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Interval cytoreduction for advanced ovarian cancer: is minimally invasive surgery ready for the next prospective randomized trial?

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A number of centers have adapted a laparoscopic approach as a tool in triaging patients with advanced ovarian cancer to primary cytoreductive surgery or neoadjuvant chemotherapy.[1] The role of laparoscopy has also been explored in the setting of tumor reduction in select patients with complete response after neoadjuvant chemotherapy, although the available data are limited to small, single-institution case series with short follow-up information.[2–4] A recent analysis of the National Cancer Database by Melamed and colleagues[5] identified a cohort of patients diagnosed with stage IIIC and IV epithelial ovarian cancer between 2010 and 2012 who underwent neoadjuvant chemotherapy and interval cytoreduction. The authors compared the 3-year overall survival between the laparoscopic and open approach as their primary objective. In that study, 3071 women met the inclusion criteria, and of these 450 (15%) patients underwent surgery initiated by laparoscopy. There was no difference in 3-year survival between patients undergoing laparoscopy (47.5%, 95% CI 41.4–53.5) and laparotomy (52.6%, 95% CI 50.3 to 55.0, p=0.12). The frequency of suboptimal cytoreduction was not different between laparoscopy and laparotomy (20.6% vs 22.6%, p=0.29, respectively). Accepting the limitations of an analysis of a national database registry, the study concluded that in select patients laparoscopic interval cytoreduction appears to have similar 3-year survival rates to the open approach. A previous single institution retrospective study (MISSION Trial) evaluated a small cohort of 30 patients with advanced epithelial ovarian cancer who underwent laparoscopic interval cytoreduction.[2] In that study, although limited by low participant numbers, the authors showed that such an approach was feasible and safe in terms of peri-operative outcomes and survival rates.

In this month's issue of the *International Journal of Gynecological Cancer*, Fagotti and colleagues[6] present the results of a multi-center study, comprising a total of 127 patients with advanced epithelial ovarian cancer, that compared the minimally invasive surgery vs open approach when performing interval cytoreductive surgery. In the methodology the authors provided very specific inclusion criteria, not only for patient selection, but also for controlling for adequacy of surgeon experience in performing the minimally invasive approach. Most patients had either a complete (29%) or partial (67%) response to the neoadjuvant chemotherapy. All patients underwent optimal (defined as residual tumor <1 cm) cytoreduction, with a median operative time of 225 (range 60–600) min and median blood loss of 100 (range 70–1320) mL. The rate of conversion to laparotomy was 3.9%. The authors reported a median follow-up of 37 (range 7–86) months. In that time, 58% of patients had recurred and 24% had died of disease. Of note, most recurrences (76%) were intra-peritoneal. The median progression-free survival was 23 months and the 5-year overall survival was 53%.

Several limitations should be noted not only in this study, but also in others evaluating the utility of laparoscopy in performing cytoreductive surgery. First, is the fact that currently there is not a concrete recommendation as to how to best assess ideal candidates for an attempt at cytoreduction in the interval setting. Currently, there is a broad range of imaging studies, such as positron-emission tomography, computed-tomography scans,magnetic resonance imaging, and even ultrasound, that are performed to determine whether a patient might be a candidate for surgery. Similarly, others have proposed the consideration of a laparoscopic assessment prior to surgery to gain a more accurate representation of the volume of disease. Second, one of the challenges in performing laparoscopic cytoreductive surgery remains the limited visualization of certain regions of the abdomen, including the retrohepatic fossa, lesser sac, root of the mesentery, or retroperitoneal lymph nodes. To that end, many would argue that a flaw of studies proposing a minimally invasive interval cytoreduction is that they fail to provide concrete evidence of reassurance that there is no residual disease. In other words, none offer confirmatory post-operative imaging to document a true complete resection of disease. Third, the fact that even though this was a multi-institutional study, the total number of patients remains low, thus indicating that the laparoscopic approach to interval surgery is not a widely

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accepted principle. This raises the question as to whether broad adaptation will be feasible in the absence of clear survival equivalency when compared with open cytoreduction. Lastly, we have very limited information regarding the adverse events associated with the laparoscopic approach, as regards to intra- or post-operative complications.

The most important consideration in this setting remains whether the laparoscopic approach is equivalent to the open approach in terms of oncologic outcomes. In other words, are we certain that we are not harming our patients when proposing a change in the standard practice? This clearly calls for the consideration of prospective randomized multi-institutional trials with the primary objective of evaluating disease-free survival and recurrence rates. The authors ought to be commended for their efforts to answer this important question in our field, and certainly for their contribution to the wealth of knowledge pertaining to the use of minimally invasive surgery in the setting of advanced ovarian cancer.

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