Cytoreduction in Advanced Ovarian Cancer: ¿all or nothing?

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“The whole is present even in the broken pieces”

Aldous Huxley

In 2008 the Gynecologic Oncology journal publishes the transcript of the debate Cytoreduction vs Neoadjuvant Chemotherapy for Ovarian Cancer? This discussion held by Dr. Dennis Chi, from the Sloan-Kettering Cancer Center in New York, and Dr. Peter Schwartz, gynecologist oncologist of Department of Gynecology at the University of Yale, revolved mainly around the controversy that existed by the time between primary surgery and neoadjuvant chemotherapy. The first question that makes both panellists moderator was: Do you think that the patient with voluminous and multifocal disease in which occurs a debulking achieving a microscopic residual disease has the same prognosis than patients with more established foci disease and it is “cytoreduced” also to only microscopic foci? Is the biology of the disease or surgery who determines the prognosis?

Chi textual response was the following:

Although for the sake of this debate it would be more interesting for my opponent and I to say one or the other, I think we both agree that it is both tumor biology and surgery that determine outcome. I think we would also agree that a patient with advanced, widespread cancer that is refractory to all chemotherapy has poor tumor biology and will not have her survival significantly prolonged by even the most complete of cytoreductive efforts. However, where our opinions differ is that I believe that there is no reliable and accurate way of predicting whether an individual patient with advanced ovarian cancer has a malignancy with “good” vs “bad” tumor biology.

Moreover, in his reply Schwartz cites the results of Scottish Randomized Trial on Ovarian Cancer (SCOTROC-1) published in 2006 in the Journal of Clinical Oncology, which showed that patients with advanced ovarian cancer who benefited from extensive debulking were those with a low score on the extent of the tumor, i.e. probably a disease with a less aggressive biology. He
concludes the answer by saying that this study shows that survival of patients adequately cytoreduced is better when the disease is focused, compared with those whose disease is multifocal and voluminous.

Before 2010, the debate was spinning on what was the best strategy in patients with advanced ovarian cancer. The divided opinions between the cytoreductionists and supporters of neoadjuvant chemotherapy followed by interval surgery were most noticeable. Rereading this transcription the fierce controversy that existed for those days can be re-edited. Only the publication of the EORTC study, in September 2010, allowed calming the differences in some ways. The iconic European multicenter study showed that interval surgery preceded by neoadjuvant chemotherapy with carboplatin and paclitaxel (QtNeo-CI), was not inferior, in overall survival, to primary cytoreduction. However, we see that although the answers of the two panelists are still located at "different sides", they agreed that the biology of tumor is a fundamental aspect in the prognosis. As well Chi points in his reply, for the moment there is no a reliable model for estimating the prognosis of the patient based on the spread of the disease, regardless a complete cytoreduction of is achieved (R0). In fact, in the first attempts by stratifying the operative findings, by laparoscopy or by tomography, most of the authors considered that the bulky disease affecting the upper abdomen was a strong criteria of irresecability. Especially for those who were supporting the QtNeo-CI. If the imaging or laparoscopic scanning determines the presence of bulky disease in upper abdomen, then the best option is considered neoadjuvant chemotherapy rather than attempting a primary cytoreduction with a high chance of being unsuccessful.

In another part of his answer, Chi wonders:

But how do they know that the patient with tumor on the liver, diaphragm, or spleen does not have “good” tumor biology, but has just had the cancer for a longer time than another patient with supposed “good” tumor biology who has more limited disease at presentation?

And he had good reason to doubt. With the exception of the SCOTROC-1, considered the pioneered serie in the concept of the tumor biology as prognostic factor, there was not a fairly acceptable evidence. Recognize in some form that in patients with a tumor with an aggressive biologic behavior, even achieving a complete debulking (R0) there is not an improved prognosis, it was dare to doubt the Holy omnipotence of cytoreductive surgery and the benefits of adjuvant chemotherapy.

To resolve this question, in March 2015 Horowitz NS et al published in the Journal of Clinical Oncology the article Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. With a convincing sample of 2,655 patients with primary ovarian cancer and peritoneal cancer stage IIIC and IV, all of them participants of the gigantic multicentre study Gynecologic Oncology Group 182 (GOG-182).

The authors set out to evaluate the effect of the spread of the disease, the complexity of the surgical procedures performed, and the residual disease after surgery, linking it with progression-
free survival (PFS) and overall survival (OS). This sample of patients, which included only patients with residual disease less than 1 cm in diameter were stratified into two groups: a) 860 (32.4%) patients without measurable residual disease (R0) and b) 1,795 (67.6%) patients with gross residual disease less than 1 cm (ER). Regarding the spread of disease was established a score index, called the Disease Score (DS), taking into account the presence of disease in organs or anatomical sectors and three groups were established: a) low DS: 173 patients, b) moderate DS: 845 patients and c) high DS: 1,636 patients. Similarly defined groups of surgical complexity (SC) in the following way: a) low SC: 456 patients, b) moderate SC: 1,770 patients and high SC: 429 patients.

The results confirm something known: those patients with residual disease less than 1 cm (MR) had a worse prognosis than patients with complete cytoreduction (R0) (PFS 15.1 vs. 23.4 months P < 0.01; OS: 40.6 vs 76.9 months P < 0.01).

But the most important finding of this study was that patients with complete cytoreduction (R0) with DS moderate/low when compared with those with R0 and high DS, the first had an PFS from 33.2 vs 18.3 months (P < 0.01) and a OS of 82.3 vs. 50.1 months (P < 0.01), respectively. This finding confirms that regardless of achieving a complete cytoreduction, patients with disseminated disease will find a PFS and OS similar to that of the patients with MR.

Of the 1,636 high DS patients in 199 a R0 was achieved (12%); in these patients despite being achieved a R0, the PFS and the SG was clearly lower. (high FPS: 15.1 vs. moderate: 23.4 vs low: 33.9 months, respectively; P < 0.01) (SG 40.2 vs 70.8 vs 86.3 months, respectively; P < 0.01).

In terms of the complexity of surgical procedures (CS) patients with more complex surgical procedures (high CS) had a worse PFS compared with those who received less aggressive surgery (high CS 14.9 vs CS moderate 18.0 vs CS low 18.5 months; P< 0.001). In relation to the OS the differences observed among the three groups were not statistically significant.

This influential study argues that the prognosis in advanced ovarian cancer is not only determined by the amount of disease at the end of the surgery, but by the volume and distribution of the neoplasm before surgery. Being the largest published series to date will most likely be a central item in the discussions and in the lines of research to come. Show that the initial tumor load and residual disease act together defining clearly the PFS and OS, joins the conclusion that the CS (complexity of surgical procedures) is not, as previously thought, an independent prognosis indicator.

With regard to morbidity, this series reports that between 20 and 25% of the patients undergoing a high CS presented serious complications, with a mortality rate of 1-2%. This finding supports a trend increasingly accepted, that just before the real possibility of a complete cytoreduction (R0), with prediction of debulking study models, is justified to undertake a high-complexity surgery.

The most important challenge in advanced ovarian cancer surgery is to achieve a complete cytoreduction (R0) and not settle for a minimal residual disease, as was thought until recently, a...
hard objective sometimes impossible to reach. This profound change of paradigm will need biological platforms to determine tumor aggressiveness and diagnostic models able to predict with certainty the true possibilities of a complete cytoreduction.


References: