



## Correspondence

**RE: Pattern of and reason for postoperative residual disease in patients with advanced ovarian cancer following upfront radical debulking surgery**


We have read with great interest the article by Heitz et al. (2016), and would congratulate with them for the effort in investigating technical reasons of suboptimal debulking in advanced epithelial ovarian cancer (AEOC). In this study, the Authors suggest that, because of a much longer median overall survival (OS) in complete/optimally resected patients, pre-operative identification of unresectable sites may help to develop adequate surgical training and to identify patients that would better benefit from alternative strategies. Their overall rate of patients unsuitable for primary debulking surgery (PDS) is 30.3%, including women primarily excluded from surgery and those not achieving RT  $\leq$  1 cm.

In the Discussion section, the Authors compare their rates of optimal debulking with those from other experiences (Gallotta et al., 2013; Chi et al., 2009; Aletti et al., 2009), questioning the role of staging-laparoscopy (S-LPS) according to Rome's experience. They refer to the paper published in 2013 (Gallotta et al., 2013), where 50.7% of patients were deemed not eligible for PDS, thus being triaged directly to neoadjuvant chemotherapy (NACT). Moreover, they extrapolate the data to the entire Rome's population, showing a final rate of complete and optimal debulking of 30% and 13.7%, respectively. They conclude "*this strategy seems to lead to a selection and separation of patients in different cohorts but without substantially improving outcome*".

In the light of these statements, some clarifications are needed.

1. As acknowledged by the Authors, the first limitation of their study lies in the comparison with data published earlier, since inclusion criteria, treatments and follow-up might be different. In particular, the first series investigating S-LPS refer to the period 2006–2010, when upper abdominal techniques were recently introduced in our practice (Gallotta et al., 2013). This is proven by the most recent publication by Petrillo et al. (2015), who reported a complete/optimal resection rates of 57.7% and 23.1% respectively, which appear in line with the ESGO recommendations (Advanced (Stage III-IV) Ovarian Cancer Surgery Quality Indicators), and consistent with those shown by the German group (66.1%  $p$ -value = 0.114; 25.4%;  $p$ -value = 0.308). The minor differences in terms of absent RT, still existing between Petrillo and Heitz's series, besides a general accepted variability, may be explained with the inclusion of FIGO stage IIIB patients in German "PDS group" (13.0%) and the exclusion of high-risk cases (data not shown in the German paper). The rate of suboptimal resection in the Rome's series was 19.2% ( $n = 45/234$  patients) with respect to 8.5% ( $n = 49/578$  patients) reported in the German's experience ( $p$ -value = 0.001). However, among the 45 Roman women with RT  $>$  1 cm, 18 of 234 (7.7%) were deemed unresectable

at S-LPS due to mesenteral retraction and/or bowel miliaric carcinomatosis and/or PIV  $\geq$  10, thus being pre-operatively excluded from PDS according to the German definition. Therefore, only an acceptable number of cases (27/234, 11.5%) received unnecessary laparotomy, thus overlapping with the German experience ( $p$ -value = 0.219).

Furthermore, we clearly and frequently stated that in our Institution the poorest ECOG-PS and/or ASA score and/or pre-operative imaging predicting sub-optimal cytoreduction are not considered a priori criteria to abort surgery. Indeed, the rate of ECOG-PS  $\geq$  2 we reported (ranging from 19.7% to 9.4%) further supports the absence of any patients' selection. In other words, all cases admitted at our Department are assessed for PDS, and represent our entire denominator. The final number of unresectable/suboptimally resected cases can be easily identified among the entire amount of S-LPS performed, and has decreased over the time reaching the value of 9.7% (Vizzielli et al., 2016).

2. To definitively solve the issue whether S-LPS is able to separate patients in different cohorts without substantially affecting the outcome but sparing unnecessary morbidity/mortality, we designed a randomized clinical trial in which AEOC women were selected based on their laparoscopic tumor load and then randomized on PDS vs. NACT (ClinicalTrials.gov identifier: NCT01461850, protocol ID: SCORPION). Here, the reported rate of complete/optimal cytoreduction at PDS is 91%, which is superimposable with that reported from the German series (Fagotti et al., 2016). The rate of 45.5% of RT = 0 reported in the PDS group seems adequate considering this setting of patients was selected for having High Tumour Load (HTL) at S-LPS, as proven by the need of upper abdominal procedures (UAP) and highly complex surgery in 100% of cases (Fagotti et al., 2016). Moreover, by this kind of selection (HTL by S-LPS), we were able to predict the risk of moderate/severe post-operative complications (52%, including pleural effusion). Survival analysis will clarify whether aggressive PDS with a high potential rate of severe complications is an acceptable treatment in AEOC women with HTL.
3. Our management is in line with the recent ASCO/SGO practice guidelines regarding the use of NACT and interval cytoreduction in stage IIIC/IV AEOC women (Wright et al., 2016). Based on the series published by Vizzielli, the majority of stage III-IV AEOC patients has low/intermediate tumor load at S-LPS, thus being suitable for immediate PDS with minimal risk for post-operative complications (Vizzielli et al., 2016). Only about 20%–30% of the entire population at stage III-IV shows HTL as assessed by S-LPS; they need an accurate evaluation to balance risks and benefits of aggressive surgery, as outlined in the SCORPION trial.
4. The last issue, which should be discussed, is the potential role of S-LPS in affecting patients' outcome. Some, including the same Authors, have shown a higher risk of port site metastases, a higher surgical treatment burden and post-operative complication rate in AEOC patients having S-LPS followed by PDS (Ataseven et al., 2016), thus advocating a detrimental effect of S-LPS on tumor diffusion. These

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conclusions could appear imperative and inconsistent. Excluding potential technical explanations to these findings (i.e. insufflation, irrigation, fascial closure, time to PDS), the most reasonable cause seems to lie in the intrinsic bias of any retrospective study. Indeed, those patients considered unresectable in other Institutions through S-LPS did receive debulking in their Hospital with aggressive surgery and related complications. Results on whether such approach assured better survival to these patients than planned NACT are still lacking from RCTs.

The issue whether S-LPS might improve survival seems more intriguing. In line with previously published data on a large series of 2655 AEOC patients from GOG182 study (Horowitz et al., 2015), we firstly demonstrated that S-LPS could identify women with HTL and shorter PFS and OS (Vizzielli et al., 2014). We also showed that this variable retained independent prognostic value at multivariate analysis together with residual tumor. In this context, S-LPS is currently one of the best tool to stratify patients with AEOC (HTL vs. LTL) and this stratification should be incorporated in data analysis from RCT of PDS vs. NACT (TRUST trial, NCT02828618), to avoid the risk of including unselected patients. We have much more information, opportunities and expectations than in the past, which cannot be ignored. The future is designing small clinical trials for groups of patients, inserted into a clear clinical scenario, showing specific markers of the disease. Here, novel therapies targeted on the molecular defect, or new schedules, doses and combinations could be tested. Only with this stratification, we will find the best recipient settings and truly clarify the potential of each strategy. In this context, S-LPS as well as any other pre-operative approach able to standardize and categorize clinical pictures, and to allow adequate tissue acquisition for molecular analysis, is able to indirectly offer an improvement in survival.

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