Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: an open-label, non-randomised, single-institution, phase 2 study

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Summary
Background Although the survival of children and adolescents with malignant germ-cell tumours has improved greatly in recent years, the outcome remains poor for those with refractory or recurrent malignant germ-cell tumours. We aimed to determine whether objective tumour response could be achieved in patients with refractory or recurrent malignant germ-cell tumours with PEI-regional deep hyperthermia as salvage treatment.

Methods Patients with refractory or recurrent non-testicular malignant germ-cell tumours after standard cisplatin-based chemotherapy were treated prospectively with PEI chemotherapy (cisplatin 40 mg/m², delivered intravenously on days 1 and 4; etoposide 100 mg/m², intravenously on days 1–4; and ifosfamide 1800 mg/m², intravenously on days 1–4) plus simultaneous 1-h regional deep hyperthermia (41–43°C) on days 1 and 4. Patients received three to four treatment courses at 21-day intervals until residual tumour resection was possible; they subsequently received one or two additional courses of PEI-regional deep hyperthermia. Local radiotherapy was given for incompletely resected tumours. Chemotherapy and hyperthermia toxic effects were assessed using WHO grading.

The primary endpoint was the proportion of patients who had an objective response as assessed with Response Evaluation Criteria in Solid Tumors version 1.0 guidelines. Secondary endpoints were the event-free survival and overall survival after 5 years. This ongoing PEI-regional deep hyperthermia study (Hyper-PEI protocol) is registered at the German Cancer Society, number 50-2732.

Findings 44 patients aged 7 months to 21 years (median 2 years 7 months) with refractory or recurrent malignant germ-cell tumours (nine patients with poor response, 23 patients with first relapse, 12 patients with multiple relapses) were included in this study. We identified 34 yolk sac tumours, eight embryonal carcinomas, one choriocarcinoma, and one dysgerminoma by histology analysis. Of the 35 patients who had sufficient clinical and radiographical data available for response assessment, 30 (86%) had an objective response to treatment (16 patients had complete remission and 14 had partial remission). 5-year event-free survival was 62% (95% CI 45–75), and 5-year overall survival was 72% (95% CI 55–83). The median follow-up of surviving patients was 82 months (range 9–195). WHO grade 3–4 neutropenia and thrombocytopenia occurred in all 181 chemotherapy cycles. Granulocytopenic fever, which required intercurrent hospital admission, was noted in 29 (66%) of 44 patients after 53 (29%) of 181 courses. Five patients experienced treatment-related grade-3 acute renal toxic effects.

Interpretation A multimodal strategy integrating PEI-regional deep hyperthermia and tumour resection with or without radiation can successfully treat children and adolescents with refractory or recurrent malignant non-testicular germ-cell tumours. The long-term prognosis of patients with poor response or after first relapse was almost similar to those receiving first-line treatment. This strategy merits further investigation.

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Introduction Paediatric malignant germ-cell tumours are rare, accounting for about 3–4% of all malignancies in children. More than 50% of paediatric malignant germ-cell tumours are diagnosed in infants and toddlers younger than 4 years, and yolk sac tumours are the most common histological subtype. More than 70% of all paediatric malignant germ-cell tumours occur at non-testicular primary sites, including the coccyx, retroperitoneum, ovary, mediastinum, and brain; by contrast, testicular cancer is the most frequent solid tumour in young men aged 20–35 years. The implementation of cisplatin-based systemic chemotherapy according to the Einhorn method, in combination with either vinblastine plus bleomycin (PVB) or etoposide plus bleomycin (BEP) greatly increases recurrence-free survival in adults with malignant germ-cell tumours. This result prompted the further
use of platinum-based chemotherapy in children as well. Today, children with malignant germ-cell tumours have a good prognosis; cure rates are about 80–90% with risk-stratified chemotherapeutic regimens, even in subgroups with unfavourable prognoses.15–20

Despite these achievements, more than 10% of paediatric malignant germ-cell tumours are refractory or recurrent and cannot be eradicated with salvage therapy in conventional doses or reiterated surgical resections, or both.2,17,18 By contrast with adult patients with predominantly distant metastases, paediatric patients with non-testicular primary tumours mainly have recurrences in local regions, emphasising that local tumour control is crucial for long-term outcome in these children and adolescents.19 As in first-line treatment, salvage chemotherapy can be used to help with tumour resection. In this context, chemotherapy resistance can hamper local tumour control; moreover, resection might be impossible when tumours have infiltrated adjacent nerves and bones because radical surgery can lead to severe mutilation.19 As a consequence, research into treatment for this group of patients has focused on new strategies to improve local tumour control. Among the possibilities is hyperthermia; in the late 1960s, isolated hyperthermic limb perfusion was reported to be useful as an additional treatment in adult patients with melanoma and sarcoma.20,21

We previously did a small pilot study22 in which simultaneous application of regional deep hyperthermia and cisplatin-based chemotherapy was well tolerated without major toxic effects in children and adolescents with recurrent or refractory tumours; this regimen achieved objective anti-tumour activity in seven of ten patients who had initially poor prognoses.22 A few centres in the USA and Europe have also done clinical trials with electromagnetic waves to increase the temperature in deep-seated malignancies, but none of these studies included paediatric patients.22–24

We report an open-label, non-randomised, single-institution, phase 2 study of a standard chemotherapy regimen with cisplatin, etoposide, and ifosfamide (PEI) plus regional deep hyperthermia as part of a multimodal, therapeutic strategy in children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours.

**Methods**

**Study design and participants**

The aims of this open-label, non-randomised phase 2 study of PEI-regional deep hyperthermia as salvage treatment were to examine whether objective tumour response can be achieved in patients with malignant non-testicular germ-cell tumour and if this multimodal therapeutic strategy can facilitate long-term cure. Because of the rarity of childhood malignant germ-cell tumours, no randomised comparison of various salvage strategies was possible. Therefore, we chose a risk-stratified multimodal strategy that takes into account experiences from first-line studies and from the regional deep hyperthermia pilot study.29 Since all patients received PEI chemotherapy as first-line therapy (cisplatin 100 mg/m², etoposide 300 mg/m², and ifosfamide 7500 mg/m² per cycles), and that the salvage chemotherapy was the same PEI chemotherapy but at a 20% lower dose for cisplatin (2×40 mg/m²), additional non-invasive microwave-induced regional deep hyperthermia was the only test variable. Patients were analysed separately according to whether they had had poor response to first-line chemotherapy, first relapse, or more than one relapse, since the prognosis might be different with respect to previous treatment. We defined poor responses as unresectable tumours in patients with stable disease, progressive disease after intensive cisplatin-based chemotherapy on imaging, or viable tumour (embryonal carcinoma, yolk sac tumour) at partial resection.

From Jan 28, 1994, through Dec 19, 2011, children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours were enrolled into this prospective study and underwent PEI-regional deep hyperthermia at the Paediatric Oncology Clinic, Haematology and Immunology, Centre for Child and Adolescent Health, Düsseldorf, Germany. Inclusion criteria were age younger than 25 years, life expectancy longer than 3 months, and regional deep hyperthermia able to reach the tumour. Exclusion criteria were cardiac pacemaker, metal implants (eg, total replacement of hip or knee joint), pregnancy, and lactation period. All patients had a histological diagnosis confirmed by a panel of independent pathologists in cooperation with the German Tumour Registry in Kiel. Tumours were classified histologically according to the WHO classification and staged according to the tumour-node-metastasis classification of soft-tissue tumours in children (for extragonadal germ-cell tumours)23 or according to the International Federation of Gynecologic Oncology staging system (for ovarian germ-cell tumours).24 We did histopathological examinations to identify tumour subtypes, with particular attention paid to the histological examination of resection margins. This study protocol was approved by the local ethics committee and the German Cancer Society, according to the intergroup procedures of the German Medicine Act. Written, informed consent was obtained from all patients or legal guardians.

**Procedures**

Baseline assessments at study entry included medical history, physical examination, complete blood count, urinalysis, serum measurements of tumour markers (α-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase) and electrolytes, and measurements of standard kidney and liver variables. We also assessed diagnostic images, including chest radiographs,
chest, abdomen, or pelvis CTs, and MRIs. Generally, treatment included thermochemotherapy before and after surgery with or without tumour irradiation.

PEI chemotherapy included 40 mg/m² per day of cisplatin, delivered intravenously on days 1 and 4; 100 mg/m² per day of etoposide, delivered intravenously on days 1–4; and 1800 mg/m² per day of ifosfamide, delivered intravenously on days 1–4. All cytotoxic drugs were given as short-term infusions via a Broviac catheter; on days 1 and 4, after a 30-min warming-up period, they were given at the same time as a 1-h regional deep hyperthermia treatment. The target temperature in the tumour area was 41–43°C. Treatment was repeated at 21-day intervals for a total of four to six cycles. Cisplatin was replaced with carboplatin (200 mg/m² per day, delivered intravenously on days 1 and 4) if the glomerular filtration rate became lower than 70 mL/min per 1·73 m² or when ototoxic effects were noted. Chemotherapy was delayed for 1 or 2 weeks in patients with less than 2000 leucocytes per mL, less than 80 000 platelets per mL, or a Karnofsky performance status lower than 70%.

Patients underwent complete surgical tumour resection when it was feasible without high risk of long-term morbidity. We classified patients as R0 when the tumour was totally removed, and no residual tumour was detectable macroscopically or microscopically; as R1 when the tumour was mostly removed, and no tumour was detectable macroscopically, but residual tumour tissue was detected microscopically; and as R2 when residual tumour was detectable macroscopically. We delivered small volumes of radiation (19·2–50·4 Gy) to children, and adolescents with different abdominal or residual tumour was detectable macroscopically. We assessed adverse events according to the WHO criteria for reporting cancer treatment results. We measured toxic effects of treatment during every course and at every follow-up visit; toxicity scoring was based on the highest grade of adverse event.

We assessed clinical response (complete or partial remission) on the basis of MRI findings after the initial three or four PEI-regional deep hyperthermia cycles, following the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines.

We defined complete remission as the absence of any detectable disease, including normal serum levels of α-fetoprotein (≤10 μg/L) and β-human chorionic gonadotropin (≤10 U/L). We defined partial remission as the absence of new lesions and at least a 30% decrease in the sum of the longest diameters of target lesions.

The primary endpoint was the objective tumour response after PEI-regional deep hyperthermia as assessed by RECIST (version 1.0), and the secondary endpoints were the event-free survival and overall survival after 5 years.

We defined event-free survival as the time from study entry until the occurrence of disease progression, relapse, second malignancy, death, or last reported contact. We considered overall survival as the time from study entry until death or the last reported contact. We analysed outcomes with Kaplan–Meier plots and did the statistical analyses with SAS 9.2. This study is registered at the German Cancer Society, ID number 50-2732.

Statistical analysis

The primary endpoint was the objective tumour response after PEI-regional deep hyperthermia as assessed by RECIST (version 1.0), and the secondary endpoints were the event-free survival and overall survival after 5 years.

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Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Results
44 consecutive children and adolescents with refractory or recurrent malignant non-testicular germ-cell tumours (nine patients with poor response, 23 with first relapse, 12 with multiple relapses) were enrolled and underwent PEI-regional deep hyperthermia (figure 1). Seven of these patients were from our phase 1–2 pilot study.8 Patients were aged 7 months to 21 years, with a median age of 2 years 7 months (table 1). All patients had already received front-line, intensive platinum-based chemotherapy with PEI (n=38), BEP (n=3), carboplatin, etoposide, and ifosfamide (n=2), cisplatin and fosfamide (n=1), or a combination of these regimens (n=7). 39 (89%) children with malignant germ-cell tumours underwent an additional tumour resection before PEI-regional deep hyperthermia. Tumour resections were not possible in five other children with malignant germ-cell tumour because of an unresectable tumour burden or tumour progression, or both. The appendix shows data for individual patients and pretreatment characteristics. Histopathological examinations identified tumour subtypes, including yolk sac tumours (n=34), embryonal carcinomas (n=8), choriocarcinoma (n=1), and dysgerminoma (n=1).

44 patients received a total of 181 PEI chemotherapy cycles in combination with 360 regional deep hyperthermia sessions. Ten patients received carboplatin rather than cisplatin due to poor renal function or ototoxicity. For 35 (80%) of these 44 patients, sufficient clinical and radiographical data were available for response assessment. Nine patients had intrasosional surgery before PEI-regional deep hyperthermia, with residual findings that were difficult to measure by MRI. An objective response to this protocol was identified in 30 (86%) of the 35 evaluable patients (16 patients had complete remission and 14 had partial remission). Additionally, seven of the nine patients with R1/R2 resections (with viable tumour) before PEI-regional deep hyperthermia (who could not be included in the response analysis) are in ongoing remissions without other local treatment options. After three or four cycles of PEI-regional deep hyperthermia treatment, 26 (59%) of 44 patients had second-look surgery; histopathological analysis revealed complete tumour resection (R0) in 16 patients, R1 resections in eight patients, and R2 resections in two patients (figure 1). Ten patients with residual viable tumour cells received additional radiotherapy after PEI-regional deep hyperthermia and surgery (figure 1). The use of radiotherapy for intensification of PEI-regional deep hyperthermia treatment led to long-term cure in eight of these ten patients whereas two patients died of disease (figure 1). The appendix includes detailed treatment results and clinical follow-up data for every patient.

The estimated probability of 5-year event-free survival was 62% (95% CI 45–75) and the 5-year overall survival probability was 72% (95% CI 55–83; figure 2). Subgroup analysis (figures 3 and 4) showed apparently better survival in patients who received PEI-regional deep hyperthermia as a salvage therapy for a poor response (5-year event-free survival 52% [95% CI 8–84]; 5-year overall survival 78% [95% CI 37–94]) or a first relapse

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### Figure 1: Outcome with respect to clinical response to combination treatment

- **Indication**: 44 patients received standard cisplatin-based chemotherapy
- **Clinical response**: 25 complete remission
- **Pathological response**: 9 necrosis, 3 teratoma, 2 viable tumour, 11 no info
- **Outcome**: 21 (83%) had complete clinical remission, 5 (36%) died

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(5-year event-free survival 74% [95% CI 51–87]; 5-year overall survival 81% [95% CI 57–93]) than in patients with multiple relapses [5-year event-free survival 43%, (95% CI 15–67]; 5-year overall survival 50% [95% CI 21–74]). The differences between event-free survival and overall survival in the subgroup with poor-responder tumours were due to a local relapse in one patient after an event-free survival observation time of more than 5 years. In this patient, additional salvage therapy was successful. To date, the median follow-up times of surviving patients in these three groups are 41 months (range 21–94) in the poor-response group, 89 months (9–166) in the first-relapse group, and 98·5 months (40–195) in the multiple-relapse group. Median follow-up for all surviving patients is 82 months (9–195).

15 patients experienced recurrences and one patient died because of complications after PEI-regional deep hyperthermia treatment. This patient had a third relapse of sacrococcygeal malignant germ-cell tumour after 5 months of complete remission. Although the treatment had been successful according to the PEI-regional deep hyperthermia protocol, the patient developed myelodysplastic syndrome and died as a result of morbidity related to stem-cell transplantation. 15 patients developed tumour recurrence (three [33%] from the poor-response group, six [26%] in the first-relapse group, and six [50%] in the multiple-relapse group). Additional treatment options, which included surgery, radiotherapy, and high-dose chemotherapy plus stem-cell rescue (one patient), were successful in four (27%) of the 15 patients with recurrences after PEI-regional deep hyperthermia. These four patients who received other treatments could have affected overall survival (figure 4). The remaining 11 patients died from non-resectable local or distant, or both, disease progression; four patients showed progression in the liver, two in the abdomen or retroperitoneum, one in the lumbar spine (additional radiotherapy was ineffective), and four in the lungs.

We assessed all 44 patients with 181 PEI-regional deep hyperthermia cycles for acute toxic effects (table 2). Myelotoxic effects were similar to those noted in other

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics</th>
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<tr>
<td><strong>Age (years, months)</strong></td>
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<tr>
<td>Median</td>
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<tr>
<td>Range</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male (&gt;16 years)</td>
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<tr>
<td>Female (&gt;16 years)</td>
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<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Yolk sac tumour</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Dysgerminoma</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
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<tr>
<td><strong>Initial tumour site</strong></td>
</tr>
<tr>
<td>Sacrococcygeal</td>
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<tr>
<td>Ovarian</td>
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<tr>
<td>Retroperitoneal</td>
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<tr>
<td>Cervix/uterus</td>
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<tr>
<td>Abdomen/liver</td>
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<tr>
<td>Penis root</td>
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<tr>
<td><strong>Site of relapse</strong></td>
</tr>
<tr>
<td>Local</td>
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<tr>
<td>Loco-regional</td>
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<tr>
<td><strong>Previous chemotherapy protocols (cisplatin-based)</strong></td>
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<tr>
<td>Previous surgical resections</td>
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<tr>
<td>Previous radiation (dose in Gy)</td>
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<thead>
<tr>
<th>Number at risk</th>
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<tbody>
<tr>
<td><strong>Time after PEI chemotherapy plus regional deep hyperthermia (months)</strong></td>
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<tr>
<td>Overall survival</td>
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<tr>
<td>Event-free survival</td>
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</table>

**Figure 2:** Event-free survival and overall survival
PEI=cisplatin, etoposide, and ifosfamide chemotherapy.

**Figure 3:** Prognostic impact of disease status on event-free survival
Patients were grouped according to initial disease status after first-line chemotherapy. PEI=cisplatin, etoposide, and ifosfamide chemotherapy.
and ifosfamide chemotherapy. Patients were grouped according to initial disease status after first-line chemotherapy. PEI = cisplatin, etoposide, ifosfamide.

### Figure 4: Prognostic impact of disease status on overall survival

Patients were grouped according to initial disease status after first-line chemotherapy. PEI = cisplatin, etoposide, ifosfamide chemotherapy.

### Table 2: Toxicity of thermochemotherapy in 44 children

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Poor response (n=9)</th>
<th>First relapse (n=23)</th>
<th>Multiple relapses (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematological toxicity</strong>†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grade 3/4 neutropenia</td>
<td>9 (100%); 30 (100%)</td>
<td>23 (100%); 95 (100%)</td>
<td>12 (100%); 56 (100%)</td>
</tr>
<tr>
<td>Grade 3/4 thrombocytopenia</td>
<td>9 (100%); 30 (100%)</td>
<td>23 (100%); 95 (100%)</td>
<td>12 (100%); 56 (100%)</td>
</tr>
<tr>
<td>Grade 3/4 infections</td>
<td>5 (56%); 7 (23%)</td>
<td>16 (70%); 23 (31%)</td>
<td>8 (67%); 17 (30%)</td>
</tr>
<tr>
<td>Next course delayed &gt;7 days</td>
<td>7 (78%); 11 (37%)</td>
<td>13 (57%); 16 (12%)</td>
<td>6 (50%); 8 (14%)</td>
</tr>
<tr>
<td><strong>Renal toxicity, creatinine increase†</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal toxicity, tubular dysfunction†</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2, transient</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3, transient</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ifsosfamide-induced neurotoxicity†</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3, Fanconi syndrome</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3, all recovered</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Values</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Represent number of patients (%)</td>
<td>12</td>
<td>180</td>
<td>1800</td>
</tr>
<tr>
<td>Number of courses (%)</td>
<td>181</td>
<td>181</td>
<td>181</td>
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<tr>
<td>Number of assessable courses (%)</td>
<td>181</td>
<td>181</td>
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Patients received cyclophosphamide (360 mg/m² per day on days 1–4) instead of ifosfamide; two of these patients were younger than 2 years of age, and four had symptoms of ifosfamide-induced encephalopathy, either before (two patients) or during (two patients) PEI-regional deep hyperthermia. Three of these patients had grade 3 renal tubular damage.

We assessed thermometric records for all 360 regional deep hyperthermia sessions. The median intratumoural $T_{\text{max}}$ was 42.4°C (IQR 41.8–42.8). The median time-averaged temperatures were 41.8°C for $T_{\text{20}}$ (41.4–42.3), 41.3°C for $T_{\text{30}}$ (40.9–41.8), and 40.5°C for $T_{\text{90}}$ (39.8–41).

During regional deep hyperthermia treatment, all patients had increased heart rates and blood pressure, but none developed signs of cardiac arrhythmia or heart failure. All sessions of regional deep hyperthermia were done with sedation; restlessness occurred during ten sessions, and these patients required deeper sedation or a reduction in microwave antennae power. Grade 1 mild skin inflammation occurred in the treatment area of five patients after 21 sessions but resolved fully within 3 days. Grade 2 anogenital blisters occurred in two patients after two sessions but healed within 1–2 weeks; no severe skin burns were noted. Mild-to-moderate grade 1 pain, described as muscle aching, was reported in the bones and muscles of the treated area of seven patients after 22 sessions. Two patients had aseptic necrosis of the left femoral head, which required orthopaedic intervention at 2 or 4 months after the end of regional deep hyperthermia treatment.

### Discussion

The results from this clinical study provided evidence that a multimodal therapeutic strategy, including cisplatin-based chemotherapy plus regional deep hyperthermia at temperatures of 41–43°C, could improve the tumour response and outcome in children and adolescents with refractory or recurrent malignant non-testicular germ-cell tumours. Only a few studies have reported clinical results for the treatment of refractory or recurrent paediatric malignant germ-cell tumours; thus, this work might have a substantial effect on future strategies for recurrent childhood germ-cell tumours. The approach was unique in that it used the same cisplatin-based anticancer drugs that are used for first-line treatment, plus additional microwave-induced regional deep hyperthermia as the test variable. In fact, the cisplatin dose in this study was 20% lower than that typically given in first-line treatment; this precautionary measure was taken with the consideration that toxic effects from platinum-based chemotherapy had accumulated during first-line treatment. Strikingly, our PEI-regional deep hyperthermia protocol produced an objective tumour response in 86% of patients, with 5-year event-free survival of 62% and 5-year overall survival of 72% at last follow-up. This survival rate is
unmatched by all other reports on recurrent childhood malignant germ-cell tumours.3,5,12,16–18

Although other data indicate that children and adolescents with malignant germ-cell tumours who relapse after chemotherapy can have some success when they receive salvage chemotherapy plus surgery, the prognosis in patients with refractory or recurrent malignant germ-cell tumours, and especially in those with multiple recurrent malignant germ-cell tumours, remains poor.5,13,10,11 The results of trials on paediatric malignant germ-cell tumours persistently show only slight differences between event-free survival and overall survival, indicating that few patients treated with modern intensive chemotherapy protocols are salvaged after relapse. The first US Children’s Cancer Group CCG-861 trial,19 which included 93 patients, reported a 4-year event-free survival of 49% and a 4-year overall survival of 54%—most patients who relapsed died (43 of 47 patients). Most relapses were related to incomplete tumour resection. Additional clinical experience plus more intensive chemotherapeutic regimens resulted in higher cure rates in the more recent US Intergroup trial;20 the 5-year event-free survival was 80-5% for patients treated with BEP (100 mg/m² cisplatin per cycle) and 89-6% for those treated with high-dose BEP (200 mg/m² cisplatin per cycle), whereas overall survival values were 86-0% with BEP and 91-7% with high-dose BEP. The results were similar when retroperitoneal and sacrococcygeal malignant germ-cell tumours were analysed separately.13,10

In the study by the UK Children’s Cancer Study Group,20 the 5-year event-free survival of patients treated with carboplatin, etoposide, and bleomycin (JEB) was 87-8% and a 5-year overall survival was 90-9% after a median follow-up of 53 months (range 0–109). Of the 14 patients who had a relapse after JEB chemotherapy, three of the five patients who received vincristine, actinomycin D, and cyclophosphamide (VAC), or VAC plus doxorubicin, or ifosfamide, vincristine, and doxorubicin were alive. Two of the four patients who were treated with chemotherapy drugs that included cisplatin were alive, as was the one patient who had alternating JEB and VAC chemotherapy. However, the three patients who were treated with various non-cisplatin-containing agents died. One patient who was only given palliative care also died. Additional radiotherapy was given to three patients, including one who survived, and two patients were treated unsuccessfully with high-dose chemotherapy.20

Poorer results were achieved with the less intensive carboplatin-based regimen (400 mg/m² per cycle) used in the French TGM study,17 with which 58% of patients experienced complete remission; however, after inclusion of cisplatin complete remission reached 90%. Notably, that report is less suitable for the analysis of salvage strategies because the first-line treatment was not as intensive as in the British16 or US studies.13

The European Group for Blood and Marrow Transplantation published a retrospective analysis21 of 24 children and adolescents who received additional high-dose chemotherapy with stem-cell support for treatment of refractory or recurrent malignant germ-cell tumours. Five of 12 patients with retroperitoneal or sacrococcygeal malignant germ-cell tumours were reported to be in ongoing remission after treatment with various high-dose chemotherapy regimens.22 However, it has been stated that salvage attempts using high-dose chemotherapy regimens might be of little benefit if the patient is not clinically disease-free at the time of haemopoietic stem-cell transplantation.16–18

Taken together, these data suggest that there is currently no standardised therapeutic strategy that is proven to be successful in patients with refractory or recurrent paediatric malignant germ-cell tumours. In fact, it is likely that long-term survival after relapse might be even worse than reported in some of these studies because the follow-up after completion of the salvage treatment might not have been sufficiently long for an accurate assessment. Otherwise, these data are in line with our experience from the early MAKEI protocols—ie, once patients with malignant germ-cell tumour relapse, the prognosis is poor.19

With this in mind, a radical approach to treating these patients is justified in an attempt to improve survival. Because refractory or recurrent malignant germ-cell tumours in children most commonly present as local relapse, it is clear that local therapy must be intensified in some way.23–25 Intensifying systemic treatment could just increase systemic toxic effects—particularly in intensively pretreated patients—without having the required effect on local tumour control.

Our rationale for the use of regional deep hyperthermia in the range of 41–43°C in combination with cisplatin-based chemotherapy was based on observations that malignant germ-cell tumours responded well to cisplatin-based chemotherapy and that cisplatin is a potent thermosensitiser, both in vivo and in vitro.46–48 Particularly, hyperthermia increases cellular uptake of cisplatin, and the subsequent increase in DNA cross-linking and hyperthermia inhibits the DNA repair that occurs in response to cisplatin damage.49–51 Additionally, cisplatin resistance can be overcome by hyperthermia, rendering cisplatin effective in patients after primary treatment failure.52–56 Accordingly, we opted to use a cisplatin-based chemotherapy protocol combined with regional deep hyperthermia to enhance local anti-tumour drug efficacy.

To the best of our knowledge, the present study involved the largest reported group of children and adolescents with refractory or recurrent malignant germ-cell tumours treated with a salvage protocol administered in a prospective, uniform way (panel). This study was not randomised because the number of patients per year was small, and no other effective salvage protocol was
We searched PubMed for articles in English with the search terms “germ cell tumors”, “germ cell tumors and children”, “sacroccygeal germ cell tumors”, “relapsed and refractory germ cell tumors (GCTs) and treatment”, “deep local hyperthermia”, and “reviews”. Reports on children with non-testicular germ cell tumours and relapse treatment are sparse. Because of the rarity of relapses in children and the lack of an established relapse strategy, most children with non-testicular malignant germ-cell tumours have been treated outside of established protocols. When the recruitment began for the current investigation, no published study had addressed the potential benefit of a salvage protocol for children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours. We designed our study on the basis of previous reports stating that treatment with additional deep local hyperthermia plus radiotherapy or chemotherapy, or both, was associated with a response benefit and an increased rate of secondary resections in refractory sarcomas of adults.

Interpretation

Our prospective study provides the first demonstration that in paediatric refractory or recurrent non-testicular malignant germ-cell tumours, the same cisplatin-based chemotherapy (cisplatin, etoposide, and ifosfamide; PEI) at a 20% lower cisplatin dosage combined with regional deep hyperthermia at 41–43°C produced objective tumour responses in 30 (86%) of 35 patients. As part of a multimodal strategy, the PEI-regional deep hyperthermia regimen allows clinicians to provide a long-term cure for most of these poor-prognosis patients. These encouraging results strongly suggest that additional microwave-induced regional deep hyperthermia with standard platinum-based chemotherapy should be introduced soon after initial treatment failure to achieve the best therapeutic strategy for each patient.

Available. Nonetheless, in view of the prognostically unfavourable characteristics of this study population before treatment, the 86% response rate associated with PEI-regional deep hyperthermia is very encouraging. Conversely, in our analysis, the assessment of tumour response was not possible in nine study patients with previous intralesional surgery (R1/R2 resections; viable tumour). Children with residual malignant germ-cell tumours after standard regimens also have poor prognoses; therefore, that seven of these nine patients with poor prognoses have ongoing remissions due to PEI-regional deep hyperthermia regimen alone without other local treatment options provides evidence that thermochemotherapy is effective. Overall, patients who received PEI-regional deep hyperthermia as a first salvage treatment had much better survival than did patients who had several relapses (figures 3 and 4). The long-term prognosis of patients with poor response or after first relapse in our study population was almost similar to that of patients receiving first-line treatment with high cure rates of about 80–90%.80,81,82,83

Cisplatin causes acute transient or irreversible nephrotoxic and ototoxic effects, and these side-effects might be enhanced by hyperthermia.84,85,86 Although ototoxic effects were mild in most instances in the present investigation, sustained renal toxic effects were reported in five patients. For those patients, PEI-regional deep hyperthermia was restricted to only three or four cycles, and ifosfamide was replaced with cyclophosphamide in some patients. Haematological toxic effects of grade 3 or higher were not generally of major clinical importance, but hospital admission for fever or neutropenia was needed in 29 (66%) of 44 patients after 53 (29%) of the 181 courses. Two children required surgery for aseptic hip injuries; however, whether this complication occurred as a result of regional deep hyperthermia, chemotherapy, radiation, or a combination of factors, including the first-line treatment is unknown.

Our patient population included children as young as 7 months, necessitating the adaptation of the heating techniques for use in very small bodies. The 30 cm, 40 cm, and 60 cm applicator arrays allowed electromagnetic waves to heat deep-seated tumours in all age groups. By contrast with previous reports in adults,52 regional deep hyperthermia treatment was well tolerated in our patient group, with no severe skin burns after regional deep hyperthermia treatments, probably thanks to fractionated sedation. Fractionated sedation did not increase the risk of burns. We believe that invasive thermometry is indispensable for providing patient safety and controlling the quality of regional deep hyperthermia treatment. It might be true that the hyperthermia method is not currently widespread for the treatment of children. However, the costs of treatment planning and heat application are similar to those of radiotherapy in combination with chemotherapy in small children. We did not observe life-threatening complications in our paediatric patient population. The children can be discharged from the hospital after 5 days, similar to those who received conventional chemotherapy alone. In compliance with quality guidelines,17 our experience with the regional deep hyperthermia technique in children can also be extended to other institutions.

In adults, intratumoural temperatures of 41–43°C correlate strongly with improved treatment outcome.54 Furthermore, cisplatin and other chemotherapeutic drugs, including carboplatin, ifosfamide, and cyclophosphamide, are most effective at temperatures higher than 41°C, a phenomenon referred to as thermo-sensitisation.55,56,57 Our instrument set-up generated intra-tumoural temperatures that were consistent with increased drug efficacy (\(T_{\text{m}}\) 41–3°C, IQR 40–9–41.8; \(T_{\text{max}}\) 42.4°C, IQR 41.8–42.8) and were therefore of paramount importance for our high overall response rate. However, further clinical research is needed to clarify the roles of heating time and thermal dose in local tumour control in paediatric patients with malignant germ-cell tumours. Although we did not systematically analyse this issue in this study, some evidence indicates that small volumes of radiation can control residual disease after PEI-regional deep hyperthermia.59

In conclusion, we report the long-term results of a salvage protocol for paediatric patients with refractory or
recently malignant germ-cell tumours; this protocol allows clinicians to provide a long-term cure for most of these patients with poor prognosis. These encouraging results for local tumour control, which is essential for a long-term cure, strongly suggest that the use of microwave-induced regional deep hyperthermia at temperatures of 41–43°C in combination with standard platinum-based chemotherapy should be introduced soon after initial treatment failure. This regimen has the potential to become a first-line treatment for tumours with locally difficult characteristics.

Contributors
RW, UG, DTS, and GC designed the study and wrote the report. RW, VF, OM, OK, SS, JL, JS, and RW collected and analysed the data. RW and OM did the statistical analysis. All authors interpreted data and approved the final manuscript.

Conflicts of interest
We declare that we have no conflicts of interest.

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