# Comparative Study on the Effect of 42 ℃ Intraperitoneal Hyperthermia Chemotherapy on Cancerous Ascites with Different Treatment Time

Zongzhi Liang, Yapeng Huang, Junfang Pang, Bin Li, Shengnan Hu, Huizhen Zhang

Department of Hyperthermia, Henan Provincial Hospital

Zhengzhou, Henan China 450000

**Abstract:**

**Objective**: The difference of curative effects of 42 ℃ intraperitoneal hyperthermia chemotherapy in the treatment of cancerous ascites with different treatment time was studied to find out the best matching treatment time of hyperthermia chemotherapy.

**Methods**: 200 cases of patients with malignant ascites from our hospital that treated with the heat intraperitoneal chemotherapy during 2004 to 2020 were selected, among which 100 cases had hyperthermia time of 60 minutes and 100 cases had hyperthermia time of 120 minutes. The curative effects, half-year and one-year survival period, and post-treatment complications of the two groups of patients were compared and analyzed.

**Results**: The treatment efficiency, half-year survival and one-year survival period of the patients in the 120 minutes treatment group were significantly better than those in the 60 minutes treatment group. The data comparison and analysis showed statistical differences. However, there was no statistical difference in the adverse reactions between the two groups of patients after treatment.

**Key words:** Intraperitoneal hyperthermia chemotherapy, cancerous ascites, hyperthermia treatment time

Malignant ascites is the abnormal accumulated liquid that caused by intraperitoneal malignant cells, occupying about 10% of all ascites causes. Gastrointestinal tumors are common in the cause of malignant ascites, among which gastric cancer, pancreatic cancer, and liver cancer are the most common. In female patients, ovarian cancer is the most common, which accounting for 30% to 54 %. The treatment of malignant ascites is a major challenge in clinical treatment [1]. Since 2004, our hospital had used 42 ℃ intraperitoneal hyperthermia chemotherapy to treat cancerous ascites and had achieved

satisfactory results. A comparative study had conducted on the efficacy of patients with different hyperthermia durations.

## 1. Materials and methods

### a) General information

Hospitalized cancerous ascites patient cases with all kinds of malignant tumor caused cancerous ascites in our hospital from 2004 to 2020 were reviewed. 200 cases of a complete course of treatment records and over one year follow-up records had screened out, which included 100 cases with 60 minutes treatment time and 100 cases with 120 minutes treatment time that used 42 ℃ intraperitoneal hyperthermia chemotherapy. The basic conditions of the two groups of patients are shown in Table 1 and Table 2. There was no statistical difference after statistical processing.

| Hyperthermia treatment time | Number of cases (male/female) | Average age (oldest/youngest) | Hypoproteinemia | kps score |
|---|---|---|---|---|
| 60 mins | 100 (57/43) | 50 (79/21) | 66 | ≥60 |
| 120 mins | 100 (55/45) | 49 (81/17) | 68 | ≥60 |

Table 1. Comparison of allocation of patients in 2 groups, $P > 0.05$ (no statistical difference).

| **Hyperthermia treatment time** | **Total number of cases** | **Liver cancer** | **Gastric cancer** | **Pancreatic cancer** | **Ovary cancer** | **Metastatic cancer** |
|---|---|---|---|---|---|---|
| 60 mins | 100 | 14 | 29 | 17 | 26 | 14 |
| 120 mins | 100 | 15 | 27 | 20 | 23 | 15 |

Table 2. Comparison of the distribution of the disease types of the two groups of patients, $P > 0.05$ (no statistical

difference).

**b) Treatment methods and temperature measurement**

**i.**

Both groups of patients were given DDP 20 mg + 5-Fu250 mg intraperitoneal injection before treatment. After the injection, the patient was instructed to turn over several times to achieve uniform distribution of the drug in the abdominal cavity. Then Jiangsu Nuowan J-9000 microwave hyperthermia machine was applied for heating abdominal treatment. Intraperitoneal temperature kept 42℃ ± 0.2℃. The duration of hyperthermia was 60 minutes for one group and 120 minutes for the other group.

**ii. Treatment plan design**

Applied weekly hyperthermia twice: the first one was hyperthermia combined with chemotherapy infusion and the second one was simple hyperthermia with 72 hours interval between each hyperthermia. 4 weeks were a course of treatment with 4 to 8 weeks of interval between each course of treatment. There were 68 patients applied with over 2 courses of treatment and 60 mins treatment time, account for 68%. And 70 patients applied with over 2 courses of treatment and 120 treatment time, account for 70%.

**iii. Temperature measurement method during treatment**

The J-9000 type microwave hyperthermia machine was equipped with a temperature measuring line and the heat-sensing tip was inserted into the abdominal cavity through a puncture needle to measure the temperature.

**iv. Efficacy evaluation standards and statistical processing methods**

The evaluation criteria of efficacy were in accordance with tumor hyperthermia Chinese Experts consensus that established by 2020 Chinese Society of Clinical Oncology Hyperthermia Special Committee (CSCO-HSC) [2].

A: CR ascites disappeared completely, and maintained >4 weeks

B : PR ascites disappeared ≥50% and <100% , and maintained for >4 weeks.

C : SD ascites disappeared <50% or increased ≤ 25% , and maintained for >4 weeks

D: PD ascites increased >25%.

The statistical method processed with SPSS17.0 statistical software for statistical processing.

## 2. Results

### a) Contrastive analysis of curative effects

Patients' B-Scan reports, medical records, and the one-year follow-up records after 6 weeks and 16 weeks treatment of 32 CR patients, 30 PR patients, 18 SD patients, and 20 PD patients with hyperthermia treatment time 60 minutes were statistically analyzed and had a total effective rate of 62%. While the effective rate of hyperthermia time of 120 minutes group was 90% with 56 CR patients, 34 PR patients, 4 SD patients, 6 PD patients. There were significant differences in treatment, see Table 3:

| Hyperthermia treatment time | Total number of cases | CR (%) | PR (%) | SD (%) | PD (%) | Total effect rate |
|---|---|---|---|---|---|---|
| 60 minutes | 100 | 32 | 30 | 18 | 18 | 20 |
| 120 minutes | 100 | 56 | 34 | 4 | 4 | 6 |

Table 3. Comparison of curative effects, P < 0.05 ( with significant statistical difference)

## 2.2 Comparative analysis of survival

After statistical analysis of 42℃ intraperitoneal hyperthermia chemotherapy with 60 minutes treatment time, 66 patients were found to reach a half-year survival and 51 patients were found to reach one-year survival; while with 120 minutes treatment time,

97 patients were found to reach half-year survival and 89 patients were found to reach one-year survival. Which had significant differences, as shown in Table 4.

| Hyperthermiatreatment time | Total number of cases | Half-year survival cases (%) | One-year survival cases (%) |
|---|---|---|---|
| 60 minutes | 100 | 66 | 51 |
| 120 minutes | 100 | 97 | 89 |

Table 4. Comparison of patients' survival rate, $P < 0.05$ (with significant statistical difference)

### 2.3 Comparative analysis of complications

The complications occurred in the two groups of patients in the course of treatment were classified and statistically processed, and there was no statistical significance, as shown in Table 5.

| Hyperthermia treatment time | Total number of cases | Skin burn | Induration of subcutaneous fat | Perineum edema | Collapse | Total (%) |
|---|---|---|---|---|---|---|
| 60 minutes | 100 | 7 | 11 | 6 | 0 | 24 |
| 120 minutes | 100 | 9 | 12 | 5 | 0 | 26 |

Table 5. Complications ratio of two groups, $P > 0.05$ ( no statistical difference)

## 3. Conclusion

Through comparative analysis of the short-term and long-term efficacy, half-year and one- year survival period, and post-treatment complications of the two groups of patients. In the treatment of malignant ascites with 42℃ intraperitoneal hyperthermia chemotherapy, the efficacy and survival time of the patient group with an treatment time of 120 minutes were significantly better than those of the patient group with an

treatment time of 60 minutes, but there was no significant difference in complications after treatment.

## 4. Discussion

### a)

Malignant ascites is a common complication of abdominal and pelvic malignant tumor, which is caused by cancer cell planting and invasion and involving peritoneum, or caused by the blocked portal venous return system by tumor compression. Refractory malignant ascites is difficult to cure in general, and common survival is about 3 to 6 months. Nearly 70% of patients died within six months [3]. A large amount of ascites will affect the respiratory function, digestive function, and the further multi-organ metastasis of the tumor. Although repeated aspiration of ascites can relieve the patient's symptoms in a short time, the loss of a large amount of protein and microelements may accelerate the death of the patient. Intraperitoneal hyperthermia chemotherapy is an effective treatment method for malignant ascites, with small side effects, and has been widely used in clinical practice. Therefore, by seizing the temperature and time of action to maximizing the efficacy and controlling the patient's tolerance time reasonably is the problem we should pay attention to.

### b) The mechanism and principle of intraperitoneal hyperthermia chemotherapy

Intraperitoneal hyperthermia chemotherapy can be effective in treating malignant ascites, which mechanism is as follows: (1) the intraperitoneal filled with perfusate that containing a chemotherapeutic agent increased the probability of contact of medicine and cancer cells in abdomen, particularly the cancer cells that infiltrated in ascites. While a decrease in the drug clearance rate lead by the barrier function of peritoneum, the drug intraperitoneally residence time increased, which significantly enhanced the action concentration and treatment time of intraperitoneal chemotherapy. (2) Due to the clearance of the peritoneal barrier, the concentration of chemotherapy drugs in the bloodstream significantly reduced and the patient's tolerance to the side effects of chemotherapy drugs increased, which improved the safety of

treatment. (3) 41℃ to 43℃ hyperthermia can inhibit DNA replication, transcription, and repair, thereby directly killing cancer cells [4]. (4) after a certain time of 42℃ hyperthermia, the temperature of the tumor will be 3 to 7 ℃ higher than surrounding normal tissues in order to cause apoptosis of cancer cells and not to damage the normal tissues [5]. At the same time, the cell membrane permeability and blood flow rate increased, so that chemotherapeutic drugs can quickly enter tumor cells in large quantities, which effectively enhanced the concentration of chemotherapeutic drugs, thereby improving the efficacy of chemotherapeutic drugs [6].

**c)**

(1) Approved by the relevant experimental studies, 42℃ hyperthermia with 60 minutes treatment time has the cell survival rate $10^{-0.8}$, and with 120 minutes treatment time has the cell survival rate of $10^{-2}$; the effect of 42℃ hyperthermia treatment is proportional to the treatment time [5]. (2) Studies have shown that high temperature can promote the combination of alkylating agents and platinum drugs with the DNA of cancer cells, and ultimately lead to the death of cancer cells [7]. The prolonged effective temperature treatment time objectively extends the effective treatment time of the drug and cancer cells, and then achieves the purpose of further improving the curative effect. (3) Hyperthermia can also effectively inhibit the expression of drug-resistant genes and enhance the sensitivity of chemotherapy drugs [8]. So, when hyperthermia stops inhibiting, the drug resistance gene expression may terminate. The longer the duration of hyperthermia action, the longer the chemotherapy drugs can effectively affect the duration of action. (4) Hyperthermia has immune system suppression like reinforcing autoimmunity effect, destroying or deblocking tumor cells secreted blocking factors, and phagocytic cells migration inhibitory factors, etc., so that the body could restore tumor immune response and stimulate immunity enhancement [9]. (5) Studies have shown that hyperthermia can enhance the sensitivity of tumor cells to NK cells and increase the anti-tumor activity of parenchymal cells that stimulate T lymphocytes. Meanwhile hyperthermia produces a large amount of heat shock protein (HSP), and forms compound with a variety of tumor complex antigens that enhance the overall B proliferative activity of cells, which induce an

immunogenic effect [10]. (6) Experimental studies have shown that 42℃ hyperthermia with 2 hours of treatment time is optimum condition for inducing gastric cancer cell apoptosis with hyperthermia combined chemotherapy [11].

In summary, the treatment time of hyperthermia is directly related to curative effect through clinical curative effect, survival time comparison, and related theoretical experimental research on the treatment of malignant ascites with 42℃ intraperitoneal hyperthermia chemotherapy. The prolongation of 42 ℃ hyperthermia treatment time within a certain range can obviously improve the effect. The 120 minutes treatment time of 42℃ chemotherapy for malignant ascites treatment has certain clinical promotion value and further in-depth research value.

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