

# Primary debulking surgery of advanced epithelial ovarian cancer in developing countries: challenges and expectations

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Ovarian cancer often presents itself in advanced stages and can be accompanied by various comorbidities. Treatment options are primary debulking surgery (PDS) followed by adjuvant chemotherapy, or alternatively, neoadjuvant chemotherapy followed by interval debulking surgery (IDS). The option taken is based on several considerations. If the patient can be treated with PDS, the absence of macroscopic residual disease becomes an independent prognostic factor. However, achieving this outcome is a challenge for the gynaecologic oncologist since advanced stage ovarian cancer generally metastasizes into the peritoneum and the upper abdominal organs. Optimal outcomes are that surgery will be safe for the patient, no macroscopic residual disease is achieved, minimal postoperative complications are encountered, and a good survival rate is obtained. Developed countries, especially Europe, have well-recognized standards of care which are followed by developing countries; however, challenges with insurance coverage and inter-departmental cooperation are recognized hurdles in developing countries. Competency improvement along with good inter-departmental communication and collaboration are keys to optimal outcomes for PDS.

## Keywords

Ovarian cancer; Primary debulking surgery; Residual disease; Interdepartmental approach; Competency

## 1. Introduction

Ovarian cancer is currently ranked second in gynaecological cancer incidence in the world based on Globocan data (2018) [1]. When analysed further, almost 60% of cases are advanced stage at initial presentation [2]. More than 90% of cases are epithelial types, which epidemiologically provide unsatisfactory progression-free survival rates [3, 4]. Current issues related to advanced ovarian cancer are whether to conduct PDS followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by IDS [5–8].

Currently, PDS is one of the main choices for therapy, and this correlates with physician competence, solid multidisciplinary teams, as well as proper instrumentation [6, 9]. Development of advanced ovarian cancer surgery methods originally devised in developed countries, especially Europe,

spread quickly to all cancer service centres around the world, including Indonesia. Good collaboration and networking have accelerated the transfer of operating procedures and skills. This article discusses the standard of PDS and how PDS should be carried out in developing countries using standards applicable to developed countries, especially Europe.

## 2. Current standard primary debulking surgery in advanced epithelial ovarian cancer in developed countries

PDS for ovarian cancer was first introduced by Dr. Joe V. Meigs in 1934. The concept of ovarian cancer PDS only became widely accepted in the mid-1970s when Dr. C. Thomas Griffiths published seminal work on PDS [10, 11]. Rationalization of cytoreduction surgery is to reduce tumour mass before chemotherapy [10].

PDS with no macroscopic residual disease is the standard therapeutic outcome sought for patients with advanced epithelial ovarian cancer [10]. Complete resection in cytoreduction surgery consists of salpingo-oophorectomy, hysterectomy, omentectomy, including several additional procedures such as bowel resection and upper abdominal surgery [12, 13]. Pelvic and para-aortic lymphadenectomy are also commonly included in cytoreduction procedures [12–14]. However, pelvic and para-aortic lymphadenectomy are recommended only in cases of advanced stage ovarian cancer with node involvement determined by preoperative radiological staging [15]. The ESGO recommendation in 2017 states that several factors, such as comorbid diseases, age, and performance scoring are patient variables that can be taken into consideration [16].

PDS is not performed on patients with diffuse carcinomatosis disease on the ileum; if so, it can result in short bowel syndrome (bowel length < 1.5 meters), infiltration to the stomach/duodenum and the head of the pancreas, celiac trunk, hepatic and left gastric artery involvement, liver metastasis in central areas, or multisegmented, multiple-lung parenchymal metastasis, and the brain metastasis [13].

Previous studies comparing PDS and IDS were conducted by Vergote *et al.* (2010) [17] on neoadjuvant chemotherapy (NACT) or primary surgery in stage III / IV ovarian cancer, and work done by Kehoe *et al.* [18] (*i.e.*, CHORUS trial) published in 2015. Both studies reported similar results, specifically, NACT followed by IDS provided survival outcomes that were not inferior to PDS [19]. Other studies compared PDS and IDS (termed the SCORPION trial) and were proposed by Fagotti *et al.* in 2016 [6]. These investigators revealed perioperative morbidity scores were more favourable in the IDS arm than in the PDS arm in patients with very high tumour load. Japan Clinical Oncology Group Study in 2016 demonstrated that NACT is less invasive than standard PDS [7]. Mahner *et al.* [14] issued their opinions on the study by Vergote *et al.* [20] and Kehoe *et al.* [18] and commented that the complete resection ratio reached is only between 50-70% and the median operating time was 120-165 minutes. The authors also questioned how radical the operation performed truly is. Therefore, Reuss *et al.* [21] initiated an international open, randomized, controlled multi-centre trial with the hypothesis that PDS is superior to IDS in terms of overall survival in patients with advanced ovarian cancer (Trial of Radical Upfront Surgical Therapy in Advanced Ovarian Cancer (TRUST) study). This study is ongoing, and the 5-year follow-up is expected to end in 2024.

### 3. Current condition in developing countries

The management of advanced ovarian cancer in developing countries is not different from that of developed countries. The protocol published by developed countries, especially based on research in European countries, has become a standard of care applied to existing cancer service centres in Southeast Asia, especially Indonesia. The development of science and technology, access to learning, and good cooperation with developed countries gradually improved implementation of all governing principles for ovarian cancer treatment, including surgical equipment, anaesthesia equipment, ICU room, and standardization of medicines used.

Efforts to remove the broadest extent of the tumour and achieve no macroscopic residual tumour is of concern to gynaecologic oncologists in Indonesia and other developing countries. To illustrate, data was obtained from Dr. Cipto Mangunkusumo National Referral Hospital in Jakarta from 2012 to 2016. The proportions of suboptimal (residual tumour  $\geq 1$  cm) and optimal PDS were found to be 51.5% and 48.5%, respectively. Most cases were stage IIIC (57.8%), and 27.3% and 1.7% were stage IVA and IVB, respectively [22].

Working conditions within various departments and insurance financing in Indonesia is a challenge in performing PDS. National insurance regulations in Indonesia are not familiar with extensive debulking involving the intestinal and upper abdominal organs by gynaecologic oncologists. In dealing with such circumstances, cooperation with related surgeons is necessary. In practice, the consultations often take place only during intraoperative periods, so prepara-

tion is minimal and optimal debulking surgery is difficult to achieve. These are challenges to be solved, with the goal that standardized PDS can be achieved for the ovarian cancer patient.

### 4. Current condition consequences in developing countries

The outcome of sub-optimal PDS results have a probability to negatively impact patient survival [10]. Many studies have stated that the achievement of no macroscopic residual disease (R0) is an independent prognostic factor in advanced ovarian cancer [14, 23]. Every operation performed requires anatomical and basic surgical skills, as well as proper perioperative management [24]. Training must be carried out continuously and scientific publications are encouraged [24]. It is unnecessary to achieve no macroscopic residual tumour, especially in the pelvic region because pelvic tumours can be removed. In developing countries, the fundamental cause of suboptimal removal of pelvic tumours in advanced ovarian cancer surgery is the lack of experience of the gynaecology oncologist with colorectal surgery and a lack of communication with surgeons in other disciplines [25, 26]. Therefore, skill training and competency improvement are necessary to achieve the desired outcome of no macroscopic residual disease [27]. The author's perspective is that the principal block to achieving this outcome is that the gynaecologic oncology education curriculum in developing countries does not adequately accommodate this particular issue.

Surgical outcomes in terms of complication rate of treated patients at Dr. Cipto Mangunkusumo Hospital is 17% in PDS and zero in IDS group [28]. Parameters of surgical aggressiveness (massive bleeding, organ injury, and post-operative ICU stay) were lower in IDS group than the PDS group [28]. The life expectancy of advanced ovarian cancer patients treated by PDS at Dr. Cipto Mangunkusumo Hospital is 28.7% and 9.4%, for 2- and 4-year survival, respectively [22]. This outcome is directly related to the high proportion of patients who only had sub-optimal debulking operations at this hospital. Considering the concept of no macroscopic residual disease as an independent prognostic factor, it is essential to perform optimal PDS. European Society Gynaecology Oncology targeted  $\geq 70\%$  resection in their quality indicator of advanced ovarian cancer surgery [29].

### 5. Learning from developed countries: European society of gynaecological oncology

Based on standard primary debulking surgery, it is important to disseminate cognitive and operating skills correctly. Consistent with the surgical philosophy revealed by Dr. Hutan Ashrafian in his book *Surgical Philosophy (Concepts of Modern Surgery Paralleled to Sun Tzu's Art of War)*, five factors determine optimal operational outcomes: patient safety and ethics; knowledge, anatomy, research; operating room, and staff; surgeon; and surgical training.

One way to understand anatomy is through direct train-

ing using cadavers [30]. Such cadaveric training is primarily conducted for oncology gynaecology trainees and is should be conducted on a yearly, ongoing basis. Inter-departmental communication and collaboration, especially with the surgeons, also must be encouraged. Skills transfer and supervision should be done during every intraoperative consultation. Within our program, the gynaecologic oncology trainee education system was reviewed and it was suggested to add special courses on upper abdominal surgery.

Important achievements have been made in terms of targeted therapies in ovarian cancer management, including after debulking surgery. One such targeted therapies that plays a pivotal role is PARP the inhibitors. This targeted therapy demonstrated improvements in PFS for newly diagnosed ovarian cancer [31, 32]. In Indonesia, addition of targeted therapy is optional for the patient and it is not yet covered by the national insurance program. To realize a benefit from this targeted therapy, we should continue efforts to identify patients who may potentially benefit from PARP inhibitors.

## 6. Conclusions

In the treatment of advanced ovarian cancer, PDS is a standard of care that should be performed by gynaecological oncologist. Standards that have been worked on in developed countries are appropriate. The gynecologic surgeon should always possess a good understanding of anatomy and continuous transfer of skills to adequately maintain competency and continued improvement. These measures should result in better survival of patients with advanced ovarian cancer.

## Author contributions

SP: conceptualization, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization, supervision, funding acquisition, data collection, and writing the paper. KYS: data curation, data collection, writing-original draft, visualization.

All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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## Conflict of interest

The authors declare no conflict of interest.

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