RESEARCH ARTICLE

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# Outcomes and Prognostic Factors of Patients with Platinum-Resistant or Refractory Epithelial Ovarian Cancer, Fallopian Tube Cancer and Peritoneal Cancer

**Suttha Hamontri, Tanitra Tantitamit***

## Abstract

**Objective:** To determine the survival outcomes and prognostic factors of the patients with recurrent platinumresistant and refractory epithelial ovarian cancer (EOC), tubal, and peritoneal cancer. **Methods:** Women with recurrent platinum-resistant and refractory EOC, tubal and peritoneal cancer who received treatment at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) between January 2010 and December 2019 were included. Demographic data, serum marker, surgical factors, pathological factors and response of treatment were reviewed. Kaplan-Meier was used to calculate survival outcome. **Result:** Forty patients were recruited in this study (platinum-resistant 24 patients and refractory 16 patients). The median survival times were 19 and 21 months in and platinum-resistant and platinumrefractory patients, respectively. There were no significant differences in overall survival according to age, comorbidity, tumor grading, primary treatment, and secondary surgery. However, histology of clear cell carcinoma may associate with increased risk of death. The median overall survival of patients with clear cell carcinoma, serous carcinoma, and others were 14.4, 22.9, and 32.2, respectively ($p = 0.003$). **Conclusion:** Almost 10 years, the survival rate of the patients in these group has not increased despite new treatments option. Novel strategies should be considered in National policy of the treatment for ovarian cancer in our country.

**Keywords:** Ovarian cancer- recurrence- survival- prognosis

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## Introduction

Ovarian cancer is the most lethal gynecological cancer. In 2020, ovarian cancer was the sixth most common cancer in Thai females with age-standardized incidence rates of 7.9 per 100,000 and age-standardized mortality rates of 4.9 per 100,000. There were 4,475 new cases diagnosed in Thailand; however, in more than 50% (2,941 cases) of those cases, deaths were reported (Sung et al., 2021). Almost all ovarian cancer cases are diagnosed at an advanced stage due to unspecific symptoms and lack of screening, leading to early recurrence and poor prognosis. Late-stage presentation has a 5-year relative survival rate of 29%, in contrast with 92% for early-stage disease (Lheureux et al., 2019). Although most patients receive standardized surgery and chemotherapy, the status of recurrent disease is heterogeneous. Recurrence is incurable in about 75% of women with advanced disease (Lheureux et al., 2019). Intrinsic resistance is seen in 10% to 15% of patients defined as platinum-refractory and is associated with a poor median survival of less than 9 months. Approximately 20% to 30% of patients have cancer which will recur or progress within 6 months of completing chemotherapy (termed platinum-resistant) and have a median overall survival of approximately 12-18 months (Lheureux et al., 2019). For patients with platinum-resistant or platinum-refractory disease, single-agent nonplatinum-based chemotherapy is used until subsequent progression or unacceptable toxicity is observed. However, the expected response rate in this setting is low (about 10–15%) (Lheureux et al., 2019; Pujade-Lauraine et al., 2019). The choice of agent for an individual patient depends on the history of prior treatment, residual toxicities, availability, cost, the convenience of treatments, and patient preferences after being fully informed (Pujade-Lauraine et al., 2019). Many prognostic indicators must be considered when determining expected prognosis and rate of response to future lines of therapy in recurrent EOC. These factors include tumor volume and histology, prior treatment and platinum-free intervals, BRCA mutation, symptoms, performance status, and comorbidity (Dockery et al., 2019).

In Thailand, there is limited data regarding outcomes and prognosis factors predicting the survival of patients with platinum-resistant or refractory epithelial ovarian cancer. The latest data published reported the median

*Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Nakhonnayok, Thailand. *For Correspondence: ttanitra@gmail.com*

overall survival of a patient with refractory disease was 20 months, which was higher than in other countries (Foley et al., 2013; Jansaka and Suprasert, 2014). Due to the inconclusive results and outdated data in our country, we conducted a study to determine the outcomes of these patients and to identify the prognosis factors of a good response after therapy.

## Materials and Methods

This study was a retrospective design, conducted between August, 2021, and July, 2022. All women with recurrent platinum-resistant or refractory epithelial ovarian cancer, fallopian tube cancer, and peritoneal cancer who received treatment at the gynecologic oncology unit, HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) between January 2010 and December 2019 were included. Those with incomplete documents were excluded. The sample size was calculated based on the results of Pitakkamkul (2013). The minimum number of patients required to determine the survival outcome was 42. However, we studied all patients who had received treatment within the last 10 years. Approval was obtained from the ethics committee of Srinakharinwirot University.

Demographic data (age, parity, comorbidity), the stage at diagnosis according to FIGO staging, the start and end of chemotherapy (first and second line), and chemotherapy protocol were documented. Eastern Cooperative Oncology Group (ECOG) performance status and the serum levels of CA125 collected before the start of second-line chemotherapy were also documented. Computed Tomography (CT scan) results before and after complete treatment were used to assess the response. The response was classified as complete or partial response (CR, PR), stable disease (SD), or progressive disease (PD) according to the radiologist's evaluation.

Descriptive data are presented as mean and standard deviation (SD) for continuous variables, and as numbers and percentages for categorical variables. Survival time was calculated from the date of the first diagnosis until death or the last follow-up visit. Kaplan-Meier was used to calculate the survival outcome. All statistical analyses were performed with STATA version 14 (Stata, College Station, TX).

Table 1. Clinical Characteristics of Platinum-Refractory and Platinum-Resistant Ovarian Cancer Patients

| Characteristics | Total (%) |
|---|---|
| Mean age (range) | 55 (21-76) |
| Co-morbidity | 19 (47%) |
| Diagnosis | |
| Epithelial ovarian cancer | 39 (97.5%) |
| Primary Peritoneal cancer | 1 (2.5%) |
| Mean total number of chemotherapy regimens (range) | 2.5 (1-5) |
| Nulliparity | 18 (45%) |
| Advanced stage (stage III, IV) | 33 (82.5%) |
| Mean CA 125 level, before treatment (SD) | 1,781.76 (2583) |
| Mean CA 125 level, at recurrent (SD) | 200 (698) |
| Histology | |
| Serous | 15 (37.5%) |
| Mucinous | 1 (2.5%) |
| Endometrioid | 5 (12.5%) |
| Clear cell | 12 (30%) |
| Adeno NOS | 3 (7.5%) |
| Mixed (serous-clear, clear-mucinous) | 2 (5%) |
| Others (Brenner tumor) | 2 (5%) |
| High grade or grade3 | 18/22 (81%) |
| Neoadjuvant chemotherapy | 17/40 (42%) |
| Complete surgical staging | 15/23 (65%) |
| Optimal surgery | 22/40 (55%) |
| Treatment | |
| Surgery + chemotherapy | 7 (17.5%) |
| Chemotherapy | 33 (82.5%) |

## Results

There were 196 patients diagnosed with EOC, fallopian tube cancer, and peritoneal cancer during 2010-2019. The numbers of patients in the platinum-refractory group, platinum-resistant group, and platinum-sensitive group were 16, 24, and 44 respectively. The patients' characteristics are presented in Table 1. Most patients were treated by using single chemotherapy agents (64%), which were gemcitabine, weekly or triweekly paclitaxel, and liposomal doxorubicin. Most of them received three lines of chemotherapy. The most common reasons for stopping treatment were poor performance status and death. Seven patients (17.5%) received secondary surgery, which aimed to eliminate macroscopic disease (cytoreductive surgery) and to alleviate the symptoms in five and two cases, respectively. However, only one patient had cancer which was optimally debulked (no residual disease).

The overall survival curve is shown in Figure 1. The median survival times were 21 months and 19 months in platinum-refractory and platinum-resistant patients, respectively (p 0.89). Table 2 shows response rates and adverse effects of treatment. The overall response rate (complete and partial response) was 12.5% in both groups of patients. Two-thirds of patients had minor toxicities

Table 2. Treatment Outcomes of the First Episode of Tumor Progression/Recurrence

| | Total (%) | Refractory (%) | Resistant (%) |
|---|---|---|---|
| Response of treatment | | | |
| Complete response (CR) | 4 (10) | 2 (12.5) | 2 (8.3) |
| Partial response (PR) | 1 (2.5) | 0 (0) | 1 (4.2) |
| Stable disease (SD) | 1 (2.5) | 0 (0) | 1 (4.2) |
| Progressive disease (PD) | 34 (85) | 14 (87.5) | 20 (83.3) |
| Adverse effect from chemotherapy | | | |
| None/ only G1-2 | 28 (70) | 11 (68.8) | 17 (70.8) |
| Hematologic effect | 11 (27.5) | 5 (31.2) | 6 (25) |
| Non-hematologic effect | 1 (2.5) | 0 (0) | 1 (4.2) |
| Further treatment (Third line chemotherapy) | 22 (55) | 14 (35) | 8 (20) |
| Number of survivors at the last contact | 9 (22.5) | 3 (7.5) | 6 (15) |

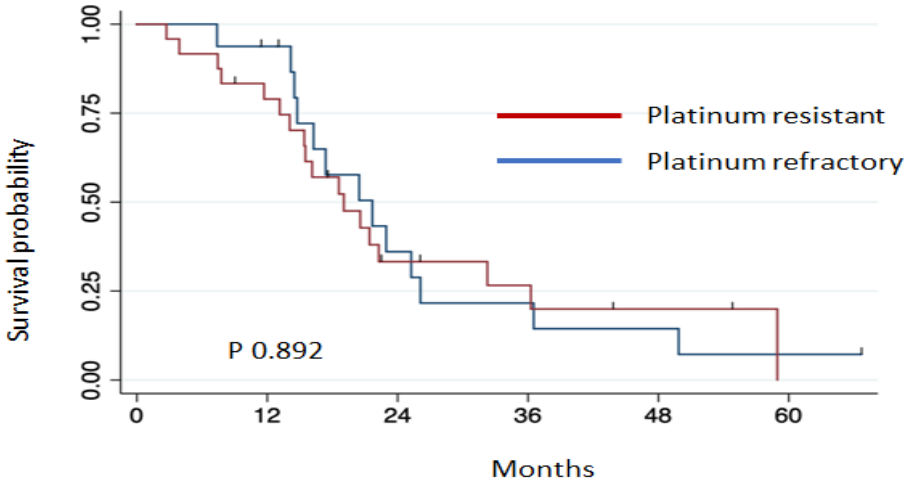


Figure 1. Overall Survival Time of Patients with Platinum-Refractory and Platinum-Resistant Ovarian Cancer

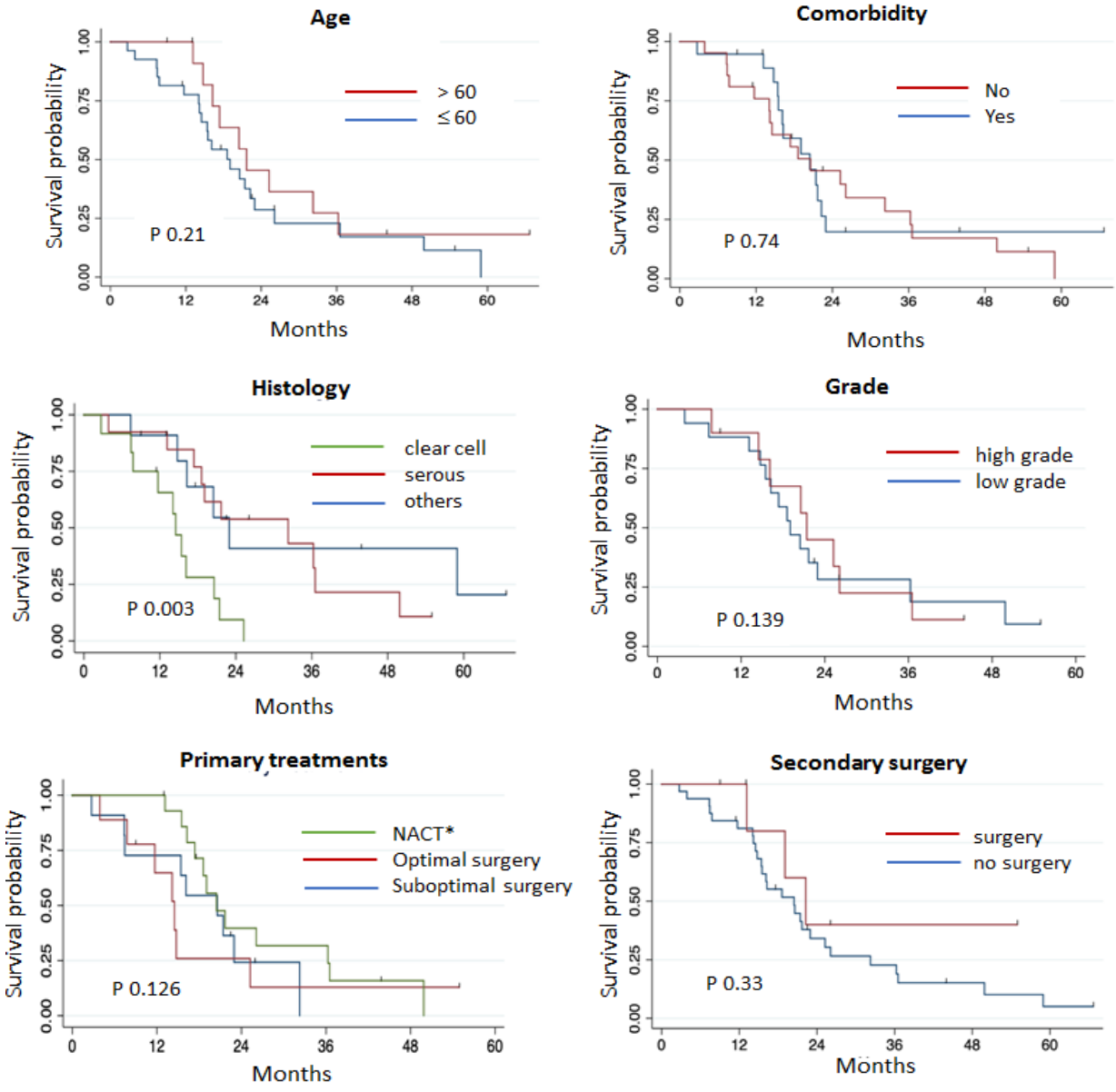


Figure 2. Overall Survival Curves for Patients with Platinum-Refractory and Platinum-Resistant Ovarian Cancer, Classified by A) age at diagnosis, B) comorbidity, C) histological type, D) grade, E) primary treatment, and F) secondary surgery. *NACT, Neoadjuvant Chemotherapy

from chemotherapy. There were no significant differences in overall survival according to age, comorbidity, tumor grading, primary treatment, and secondary surgery. However, the median overall survival of patients with clear cell carcinoma, serous carcinoma, and others were 14.4, 22.9, and 32.2, respectively (p 0.003) (Figure 2).

## Discussion

The patients with refractory and platinum-resistant disease had a median overall survival time of 19-21 months. This result was similar to another previous study in Thailand. Jansaka (2014) reported the median overall survival times were 20 and 14 months in platinum-refractory and platinum-resistant patients, respectively. However, they were slightly longer than those found in other studies (Foley et al., 2013; Pujade-Lauraine et al., 2019; Kerio et al., 2022). This might be due to the small number of patients. In our center, the patients were followed up every 3 months during the first 2 years after primary treatment. They were diagnosed with refractory or recurrent disease when the disease was detected by physical examination or rising CA125 values outside the normal range, regardless of their symptoms. Imaging including USG or CT scan was used to confirm the diagnosis in some cases. Using elevated CA125 levels alone could result in platinum-sensitive patients being falsely classified as platinum resistant. This might explain why the survival time found in this study was longer. A multi-institute European trial evaluated the benefits of early treatment based on elevated CA125 levels versus delaying treatment until clinically indicated. The results showed no evidence of a difference in overall survival between the two groups (Rustin, 2011). Regarding the response to treatment, the overall response rate was 12.5%, which was similar to a previous study in Thailand (Pitakkarnkul et al., 2013). Most of the patients received subsequent chemotherapy with gemcitabine and paclitaxel. Use of other types of chemotherapy, including targeted therapy, was limited by Thailand's Universal Health Coverage. The mean total number of chemotherapy regimens was 2.5 (range 1-5). None of the patients in this study had received target therapy. Our practice in the treatment of recurrent ovarian cancer was similar to that found in the survey of Thai gynecologic oncologists. The results of the survey taken by 170 responders showed best supportive care was given more frequently after a failure of second-line chemotherapy. Targeted therapy was prescribed to only 5% of patients (Manchana et al., 2020).

Regarding factors influencing the survival of patients, one study revealed that prolonged post progression survival of recurrent ovarian cancer patients was associated with post recurrence treatment, including secondary debulking surgery, favorable response to second-line therapy, and more than two chemotherapy regimens after the first recurrence (Soyama et al., 2017). Hilal (2016) reported that long-term survival of recurrent ovarian cancer was characterized by a young age, low tumor stage, long recurrence-free interval, and combined modality treatment with optimal cytoreductive surgery and systemic chemotherapy. Multiple retrospective studies suggested that a greater number of neoadjuvant chemotherapy cycles (more than 3 or 4 cycles) may be associated with worse outcomes (Colombo et al., 2014; Altman et al., 2017; Lui et al., 2020). In our study, the number of neoadjuvant cycles ranged from 2-6. Thirty five percent (6/17) of patients receiving more than 4 cycles. This might be another factor that influence survival after treatment. Due to the small number of patients, we couldn't accurately estimate the effect of treatment to identify the prognostic factors. However, we found that patients with histology of ovarian clear cell carcinoma (OCCC) had the worst survival outcome. A large prospective randomized trial found that in the early stages, OCCC had a better outcome than serous carcinoma, however, in late-stage patients, OCCC was significantly associated with decreased overall survival (OS) compared to serous carcinoma (Oliver et al., 2017). The results of a recent study from Korea also showed that advanced-stage OCCC had a worse OS than advanced-stage serous carcinoma (Oliver et al., 2017; Kim et al., 2022). The proportion of patients with clear cell carcinoma was higher in East Asian women while there was no improvement in overall survival (Matz et al., 2017; Park et al., 2017; Kim et al., 2022). Therefore, the development of innovative strategies and precision medicine is important and further clinical trials are still needed.

Only a few studies have presented the survival outcomes of the patients in this group. Studies on these patients have been published since 2014. The strength of our study is that it keeps researchers up to date with the real situation of patients with refractory and platinum-resistant EOC in Thailand. We found that for almost 10 years, the survival rate of the patients in these two groups has not increased despite a new treatment option. Current practice has been limited by Thailand's Universal Health Coverage. Our data could be used to improve the policy of treatment for ovarian cancer in Thailand. There may be some possible limitations of this study. First, its retrospective design, missing data and the small number of patients may have influenced the results. A multi-center study covering every region in the country could provide more accurate results on patient outcomes. Second, we didn't assess the quality of life (QoL), which is an important factor to consider before deciding on the treatment option. One study in Thailand reported that in the setting of this group of patients, salvage chemotherapy has a QoL score comparable with that of palliative care alone (Srisuttayasathien and Khemapech, 2013). Further studies regarding cost-effectiveness of chemotherapy, new strategies or targeted therapy, and palliative treatment will have an impact on the decision-making of treatment for recurrent ovarian cancer in a developing country.

In conclusion, the survival outcome of patients with refractory and platinum-resistant EOC remains poor. Novel strategies based on molecular biologics have been studied in clinical trials with encouraging results. This may offer longer survival and better quality of life to the patients.

## Author Contribution Statement

All authors contributed to the study's conception and design. The first draft of the manuscript was written by Tanitra T. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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*Ethical Declaration*

Approval was obtained from the ethics committee of Srinakharinwirot University. The procedure used in this study adheres to the tenets of the Declaration of Helsinki.

*Availability of data*

The datasets used and analysed during the present study are available from the corresponding author on reasonable request.

*Competing interests*

The authors have declared no conflicts of interest.

## References

Altman AD, McGee J, May T, et al (2017). Neoadjuvant chemotherapy and chemotherapy cycle number: A national multicentre study. *Gynecol Oncol*, **147**, 257-61.

Colombo PE, Labaki M, Fabbro M, et al (2014). Impact of neoadjuvant chemotherapy cycles prior to interval surgery in patients with advanced epithelial ovarian cancer. *Gynecol Oncol*, **135**, 223-30.

Docker LE, Rubenstein AR, Ding K, et al (2019). Extending the platinum-free interval: The impact of omitting 2nd line platinum chemotherapy in intermediate platinum-sensitive ovarian cancer. *Gynecol Oncol*, **155**, 201-6.

Foley OW, Rauh-Hain JA, del Carmen MG (2013). Recurrent epithelial ovarian cancer: an update on treatment. *Oncology (Williston Park)*, **27**, 288-94, 98.

Hilal Z, Schultheis B, Hartmann F, et al (2016). What Characterizes Long-term Survivors of Recurrent Ovarian Cancer? Case Report and Review of the Literature. *Anticancer Res*, **36**, 5365-71.

Jansaka N, Suprasert P (2014). Survival outcomes of recurrent epithelial ovarian cancer: experience from a Thailand northern tertiary care center. *Asian Pac J Cancer Prev*, **15**, 10837-40.

Kerio P, Abid K, Hassan A, Shah A, Manzoor A (2022). Treatment Outcomes of Epithelial Ovarian Cancer-A Longitudinal Study. *Asian Pac J Cancer Care*, **7**, 253-9.

Kim SI, Ha HI, Eoh KJ, et al (2022). Trends in the Incidence and Survival Rates of Primary Ovarian Clear Cell Carcinoma Compared to Ovarian Serous Carcinoma in Korea. *Front Oncol*, **12**, 874037.

Lheureux S, Braunstein M, Oza AM (2019). Epithelial ovarian cancer: Evolution of management in the era of precision medicine. *CA Cancer J Clin*, **69**, 280-304.

Lheureux S, Gourley C, Vergote I, Oza AM (2019). Epithelial ovarian cancer. *Lancet*, **393**, 1240-53.

Lui YL, Zhou QC, Lasonos A, et al (2020). Pre-operative neoadjuvant chemotherapy cycles and survival in newly diagnosed ovarian cancer: what is the optimal number? A Memorial Sloan Kettering Cancer Center Team Ovary study. *Int J Gynecol Cancer*, **30**, 1951-21.

Manchana T, Charakorn C, Lertkhachonsuk A-a, et al (2020). Treatment of Recurrent Ovarian Cancer: Survey of Practice among Thai Gynecologic Oncologists. *J Med Assoc Thai*, **103**, 90-7.

Matz M, Coleman MP, Sant M, et al (2017). The histology of ovarian cancer: worldwide distribution and implications for international survival comparisons (CONCORD-2). *Gynecol Oncol*, **144**, 405-13.

Oliver KE, Brady WE, Birrer M, et al (2017). An evaluation of progression free survival and overall survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: An NRG Oncology/Gynecologic Oncology Group experience. *Gynecol Oncol*, **147**, 243-9.

Park HK, Ruterbusch JJ, Cote ML. (2017). Recent Trends in Ovarian Cancer Incidence and Relative Survival in the United States by Race/Ethnicity and Histologic Subtypes. *Cancer Epidemiol Biomarkers Prev*, **26**, 1511-8.

Pitakkarnkul S, Tangjitgamol S, Srijaipracharoen S, et al (2013). Treatment outcomes of paclitaxel for refractory or recurrent epithelial ovarian cancer patients in Thailand. *Asian Pac J Cancer Prev*, **14**, 2421-7.

Pujade-Lauraine E, Banerjee S, Pignata S (2019). Management of Platinum-Resistant, Relapsed Epithelial Ovarian Cancer and New Drug Perspectives. *J Clin Oncol*, **37**, 2437-8.

Rustin GJ (2011). Follow-up with CA125 after primary therapy of advanced ovarian cancer has major implications for treatment outcome and trial performances and should not be routinely performed. *Ann Oncol*, **22**, viii45-8.

Soyama H, Takano M, Miyamoto M, et al (2017). Factors favouring long-term survival following recurrence in ovarian cancer. *Mol Clin Oncol*, **7**, 42-6.

Srisuttayasathien M, Khemapech N (2013). Quality of life in ovarian cancer patients choosing to receive salvage chemotherapy or palliative treatment. *Asian Pac J Cancer Prev*, **14**, 7669-74.

Sung H, Ferlay J, Siegel RL, et al (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, **71**, 209-49.