Laparoscopic secondary cytoreductive surgery: let's not make the same assumptions

Pedro T Ramirez ,[1] Rene Pareja [2]

[1]Department of Gynecologic Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]Gynecology, Gynecologic Oncology, Clinica ASTORGA, Medellin, and Instituto Nacional de Cancerología, Bogotá, Colombia, Medellin, Colombia

Correspondence to
Dr Pedro T Ramirez, University of Texas MD Anderson Cancer Center, Houston, USA; peramire@mdanderson.org

Received 23 December 2022
Accepted 1 January 2023

► http://dx.doi.org/10.1136/ijgc-2022-003904

To cite: Ramirez PT, Pareja R. *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2022-004255

The role of secondary cytoreductive surgery in advanced ovarian cancer has been explored for several years. Retrospective data demonstrated that there might be a survival advantage in patients who underwent secondary cytoreductive surgery, particularly those who had no gross residual disease at completion of surgery.[1] Subsequently, two landmark studies were published evaluating overall survival outcomes in patients with recurrent ovarian cancer, comparing secondary surgical cytoreduction followed by chemotherapy vs chemotherapy alone.

In the first of these, Gynecologic Oncology Group (GOG) 213, 485 patients were randomized (240 to secondary cytoreduction before chemotherapy and 245 to chemotherapy alone).[2] Patients had to have a platinum free interval of 6 months or more and had to have investigator determined resectable disease (to no macroscopic residual disease) prior to secondary surgery; patients then received platinum based chemotherapy or platinum based chemotherapy alone. Complete gross resection was achieved in 67% of patients. The investigators found that after a median follow-up of 48.1 months, the hazard ratio (HR) for death (surgery vs no surgery) was 1.29 (95% confidence interval (CI) 0.97 to 1.72; p=0.08). This corresponded to a median overall survival of 50.6 months and 64.7 months, respectively. The study concluded that secondary cytoreduction followed by chemotherapy did not result in longer overall survival than chemotherapy alone.

The second study, DESKTOP III (A Randomized Multicenter Study to Compare the Efficacy of Additional Tumor Debulking Surgery vs Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer), was also a randomized controlled trial of patients with recurrent ovarian cancer and a platinum free interval of 6 months or more.[3] Patients were randomized to undergo secondary cytoreductive surgery and then to receive platinum based chemotherapy or to receive platinum based chemotherapy alone. The primary endpoint of the trial was also overall survival. Here, 407 patients were randomized (206 were assigned to cytoreductive surgery and chemotherapy, and 201 to chemotherapy alone). Complete resection rate was 75%. Median overall survival was 53.7 months in the surgery group and 46 months in the no surgery group (HR for death 0.75; 95% CI 0.59 to 0.96; p=0.02). The authors concluded that in patients with recurrent ovarian cancer, cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone.

Now, this brings us to the point of the surgical approach; for these two previous randomized trials, this was via laparotomy. The findings from such level I evidence confirms that these results are achievable through an open approach. Naturally, some might argue that if a patient meets the criteria for secondary cytoreduction and ideally has a single site of disease, in an 'easily accessible' location, then a laparoscopic approach might seem like a reasonable option. However, in the field of gynecologic oncology, we were all witness to what happens when we make assumptions about the oncologic safety of a minimally invasive approach without appropriately testing it in a prospective manner. The LACC (Laparoscopic Approach to Cervical Cancer) trial[4] was a medical reversal of a paradigm where the community of gynecologic oncology assumed that a laparoscopic or robotic radical hysterectomy offered similar oncologic outcomes to an open approach in patients with early cervical cancer. The well known results of this trial showed an unexpected finding, as evidenced by a higher recurrence rate and worse disease free survival and overall survival in the minimally invasive group.

In this month's issue of *International Journal of Gynecological Cancer*, Conte et al[5] retrospectively evaluated the feasibility and survival outcomes in patients with recurrent ovarian cancer who underwent secondary cytoreduction via an open versus minimally invasive surgical approach. The authors included platinum sensitive patients with recurrent epithelial ovarian cancer and had preoperative positron emission tomography (PET)/computed tomography (CT) and diagnostic laparoscopy before embarking on the secondary cytoreduction. A total of 276 patients (62 minimally invasive and 214 open) were included and the complete gross resection rate was 95%. As generally anticipated, early postoperative complications were significantly higher in the laparotomy (33%) versus the minimally invasive surgery (10.3%) group (p=0.004). With a median

follow-up of 32 months (range 1–92), median post-recurrence survival was 81 months in the minimally invasive group and not reached in the open group (p=0.11). The investigators concluded that patients with single or oligometastatic recurrences may be offered a minimally invasive secondary cytoreduction. The authors should be congratulated for their efforts in exploring this important question and for clearly defining strict inclusion criteria.

Here are a few factors to be considered before full conviction that a minimally invasive approach is safe, feasible, and that it offers similar oncologic outcomes. In others words, let's pause and consider! First, let's proceed to the obvious; the numbers are small (only 62 patients in the minimally invasive group). We know that we cannot make an adequate evaluation of oncologic outcomes with such few numbers of patients, particularly when we do not have the data on follow-up time in that particular group versus the open surgery group. Second, this study includes a very select group of patients who underwent stringent evaluation with preoperative PET/CT and screening laparoscopy for cytoreduction. In other words, these are patients who clearly had the highest chances of achieving cytoreduction to no gross residual disease. Third, the procedures were performed by a highly specialized group of surgeons with an annual volume of radical surgeries in advanced ovarian cancer of more than 30 cases, both by open and minimally invasive approaches, further reaffirming that this is a group of patients that is likely to have improved outcomes. Fourth, we do not have information regarding post-surgery treatment or treatment at the time of subsequent recurrence or progression. These could have impacted the outcomes, particularly in an era of poly ADP ribose polymerase (PARP) inhibitors favoring improved outcomes in those patients with BRCA mutations. Fifth, the groups are not balanced in terms of type of recurrence, with 50% of patients undergoing minimally invasive surgery having a single site of disease recurrence versus only 26% in the open surgery group. The groups were also not balanced for the rate of extensive procedures, such as peritonectomy (38.7% in the minimally invasive group vs 61.7% in the open surgery group) or large bowel resection (1.6% in the minimally invasive group vs 22% in the open surgery group). This could potentially mask a detrimental effect of minimally invasive surgery, if there is one, by having the benefit of a more favorable group of patients.

In the end, what can we take from these data? A few things should be recognized, which include that minimally invasive secondary cytoreduction in very select patients is feasible and safe, although in select centers and by select surgeons proficient in such an approach. When considering oncologic outcomes, that's when we must stop (hard stop!) and remember what happened in the LACC trial. To that end, we should call for prospective randomized trials. However, experience tells us that this will be unlikely as large numbers of very select patients would be needed, the cost of conducting such trials would likely be prohibitive, added to that the stratifications (prior bevacizumab or PARP inhibitors, time to recurrence, single site vs oligometastatic, treatment at subsequent recurrence, and enrollment, for some, in clinical trials at some time during recurrence), and likely we are left with data on just feasibility and aiming for large registries at best.

Twitter Pedro T Ramirez @pedroramirezMD and Rene Pareja @RParejaGineOnco

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

ORCID iDs
Pedro T Ramirez http://orcid.org/0000-0002-6370-8052
Rene Pareja http://orcid.org/0000-0003-0093-0438

REFERENCES

1 Al Rawahi T, Lopes AD, Bristow RE, *et al*. Surgical cytoreduction for recurrent epithelial ovarian cancer. *Cochrane Database Syst Rev* 2013;2016.
2 Coleman RL, Spirtos NM, Enserro D, *et al*. Secondary surgical cytoreduction for recurrent ovarian cancer. *N Engl J Med* 2019;381:1929–39.
3 Harter P, Sehouli J, Vergote I, *et al*. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. *N Engl J Med* 2021;385:2123–31.
4 Ramirez PT, Frumovitz M, Pareja R, *et al*. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 2018;379:1895–904.
5 Conte C, Marchetti C, Loverro M, *et al*. Role of minimally invasive secondary cytoreduction in patients with recurrent ovarian cancer. *Int J Gynecol Cancer* 2023. doi:10.1136/ijgc-2022-003904