

Oncologic therapy in St. George hospital

The treatment of malignant diseases represents a mainly function of the St. George hospital. Within the scope of an integrative cancer therapy, hyperthermia treatment is used as a complementary method, which is combined with other anticancer treatment as chemotherapy or radiotherapy to enhance the effectiveness of the conventional therapy. Dependent on the localization and stage of the tumor, local, regional or whole body hyperthermia is applied. Annual 1000- 1200 patients are treated in the St. George Hospital; 400- 500 whole body hyperthermia and 300- 400 regional or local hyperthermia treatments are carried out.

For assessment of the therapy success and for preparation of prospective studies the outcome of different malignant diseases were evaluated. In all cases the patients suffered on advanced tumor stages with bad prognosis. In retrospective analysis the data of patients, which were treated in a distinct period with a special therapy protocol, were worked up. The main objectives of an anticancer treatment of advanced and metastatic tumors were the relieve of tumor symptoms and , if possible, an increase of the survival time. The remission rate, which indicates the decrease of the tumor size as a measure of the treatment success, and the toxicity grade were used to describe the effects of hyperthermia therapy.

Metastatic cancer

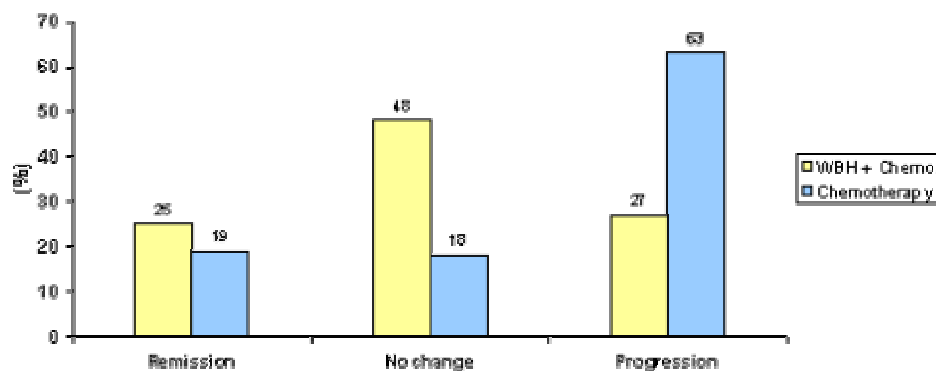
Available treatment regimens for metastatic cancer have yielded disappointing results, with the majority of responses being also of short duration. Thus it is necessary to examine the impact of new treatment modalities to improve response rates and survival of ovarian cancer patients with recurrent disease. The primary cause of the limited effectiveness of second or third line chemotherapy in the treatment of recurrent or metastatic carcinoma is multi-drug resistance (MDR) of cancer cells to antineoplastic drugs. To overcome MDR either the effectiveness of the drugs used or the vulnerability of the cancer cells must be enhanced.

Whole body hyperthermia (WBH) in combination with chemotherapy in treatment of ovarian cancer

Effects of hyperthermia on ovarian cancer were described in many preclinical and clinical studies. In vitro experiments showed an enhanced effectiveness of antineoplastic substances and an overcoming of resistance against platinum drugs in ovary cells (Averill 1999, Raaphorst 1996). The thermal enhancement ratio of cisplatin, which represents the ratio of the dose causing cell death in presence or absence of hyperthermia, was up to 3,8 measured in platinum resistant cells (Wallner 1986).

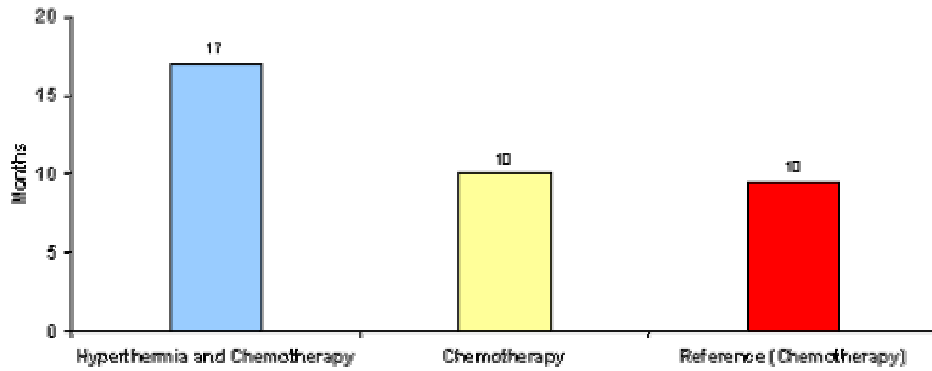
In the last years (1996-2002) 123 patients suffered on advanced and recurrent ovarian cancer were treated with whole body hyperthermia (WBH) and chemotherapy. The therapy results were compared with the effects of chemotherapy alone (50 patients).

The results obtained showed remarkable differences between patients treated with the combined therapy and patients treated only with chemotherapy. In the hyperthermia-treated group 48% showed no change of the tumor growth (stable disease), compared to 18% in the chemotherapy group. On the other side, 63% of patients treated with chemotherapy alone showed a progressive disease compared to 27% of patients treated with hyperthermia and chemotherapy. Not only the responder rate, but also the median survival time was higher in the hyperthermia treated patients (17 months) compared to 10 months in the chemotherapy group or survival times described in the literature.



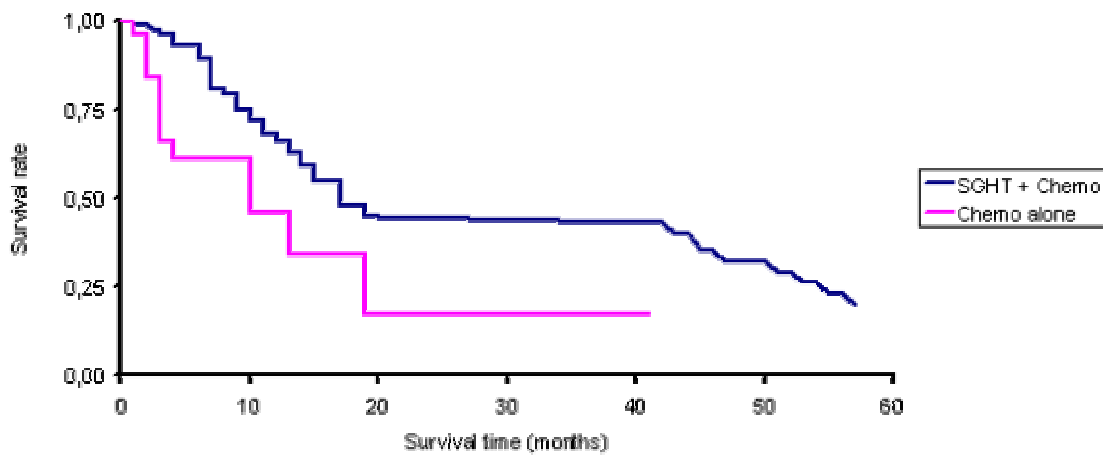
Fig

The therapy results of a combined therapy with whole body hyperthermia/chemotherapy are compared to the results of chemotherapy alone. Patients treated with chemotherapy alone showed a higher rate of progressive disease, in the group treated with whole body hyperthermia most of the patients had a stable disease (no change).



Fig

The median survival time of patients with recurrent ovarian cancer treated with whole body hyperthermia exceeds the survival time of patients treated with chemotherapy alone.



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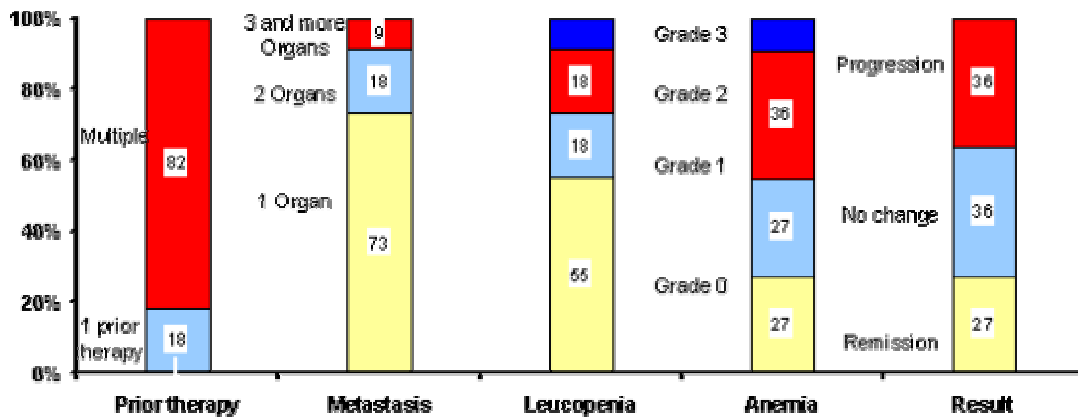
Comparison of survival rates of patients with recurrent ovarian cancer treated with whole body hyperthermia combined with chemotherapy and chemotherapy alone (Kaplan-Meier-diagram).

Therapy according to the DOLPHIN- study

A randomized phase III clinical trial with whole body hyperthermia and an ifosfamide/ carboplatin chemotherapy in recurrent ovarian cancer (DOPHIN-study) was planed by the gynaecologic department of the LMU Munich. The main objective of the study was to improve the response of a second line chemotherapy in patients, which suffered on a relapse after a platinum based chemotherapy.

The main inclusion criteria of the study protocol were a prior treatment with a platinum containing chemotherapy, the evidence of a measurable tumor lesion, and a sufficient function of the cardiovascular system. Exclusion criteria were brain metastasis and failure of liver or kidney function. The treatment schedule contained 6 cycles of chemotherapy with carboplatin/ifosfamide combined with whole body hyperthermia. In St. George Hospital 11 patients were treated according to the study protocol.

Most of them had multiple prior chemotherapies and all patients had metastasis in 1 or more organs. In sight of the advanced stage of the disease and the recurrence after multiple zytostatic pretreatments, the rate of responder (27%) and stable disease (36%) is remarkable. The results point to an hyperthermia- induced overcoming of the resistance against zytostatic substances.



The results of a treatment of recurrent ovarian cancer with whole body hyperthermia and carboplatin/ifosfamide according to the protocol of the DOLPHIN study (2001-2002;n = 11). The percentage of prior therapies, the extend of metastasis, and the haematological toxicity are shown.

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- Raaphorst GP, Doja S, Davis L, Stewart D, Ng CE. A comparison of hyperthermia cisplatin sensitization in human ovarian carcinoma and glioma cell lines sensitive and resistant to cisplatin treatment. *Cancer Chemother Pharmacol.* 1996;37:574-80.
- Wallner KE, DeGregorio MW, Li GC. Hyperthermic potentiation of cis-diamminedichloroplatinum(II) cytotoxicity in Chinese hamster ovary cells resistant to the drug. *Cancer Res.* 1986;46:6242-5.