Advanced Ovarian Cancer: The Canadian Experience

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What I've taken into account throughout all these years (and still keep doing) is the honest recognition that if I write is because of some kind of force that has been bestowed. I captured that opportunity by pure chance and fortune turned me into a novelist. Even if it's talking from the perspective of the results, something or someone gave me that faculty. I can only thank in all honesty what has happened to me so far.

Haruki Murakami, What I talk about when I talk about running, 2015.

With the publication of the study of EORTC *Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer* in 2010[1] and of the study *Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer* (CHORUS) [2] in 2015, it was demonstrated that overall survival, after neoadjuvant chemotherapy for 3-4 cycles with carboplatin and paclitaxel and interval surgery (NACT), is not inferior to that obtained after optimal primary cytoreductive surgery plus adjuvant chemotherapy (PCS). Despite the low rate of optimal primary debulking reported (41.6%), especially in the EORTC, compared to a rate of 71% in the series of Chi D et al[3], under the same inclusion criteria of the EORTC, the NACT has been gradually positioning itself in the community of oncology gynecologists of North America, as an alternative in the management of patients with advanced ovarian epithelial cancer. Today it is still considered that PCS is the treatment of choice in this group of patients, and is especially aimed at those patients in whom it is feasible to achieve complete cytoreduction (R0) or at least with residual disease less than 1 cm. The guidelines of the Society of Gynecologic Oncology in conjunction with the American Society of Clinical Oncology, published in 2016[4] have reiterated this recommendation. However, one of the topics that remains to be delineated is the need to predict, with a high level of certainty, the probability of achieving complete or optimal cytoreduction through the use of algorithms based on imaging or laparoscopic findings before treatment, which was widely discussed in a previous article on this site and published in April 2015[5].

In April 2018, *The Canadian Retrospective and Multicenter Cohort Study Examining Survival Outcomes of 852 Women With Advanced Ovarian Cancer: A Multi-institutional Cohort Study*[6] was published in the *International Journal of Gynecologic Cancer*. A series that included 852 patients

diagnosed with high-grade serous ovarian cancer stages IIIC and IV. The sample was collected in four Canadian cancer care centers between January 2007 and December 2013. With an average follow-up of 4.1 years, the objective was to evaluate the overall survival. To this end, 449 patients undergoing PCS were compared, which constituted 53% of the sample, with 403 patients (47% of the sample) who received NACT. The overall complication rate for the series was 8% (72 patients), of which 39% had undergone highly complex surgeries that included extensive intestinal, peritoneal or diaphragmatic resections, liver resections or splenectomies.

In the results, overall survival at 5 and 7 years for the complete sample, regardless of the volume of residual disease, in the PCS group was 42% and 30%, respectively. While for the NACT group it was 22% and 0.75%, for the 5 and 7 years, respectively. This difference was statistically significant.

When analyzing the sample, based on the amount of residual disease, in the PCS group the overall survival at 5 and 7 years, in the group without residual disease (R0) was 68% and 55%, respectively. In the group, residual disease between 1 mm and 9 mm was 34% and 24%, respectively. While for the group with residual disease equal to or greater than 10 mm, overall survival at 5 and 7 years was 27% and 17%.

In the group undergoing NACT, overall survival at 5 and 7 years in patients without residual disease was 32% and 0%, respectively. In the group of patients with residual disease between 1 mm and 9 mm, it was 15% and 0%, while those with residual disease equal to or greater than 10 mm, was 0% for 5 and 7 years.

Regarding the average overall survival time, stratified by therapeutic modality and residual disease, the following data were obtained:

	Without residual disease	Disease between 1 mm and 9 mm	Disease equal to or greater than 10 mm
PCS	73.5 months	42.4 months	33.6 months
NACT	38.2 months	23.9 months	21.1 months

p<0,001

When comparing overall survival between the PCS group with residual disease between 1 mm and 9 mm (42.4 months) and the NACT group (38.2 months), without residual disease, the statistical difference was not significant. (p = 0.17)

A study with interesting conclusions and recommendations, whose main contribution is the analysis of a significant sample of patients exclusively diagnosed with high-grade serous carcinoma or ovarian cancer type II, something unpublished. This study confirms once again that patients in the PCS group, with complete cytoreduction (R0), have the best prognostic profile.

However, it is a series with the expected limitations due to its design as a retrospective cohort study, with some methodological biases that need to be evaluated. The criteria used to assign patients to one group or another is not clearly specified. In fact, the authors declare in the discussion that this constituted a limitation in its development. This methodological bias was

overcome, several years ago, with the publication of EORTC and CHORUS. In these studies, patients were assigned, for the first time, in each treatment modality at random and not based on the possibility of cytoreduction. Both studies came to break with the design that prevailed for the time, in which the patients assigned to the NACT group were usually patients with a more precarious clinical profile and/or had a disease markedly more widespread at the time of diagnosis, which was an evident methodological distortion that did not allow a fair comparison between both treatment modalities. The true strength of EORTC and CHORUS, as robust evidence, underlies a casuistry of almost 1,200 patients, with a prospective, randomized design and with the participation of more than one hundred centers around the world. The evidence emanated from these two large studies has allowed us to better delineate the ideal therapeutic strategy in advanced ovarian cancer.

Currently, decision-making must take into account that the treatment of choice in advanced ovarian cancer is undoubtedly primary surgery with adjuvant chemotherapy. However, a good proportion of patients present a clinical profile, imaging or laparoscopic criteria that point to a high probability of not being able to achieve optimal cytoreduction. In these cases the alternative of NACT emerges. One of the recommendations made by the authors of the Canadian series is that all patients with advanced ovarian cancer should be referred and evaluated by a team of specialists with experience in this pathology and avoid indicating, without first evaluating the possibilities of optimal debulking, the use of NACT.

Definitely the stage in which both treatment modalities discussed the place as standard therapy, today can be considered as a moment already overcome. PCS remains the most recommended behavior, as long as the patient's clinical conditions allow it, once they have been screened by a reliable algorithm to predict the possibility of achieving optimal debulking, or in the best case scenario. a complete cytorecution. Insist on seeing them as opposed modalities, it is ultimately a wrong perception.

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References

1. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. New Engl J Med. 2010;363:943-953.
2. Kehoe S, et al., Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015;386 (9990: 249–257.
3. Chi DS, Musa F, Dao F, et al. An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol 2012;124:10Y14.
4. Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Gynecol Oncol 2016;143 (1):3-15.

5. Sánchez-Lander J. It is possible to predict optimal debulkingin advanced ovarian cáncer? https://intervalolibre.files.wordpress.com/2015/04/prediccion-en-cc3a1ncer-de-ovario-2015-ingles.pdf
6. May T, Altman A, McGee J, Lu L, Xu W, Lane K, Ghatage P, Rosen B. Examining Survival Outcomes of 852 Women With Advanced Ovarian Cancer: A Multi-institutional Cohort Study. Int J Gynecol Cancer 2018 Apr 4. doi: 10.1097/IGC.0000000000001244