Reviewer: 1

1. We made critics in relation to lack of information about the primary tumor and the used vehicle.

We have supplemented additional data concerning primary tumor in MATERIALS AND METHODS, Human cancer cell lines section.

WAS: The AGS gastric adenocarcinoma and Caco-2 colorectal adenocarcinoma cell lines were purchased from American Type Cell Culture (ATCC Manassas, VA, United States). The T3M4 metastatic pancreatic ductal adenocarcinoma cell line was obtained as a gift from the European Pancreas Center (Heidelberg, Germany).

CHANGED TO: The AGS and Caco-2 cell lines were purchased from American Type Cell Culture (ATCC Manassas, VA, United States). AGS cell line is derived from a gastric adenocarcinoma of the stomach of a 54 year-old Caucasian female with no prior anti-cancer treatment. Caco-2 cells were isolated from a primary colonic tumor in a 72-year-old Caucasian male using the explant culture technique. Forms moderately well differentiated adenocarcinomas consistent with colonic primary grade II, in nude mice. T3M4 cell line was obtained as a gift from the European Pancreas Center (Heidelberg, Germany). This cell line was derived from a lymph node metastasis of the Japanese male patient, diagnosed with pancreatic ductal adenocarcinoma. It is characterized as pancreatic adenocarcinoma producing CEA, K-ras activated, and with slow cell growth.

Reviewer: 2

1. In this article, the apoptosis , toxicity and intracellular concentration of cisplatin on cells is analyzed to study peritoneal invasion of gastrointestinal tumor cells responding to cisplatin and high temperature. The study selected one of the three tumor cell lines, including gastric cancer, colon cancer and pancreatic cancer. Given the reliability of the findings, each of the 2~3 additional cell lines could be added to each kind of tumor.

We fully agree with your comment. However, we wanted to show that tumors of different origin have unlike response to hyperthermia and cisplatin treatment in terms of viability and apoptosis. We agree, that more detailed studies are needed, analyzing more than one cell line per corresponding tumor and/or specific anatomical location. It is very likely that different cells from the tumors of the same type could potentially respond very differently to the same treatment, as many studies point out that overall cancer cell population is very heterogeneous even in the same tumor. Nevertheless, this is out of the scope of this particular study. A more in depth analysis of the response of different cancer cell lines from the same GI tract location to the heated chemotherapy would be the next step of our research in the very near future.

2. In the intraperitoneal hyperthermic chemotherapy, the liver cancer cells could be with strong lethality with high concentration of chemotherapy drugs through the portal vein into the liver, but the article does not involve the corresponding description of

researches about liver cancer and liver cell lines, which would be need for the corresponding description and research.

Primary liver cancer and metastatic liver disease are not in the scope of our study. Our goal was to analyze the tumors that most commonly invade the peritoneum and HIPEC is used to treat them.

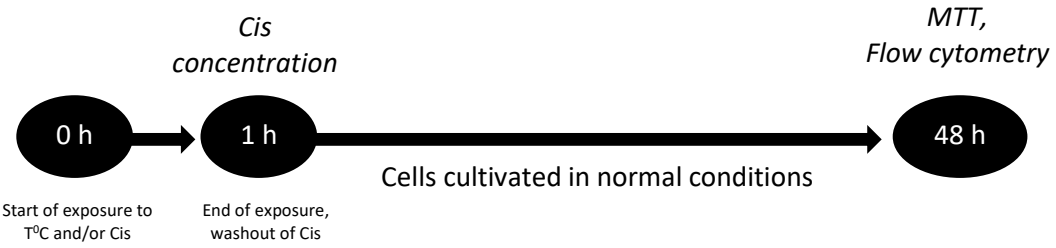
3. Intraperitoneal hyperthermic chemotherapy is a standard treatment for the peritoneal gastrointestinal cancer as we all know. The study on this basis to explore the optimal temperature and obtain the best therapeutic effect has a certain clinical significance. However, the results of in vitro experiments often do not necessarily coincide with the situation in vivo because of their limitations. Therefore, it is more meaningful for the conclusion of the study to increase the in vivo tests.

We absolutely agree that in vitro results not necessarily coincide with in vivo ones. This study and it's results provide some basic knowledge of the cellular response to hyperthermia and cisplatin treatment, which only to some extent could be applicable to the in vivo situation. However, this data allows for better and more targeted in vivo research in the future. Moreover, we expect to carry out in vivo experiments in the future allowing for the comparison of differences and similarities of in vitro and in vivo environment.

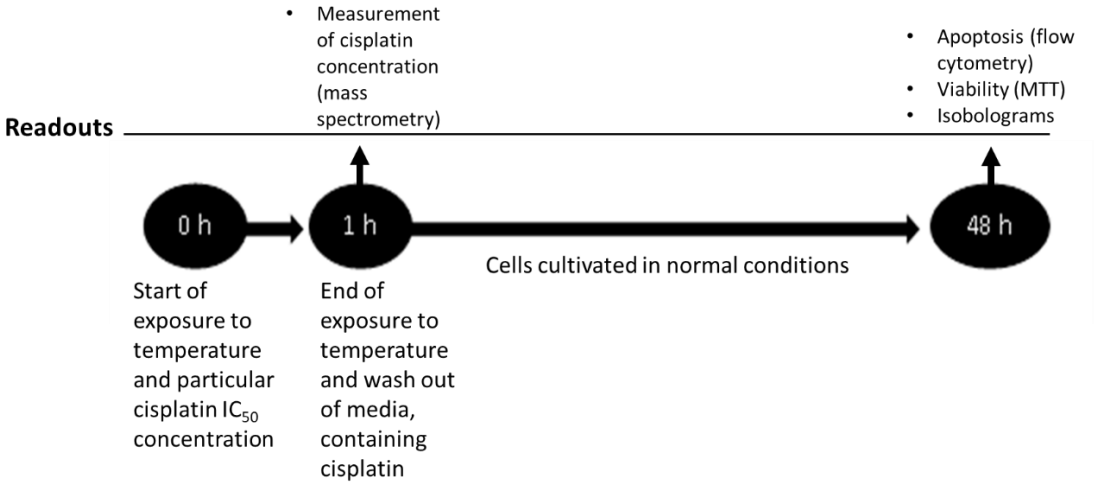
4. Figure 1 is too simple to describe about design of the whole experiment.

We agree with your comment and have supplemented Figure 1.

WAS:



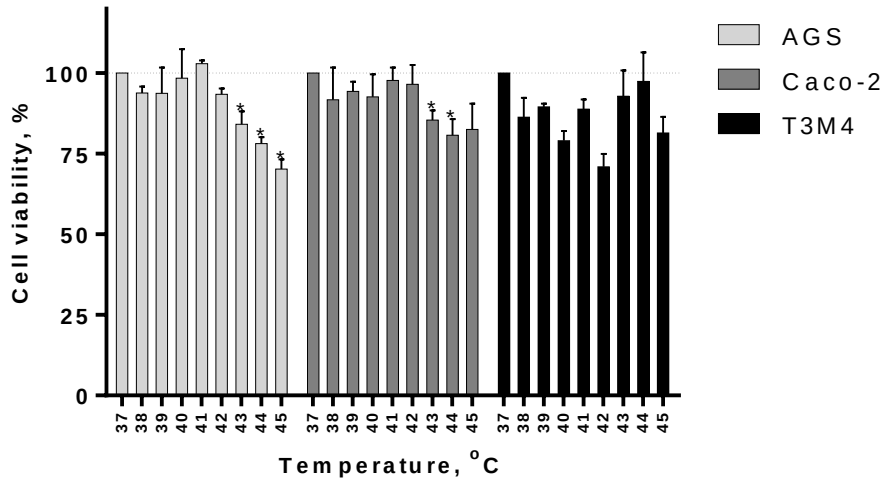
CHANGED TO:



5. In Figure 2, the T3M4 group is not marked with an asterisk on the chart to see if it is statistically significant.

Thank you for the insight. We have revised the data and changed the Figure 2.

WAS:



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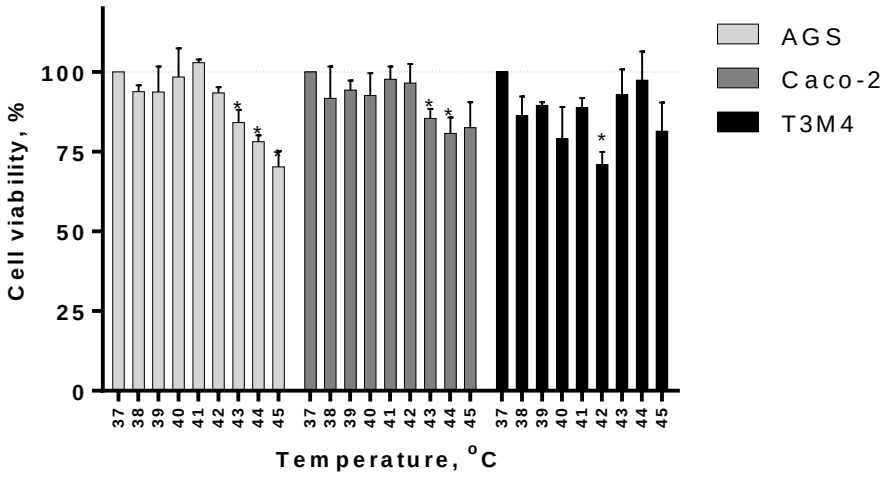

6. English expression may not be appropriate considering grammatical errors and single and plural usage errors. For example, the second sentence of paragraph 1 in Page 10 "AGS cells were the most sensitive to hyperthermia" should be changed to " AGS cells were the most sensitive one to hyperthermia ".

We fully agree with your comment, and changed the sentence in the 5th line of Results "Different cell lines have specific responses to hyperthermia" section to "AGS cells were the most sensitive one to hyperthermia. "