J Gynecol Oncol. 2019 Nov;30(6):e116
https://doi.org/10.3802/jgo.2019.30.e116
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Editorial

Which patients benefit from secondary cytoreductive surgery in recurrent ovarian cancer?

Rongyu Zang,[1] Jianqing Zhu[2]

[1]Ovarian Cancer Program, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Fudan University Zhongshan Hospital, Shanghai, China
[2]Department of Gynecologic Oncology, University Cancer Hospital of Chinese Science Academy, Hangzhou, China

▸ See the article "The efficacy of secondary cytoreductive surgery for recurrent ovarian, tubal, or peritoneal cancer in Tian-model low-risk patients" in volume 30, e100.

Received: Aug 30, 2019
Accepted: Aug 30, 2019

Correspondence to
Rongyu Zang
Ovarian Cancer Program, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Fudan University Zhongshan Hospital, 180 Fenglin Road, Shanghai 200032, China.
E-mail: zang.rongyu@zs-hospital.sh.cn

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Most women with advanced ovarian cancer develop recurrent disease after the first-line therapy, and chemotherapy remains the standard care of women with platinum-sensitive recurrent ovarian cancer. The randomized studies (NCT00565851, NCT01166737, NCT01611766) comparing surgery with chemotherapy alone are on the way, and matured data will be reported in recent years [1,2]. The results of these studies may be different because of different clinical practice and different patient population. Different clinical practice came from years of experience and training background of secondary surgical cytoreduction in recurrent ovarian cancer from retrospective or prospective studies.

The first report of secondary cytoreductive surgery was demonstrated by Dr. Berek in 1983 [3]. Then several retrospective studies and few prospective but non-randomized trials were reported [4-7]. Four randomized trials were initiated in the 2010s and the patient recruitment lasted for a long period, ranging from 4.5–9.5 years [8]. Despite one trial dropped because of the delayed enrollment, all the other 3 trials completed the patient enrollment, and 2 of them were presented at the 2017 and 2018 American Society of Clinical Oncology Annual Meetings respectively [2]. In countries such as Netherlands and China, patients and the gynecologic oncological surgeons have a strong belief in secondary cytoreductive surgery because of several publications. This explains why these trials have lasted for so long time or being earlier stopped.

In this issue of the journal, Dr. So and their colleagues [9] show in their retrospective study that women with recurrent ovarian cancer may derive significant survival benefit from secondary cytoreductive surgery. A set of patients with platinum-sensitive recurrent ovarian cancer (treatment-free interval more than 6 months) treated by either secondary cytoreductive surgery or chemotherapy alone were reviewed in So et al.'s study [9], and 52 patients with low-risk iMODEL (also called TIAN model [10]) at a median score of 2.3 were evaluated. Of them, 22 patients received surgery, and other 22 patients with second-line chemotherapy alone were matched using the propensity-score matching method. The survival in patients with recurrence was greater in those treated by secondary surgical resection than in those with chemotherapy alone. The limitations of the study are the small

sample size and the large span from 2004 to 2016 with the heterogeneity among patients either in improvement of surgical techniques or updated standard care.

The progression-free survival in this study was quite similar to that of DESKTOP 3 study. In recent studies on platinum-sensitive recurrent ovarian cancer, the median progression-free survival increased from 14.0 m to 19.6 m (DESKTOP 3), 16.5 m to 18.2 m (GOG 213), when compared with 5.5 m to 11.9 m (AVANOVA2) in the combination of niraparib-bevacizumab, so called chemo-free therapy [11]. So, surgery is not worse than combined target therapy, but it is more cost-effective than the target therapy. In an international collaborative pooled analysis, the median overall survival of patients with recurrent ovarian cancer undergoing secondary surgery was 57.7 m, 27.0 m, 15.6 m in R0, R1 (residual disease ≤1 cm), R2 (residual disease >1 cm) groups respectively [5].

The rate of R0 increased from 39.4% (earlier pooled data) to 78.6% (recently closed trial) in non-selected or selected patients with recurrent ovarian cancer [2,5-7,9]. Neither progression-free survival nor overall survival in GOG 213 was significantly improved in patients who underwent secondary cytoreductive surgery compared to chemotherapy alone [12]. As stated by the authors, more than 80% of the patients received combined bevacizumab. While recognizing the difficulty in evaluating the effect of bevacizumab on the study results, more studies are needed to confirm whether bevacizumab or other target therapy may reduce the potential survival benefit associated with surgery. Notably, in the previous report (objective #1) of GOG 213, the median overall survival in the chemotherapy and bevacizumab group was only 42.2 m (95% confidence interval [CI]=37.7–46.2) and 37.3 m (95% CI=32.6–39.7) (NCT00565851) [13]. Although there existed large variation in patient population, the authors had difficulty to understand the huge survival difference, 42.4 m versus 65.5 m, in patients treated with the same bevacizumab.

Which patient with recurrent ovarian cancer can benefit from secondary cytoreductive surgery? Which surgeon can most successfully operate on these patients? These are 2 critical questions when we make the subsequent surgical effort. Since surgical experience was an important factor determining the survival in recurrent ovarian cancer, we considered it as a factor when we established the iMODEL. In our previous study, all the participating centers had at least 10 years of experience with a series of publications. Thus, we finally eliminated the factor of surgical experience in the final iMODEL. According to the data, the rate of complete surgical resection (R0) was 39.4%, and it increased from 8.3% to 40.7% over the period of 1986–1997, 2002–2006 in the leading center [5].

There are two steps to consider secondary cytoreductive surgery as the standard care for women with recurrent ovarian cancer. Since the patients with Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) positive score are part of the iMODEL (**Fig. 1**), the first step is to confirm the survival benefit in DESKTOP 3 study, and then in Shanghai Gynecologic Oncology Group (SGOG) SOC-1 study [2]. The second step is the early detection of the recurrences. Patients' compliance of follow-up, a combination of progression-free interval and the serum level of CA125, should also be considered during the recruitment. Some patients had longer progression-free interval, but their prognosis was worse because of the late recurrence diagnosis. Those patients will be less likely to benefit from secondary cytoreductive surgery even R0 resection. Most studies have confirmed the survival benefit of surgery for solitary recurrence. In the current study, solitary recurrence was associated with excellent outcome. All 6 patients (100%) with solitary disease were alive and 5 out of

https://doi.org/10.3802/jgo.2019.30.e116

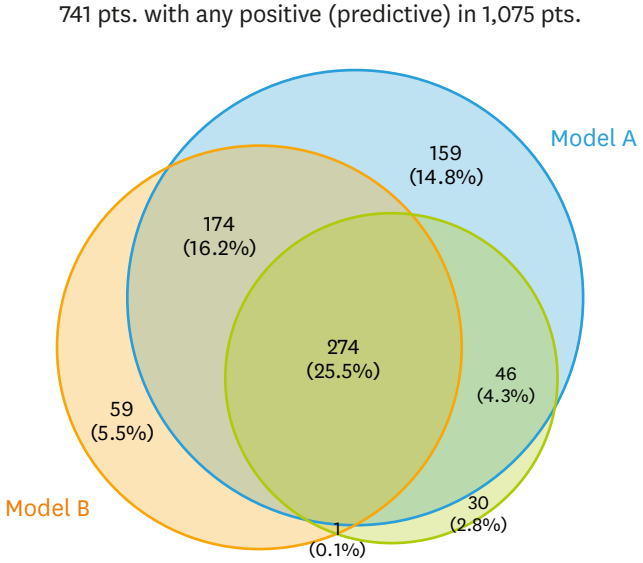

Fig. 1. Distribution of the patients in the iMODEL (model A, in blue) and the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) model (in light green), data were from the international collaborative pooled analyses (with thanks to Drs. Dennis Chi and Philipp Harter's permission to use the data) [5,9].

6 patients (83.3%) survived without disease at the median follow-up of 60.2 m. Positron emission tomography-computed tomography scan has more positive findings in patients with suspect recurrence who have rising CA125 levels despite negative results on standard magnetic resonance imaging or computed tomography; it can modify the management by accurately mapping the distribution of recurrent disease, and it is definitely associated with a real R0 status after secondary cytoreductive surgery [14].

REFERENCES

1. Du Bois A, Vergote I, Ferron G, Reuss A, Meier W, Greggi S, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. J Clin Oncol 2017;35 suppl:abstr5501.
PUBMED | CROSSREF
2. Shanghai Gynecologic Oncology Group. Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC 1 Trial)? [Internet]. Bethesda, MD: National Library of Medicine; 2018 [cited 2019 Sep 15]. Available from: www.clinicaltrials.gov/ct2/show/record/NCT01611766.
3. Berek JS, Hacker NF, Lagasse LD, Nieberg RK, Elashoff RM. Survival of patients following secondary cytoreductive surgery in ovarian cancer. Obstet Gynecol 1983;61:189-93.
PUBMED
4. Chi DS, McCaughty K, Diaz JP, Huh J, Schwabenbauer S, Hummer AJ, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer 2006;106:1933-9.
PUBMED | CROSSREF
5. Zang RY, Harter P, Chi DS, Sehouli J, Jiang R, Tropé CG, et al. Predictors of survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery based on the pooled analysis of an international collaborative cohort. Br J Cancer 2011;105:890-6.
PUBMED | CROSSREF
6. Gockley A, Melamed A, Cronin A, Bookman MA, Burger RA, Cristae MC, et al. Outcomes of secondary cytoreductive surgery for patients with platinum-sensitive recurrent ovarian cancer. Am J Obstet Gynecol 2019:S0002-9378(19)30773-2.
PUBMED | CROSSREF

7. Bickell NA, Egorova N, Prasad-Hayes M, Franco R, Howell EA, Wisnivesky J, et al. Secondary surgery versus chemotherapy for recurrent ovarian cancer. Am J Clin Oncol 2018;41:458-64.
PUBMED | CROSSREF
8. van de Laar R, Kruitwagen RF, Zusterzeel PL, Van Gorp T, Massuger LF. Correspondence: Premature stop of the SOCceR trial, a multicenter randomized controlled trial on secondary cytoreductive surgery: Netherlands Trial Register Number: NTR3337. Int J Gynecol Cancer 2017;27:2.
PUBMED | CROSSREF
9. So M, Miyamoto T, Murakami R, Abiko K, Hamanishi J, Baba T, et al. The efficacy of secondary cytoreductive surgery for recurrent ovarian, tubal, or peritoneal cancer in Tian-model low risk patients. J Gynecol Oncol 2019;30:e100.
CROSSREF
10. Tian WJ, Chi DS, Sehouli J, Tropé CG, Jiang R, Ayhan A, et al. A risk model for secondary cytoreductive surgery in recurrent ovarian cancer: an evidence-based proposal for patient selection. Ann Surg Oncol;2012;19:597-604.
PUBMED | CROSSREF
11. Mirza MR, Avall-Lundqvist E, Birrer MJ, Christensen RD, Nyvang GB, Malander S, et al. Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: a randomized controlled chemotherapy-free study—NSGO-AVANOVA2/ENGOT-OV24. J Clin Oncol 2019;37 suppl:abstr5505.
CROSSREF
12. Coleman RL, Enserro D, Spirtos N, Herzog TJ, Sabbatini P, Armstrong DK, et al. A phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC), with or without bevacizumab (B) in platinum-sensitive, recurrent ovarian cancer (PSOC): a NRG Oncology/Gynecologic Oncology Group (GOG) study. J Clin Oncol 2018;36 suppl:abstr5501.
CROSSREF
13. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:779-91.
PUBMED | CROSSREF
14. Vargas HA, Burger IA, Goldman DA, Miccò M, Sosa RE, Weber W, et al. Volume-based quantitative FDG PET/CT metrics and their association with optimal debulking and progression-free survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery. Eur Radiol 2015;25:3348-53.
PUBMED | CROSSREF