Review of: "Resectable Pancreatic Cancer With Peritoneal Metastases: Is Cytoreduction Combined With Hipec Effective and When?"

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Potential competing interests: No potential competing interests to declare.

The author reported a case series of patients with pancreatic cancer with peritoneal metastasis treated with cytoreduction combined with HIPEC. The manuscript aims to provide further insights on a rarely explored argument, a patient-tailored treatment currently outside guidelines, that otherwise might have clinical relevance in the future.

There are many critical issues regarding the manuscript, and some of them are summarized below:

-The title suggests that the authors will demonstrate if and when cytoreduction combined with HIPEC is effective for pancreatic cancer, but the small sample size, the absence of a control group, and the structure of the statistical analysis cannot help to do so. I'd change the title to a less assertive one.

-The case load of pancreatic resections per year by the surgical team would help to understand the experience of the department.

- Endpoints are not specifically defined (primary and secondary), neither in the text nor in the abstract.

- There isn't a table with a description of the general characteristics of the population.

- The considered population is too heterogeneous, both from a demographic and especially an oncological point of view, resulting in a high risk of bias. For example, no selection was made between patients who received neoadjuvant therapy and those who did not. The same is true for patients who underwent secondary cytoreduction because of recurrence.

-The extent of peritoneal disease has been previously identified as one of the most significant variables of survival in diseases presenting with peritoneal malignancy; the authors included patients with high variability in PCI (max 20); the authors should explain more precisely how they selected patients. In addition to tumor load, how did they select patients in relation to chemotherapy response? On which basis did they decide how long neoadjuvant therapy should last? The preoperative therapy strategies are critical in these tailored therapeutic programs.

-Peritoneal metastases are not uncommonly discovered at the time of planned surgery, as an incidental diagnosis. Were all the cases of peritoneal metastases discovered before the planned surgery, or were some sometimes unexpected? How did the authors proceed in this latter case? Did they postpone the treatment after a course of chemotherapy?

-Why wasn't neoadjuvant chemotherapy considered in all patients before surgery?

-Why did the authors use different agents during perfusion? "In 7 cases, gemcitabine (1000mg/m2) was used during perfusion, and in 3 cases, a combination of cisplatin (50mg/m2)+Mit-C (10mg/m2) was used."

-A detailed description of postoperative complications should be reported.

-"Three patients underwent secondary cytoreduction additionally because of recurrence". Authors considered these 3 as different cases in the analysis; even if they are different procedures, it is not correct to include them since, by doing this, 3 patients are considered 2 times in the same analysis.

-Univariable and multivariable analysis have no sense in a case series with such a small sample size; additionally, multivariable analysis of 10 patients is statistically incorrect, and so are the results derived from it. The authors should only present descriptive results of their series.

-How can the median follow-up be so inferior to median survival (11 vs 28 months)? This suggests that a high percentage of patients were soon lost at follow-up (censored in the survival analysis), and this, in a study with only 10 patients, cannot lead to any significant conclusions.

-Looking at the survival function, it seems that the 2 patients who died after surgery for complications are excluded from the analysis; 2 out of 10 patients died after surgery, they should be considered!!

-"Currently, 1 patient (9.1%) remains alive without disease 38 months after initial treatment, 5 (45.5%) died because of disease recurrence, 1 patient (9.1%) died because of reasons unrelated to the disease, and 4 patients (36.4%) are alive with disease recurrence." From this sentence, it seems that no patient was lost at follow-up, but from Figure 1, it can be noted that 5 patients were censored! Please explain.

Best regards.