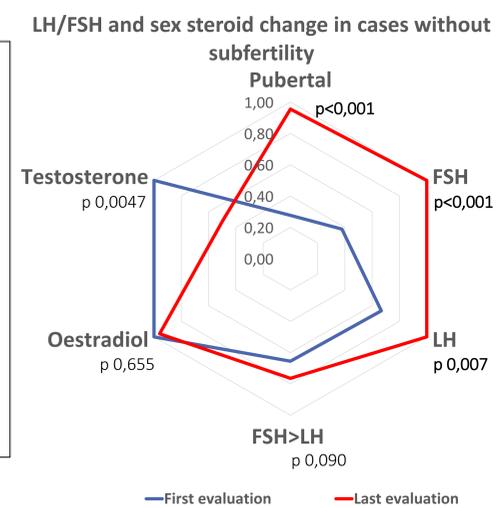
**Graph 2. fertility parameters in patients without subfertility diagnosis**

## SUMMARY AND CONCLUSIONS

- There is a significant prevalence of subfertility after PNET therapy, especially in girls (40% F vs 11% M), which may increase with time as patients mature.
- Any CT escalates the time to subfertility and increases its prevalence.
- RT gonadotoxicity effects appear confined to older 'spinal spade' (abandoned)
- Gonadotropin deficiency is not a RT consequence, even at a long 9.4y follow-up

- Consider pretreatment fertility preservation in adolescent boys
- Warn females of likely subfertility after CT and need for early HRT assessment

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