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Letter to the Editor

Commment on the review entitled "A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer" by Chiva LM and Gonzalez-Martin A.

We have read the recent review on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) to treat advanced epithelial ovarian cancer written by Chiva & Gonzalez-Martin and we remained deeply concerned due to numerous severe imprecisions and misleading reasoning of the authors (Chiva and Gonzalez-Martin, 2015).

After a systematic revision of the literature the authors focused the analysis on the role of cytoreductive surgery and HIPEC in two time points of the natural history of advanced epithelial ovarian cancer (EOC): front line therapy and platinum sensitive recurrent disease. They came to the conclusion that the average weighted median overall and disease free survivals were 37.3 and 14.4 months, respectively for cases treated with the combined procedure at front line and recurrent disease.

A close analysis of Table 3 of the review, that gathers the information on 248 patients from 11 studies on the use of the combined therapy in front-line setting, leads us to raise two major criticisms: 1) the paper by Massari et al. that contributed with only two patients should be excluded due to the small sample size; (Massari et al., 2014); and 2) calculating the weighted average of the median OSs in this population of 248 patients is highly disputable as it penalizes the results of two studies in which the survival outcome was so favorable that the median was not reached. In the series by Roviello et al. the study was closed after a median follow-up of 27 months and 5 year OS was 55% (Roviello et al., 2010). On the other hand Deraco et al. reported a 5 year OS of 60.7% after a median follow-up of 25 months (Deraco et al., 2011). In both studies the median OSs, if the follow-ups were longer, it could be expected to be of at least of 60 months. If these hypothetical figures were considered in the calculation of the weighted average of median OS the results would be 42.1 months and not 37.3 months.

Moreover, we do not agree that the results obtained with cytoreductive surgery and HIPEC in the first-line setting could be compared with those reported by Bookman et al., the largest cohort of advanced EOC patients ever reported in the context of a phase III clinical trial (Bookman et al., 2009). Firstly, both populations have been staged using different systems (Peritoneal Cancer Index vs. FIGO stage). Secondly, 85% of patients in the Bookman trial had FIGO stage III disease. This does not necessarily mean that all these patients had extensive peritoneal carcinomatosis, as stages IIIa and IIIb are characterized by microscopic peritoneal disease and peritoneal implants of less than 2 cm. Considering that the average of peritoneal cancer index in patients treated in primary setting with CRS and HIPEC was 14 it is reasonable to consider that the cohort of patients from ICON-5 trial, on the average, had at least less extensive peritoneal disease.

In any case, the major caveat in the Chiva's review is the fact that the authors focus their discussion on the role of HIPEC and simply ignore the importance of cytoreductive surgery in the final prognostic gain of advanced EOC patients. It is well known that the dimension of the residual disease left behind after a cytoreductive surgery is the most powerful determinant of the outcome (Chang et al., 2013).

They depart from the assumption that the so-called debulking surgery performed by gynecologic oncologists is the same thing as the cytoreductive surgery done by peritoneal surgeons. Be this assumption true it could be troublesome to justify why in the recent multicentric randomized study by Vergot et al., only 42% of patients in the study group submitted to upfront surgery had residual disease of less than 1 cm (Vergote et al., 2010). Worse still, the overall rate of complete cytoreduction was 19.4%. This unacceptably low rate of optimal surgeries is likely a result of a nonproper surgical training in multivisceral resection surgeries and peritonectomy procedures and above all, to a lack of standardization of the so-called debulking surgery among gynecologic oncologists (Naik and Barton, 2010). Fortunately, there are some exceptions to this trend in the gynecologic oncology field. Dr. Chi et al. at the Memorial Sloan Kettering have actively changed the attitude toward the issue of surgical approach to EOC. They have started adopting a more aggressive policy to treat advanced EOC by means of a multidisciplinary collaboration with surgeons, especially to approach extensive disease in the upper abdomen and this resulted in positive impact both in terms of overall and disease free survivals (Chi et al., 2009).

Another disputable issue approached by Chiva & Gonzalez-Martin is that of morbidity and mortality related to the combined procedure. It is unfair to highlight the results of the randomized trial, in which I myself was the co-investigator, the rates of 57% of severe morbidity and 28% of mortality. First, because these outcomes were calculated on a population of 7 only patients recruited to the experimental arm during the entire period of activity of the trial. Second, because the eligibility criteria for this trial was platinum resistant recurrent or persistent disease after the completion of first line chemotherapy – that represents a completely different population from the subsets elected by Chiva. Third, the major reason for the closure the trial was not the high rates of severe side effects but the slow patient accrual.

We are aware that the conduction of systematic reviews is very challenging, especially in the field of peritoneal surface malignancies, where the level of evidence is still low. Although we strongly agree with the authors regarding the experimental nature of the combined treatment – the motif why it should only be offered to patients in the context of a clinical trial–, we cannot accept inaccurate and superficial analysis that could lead to misleading and counterproductive conclusions. In any case, a definitive answer regarding the actual contribution of cytoreductive surgery and HIPEC in prognosis of advanced EOC will only be provided by the eagerly awaited results from the ongoing randomized trial on this issue.

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Marcello Deraco
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Department of surgery, Colorectal Cancer Unit, Peritoneal Surface Malignancies Program, Via Venezian, 1, Milano, MI Cap 20133, Italy
Corresponding author.
E-mail address: marcello.deraco@istitutotumori.mi.it

Shigeki Kusamura
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Department of surgery, Colorectal Cancer Unit, Peritoneal Surface Malignancies Program, Via Venezian, 1, Milano, MI Cap 20133, Italy

Dario Baratti
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Department of surgery, Colorectal Cancer Unit, Peritoneal Surface Malignancies Program, Via Venezian, 1, Milano, MI Cap 20133, Italy

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