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Editorial

How to predict treatment failure in frail patients with advanced epithelial ovarian cancer: strategies to personalize surgical effort

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▸ See the article "Characteristics and survival of ovarian cancer patients treated with neoadjuvant chemotherapy but not undergoing interval debulking surgery" in volume 31, e17.

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The principle of surgical cytoreduction, as applied in epithelial ovarian cancer (EOC), has been an inspiring example of how the evolution of a treatment, enwrapped with the refinement of surgical skills and expertise, optimization of infrastructural support and collective team effort can contribute to the overall improvement of patients' outcome, potentially even overcoming adverse aspects of a presumed less favorable tumor biology in extensive tumor dissemination [1,2]. In a disease where cure rates remain dismal, the gynecological oncological community, in its different facets, has largely managed to change its course towards a rather chronic condition, where patients may live longer, even if in need of repeated sequence of therapies [3].

Nevertheless, this increased "radicality" in both surgical but also systemic therapeutic approaches, has brought in novel aspects of an iatrogenic morbidity profile, which renders the implementation of any innovative techniques in special subpopulations highly challenging and with even questionable benefit. This labile balance between the hoped survival benefit and the actually generated side effects, represents one of the most common and major caveats of our therapeutic attempts, so that adequate patient selection and allocation of the right patient to the optimal treatment pathway is the key for overall success [4-7].

In this issue by Liu et al. [8], the team from Memorial Sloan Kettering Cancer Center has demonstrated that more than a quarter of women with advanced EOC who are treated with neoadjuvant chemotherapy (NACT) do not ever reach the point of being able to undergo cytoreductive surgery at an interval setting (IDS). Advanced age, lower albumin levels, frailty scores and extensive disease of predominantly high-grade serous histology, were identified as the most significant risk factors for inability to undergo surgery. The reasons of that were mainly quoted as 1) extent of disease not amenable to surgery or lack of response to NACT; 2) patient comorbidities preventing surgery; 3) both extent of disease and patient comorbidity [8]. The findings of this study confirmed the intuitive expectation that these, never operated, patients will have a >3-fold increase in all-cause mortality compared to those who underwent surgery at some point in their journey, even after risk adjustment for age, tumor dissemination patterns and dose reductions. These findings demonstrate the unmet need for systematic studies and algorithms to identify optimal treatment strategies in this high-risk,

elderly and/or frail population, in an attempt to maximize outcomes without detrimental increase of iatrogenic toxicity. The numbers quoted in the present study (28%) are higher than the ones reported in the European Organisation for Research and Treatment of Cancer (12%)- and CHemotherapy OR Upfront Surgery (14.2%)- NACT-studies [4,5], most probably due to the known selection bias of prospective randomized studies, where more fragile or older patients are a priori not considered for trial participation.

In times of significant and continuous increase of the elderly population worldwide and hence the increased average age of the patients that we, as gynecological oncology community, are called to treat, it is high time we developed and established validated geriatric scores for the adequate stratification of our patients. In the paper by Liu et al. [8] 74% of the patients in the non-surgical group was ≥70 years of age compared with only 36% in the surgical group. The non-surgical group was also on average 8.8 years older compared to the surgical group; data correlating with similar experiences in numerous other studies, where the aging population represents a considerate challenge in the implementation of traditional treatment strategies [8].

One the most important attempts to identify fragility scores in gynecological cancer surgery, is the AGO-OVAR OP.7/AGO-OVAR19-Fragile study, which is part of the phase-III, prospective randomized TRUST-study (NCT02828618) [9]. Aim of the study is to identify the cohort of patients who may not benefit from standard surgery and chemotherapy, defined as progression within 10 months after registration/randomization. The fragility evaluation has been composed of following parameters: age adjusted Charlson-Comorbidity-Index, timed 'up and go' test, Hospital Anxiety and Depression Scale-Score, serum albumin levels, full blood count and urea and electrolytes, CA125, American Society of Anesthesiologists and Eastern Cooperative Oncology Group scores, presence of tumor related symptoms requiring intervention such as abdominal pain & bloating, shortness of breath, suspected stage-IV disease, age and biometric data, volume of ascites and or pleural effusion. The results of that study will provide important guidance of how to identify patients who are less likely to benefit from our standard and traditional treatment strategies already at the initial presentation of the disease and not after failure of our therapeutic efforts.

Another study towards the same direction is the National Cancer Research Institute currently under development FAIR-O-study (REC-reference:19/LO/1741/IRAS:263916) which will address the feasibility of frailty assessment and implementation of protocol-led geriatric interventions during oncologic treatment in women with EOC over the age of 70. Evaluation of further risk factors such as sarcopenia, loss of muscle mass and reduced muscle attenuation at baseline will aim to establish additional predictive factors for reduced tolerance to oncologic treatment, functional decline and ultimately poorer survival outcomes.

A further point of interest in the paper by Liu et al. [8], is that one of the reasons for patients not undergoing IDS was stable/mixed response at NACT. There are indeed very few large-scale prospective studies to assess value of debulking surgery in patients with stable disease after NACT. However, the recently presented ICON-8 data demonstrated interestingly, that both progression free survival and complete/optimal debulking rates were similar in patients with stable disease and those with complete- or partial response after NACT, suggesting that also patients with stable disease after NACT are worth being offered IDS [10].

In conclusion, there is a strong rationale towards a personalization of surgical treatment in patients with advanced EOC and to implement predictive and prognostic scores that

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will already at the onset of the disease predict failure of treatment and patients' inability to cope with our traditional strategies. All that within the restrains of national health systems with the known infrastructural limitations. Liu et al. [8] address marginally the practice modifications necessary to facilitate surgery in designated cancer centers, as they are reflected for example in higher IDS rates. Our ultimate goal will be to adequately and wisely allocate the right treatment to the right patient to avoid unnecessary iatrogenic toxicity but also unopposed exhaustion of infrastructural and healthcare resources.

REFERENCES

1. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248-59.
PUBMED | CROSSREF
2. Hall M, Savvatis K, Nixon K, Kyrgiou M, Hariharan K, Padwick M, et al. Maximal-effort cytoreductive surgery for ovarian cancer patients with a high tumor burden: variations in practice and impact on outcome. Ann Surg Oncol 2019;26:2943-51.
PUBMED | CROSSREF
3. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC Jr, Beral V, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer 2015;15:668-79.
PUBMED | CROSSREF
4. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-53.
PUBMED | CROSSREF
5. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015;386:249-57.
PUBMED | CROSSREF
6. Fotopoulou C, Sehouli J, Aletti G, Harter P, Mahner S, Querleu D, et al. Value of neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer: a European perspective. J Clin Oncol 2017;35:587-90.
PUBMED | CROSSREF
7. Meyer LA, Cronin AM, Sun CC, Bixel K, Bookman MA, Cristea MC, et al. Use and effectiveness of neoadjuvant chemotherapy for treatment of ovarian cancer. J Clin Oncol 2016;34:3854-63.
PUBMED | CROSSREF
8. Liu YL, Filippova OT, Zhou Q, Iasonos A, Chi DS, Zivanovic O, et al. Characteristics and survival of ovarian cancer patients treated with neoadjuvant chemotherapy but not undergoing interval debulking surgery. J Gynecol Oncol 2020;31:e17.
CROSSREF
9. Reuss A, du Bois A, Harter P, Fotopoulou C, Sehouli J, Aletti G, et al. TRUST: trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). Int J Gynecol Cancer 2019;29:1327-31.
PUBMED | CROSSREF
10. Clamp AR, McNeish IA, Dean A, Gallardo-Rincon D, Kim J-W, O'Donnell DM, et al. Response to neoadjuvant chemotherapy in ICON8: a GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/fallopian tube/primary peritoneal carcinoma (EOC) treatment. Ann Oncol 2018;29:viii336.
CROSSREF