
GYNAECOLOGY

Treatments and Outcomes of Epithelial Ovarian Cancers in Srinagarind Hospital

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ABSTRACT

Objectives: To compare treatments of epithelial ovarian cancers (including fallopian tube cancer and primary peritoneal adenocarcinoma) with national guidelines and oncological outcomes between standard and non-standard treatment groups.

Materials and Methods: Retrospective chart reviews were performed on patients with epithelial ovarian cancers, fallopian tube cancer and primary peritoneal adenocarcinoma (n = 318) who had been registered in Department Obstetrics and Gynecology, Srinagarind Hospital, between January 1st, 2014 and December 31st, 2019. Surgical treatments and adjuvant treatments were compared with national guidelines. Oncological outcomes were compared between standard and non-standard treatment groups. Univariate and multivariate logistic regression analyses were used for factors to receive which treatment. Survival rates were analyzed by Kaplan-Meier and prognostic factors were compared among the two groups by Cox-regression for factors to receive longer overall survival.

Results: A total of 318 patients were recruited. Most patients were diagnosed with epithelial ovarian cancers (89.9%). The major pathology was high grade carcinoma (53.8%). Surgeries were done in most patients (92.1%), which were primary cytoreductive surgery (72.4%) and complete surgical staging (80.5%). Residual tumors of more than 5 mm in diameter were left in 42.3%. Standard and non-standard treatment of epithelial ovarian cancers were found in 60.4% (95% confidence interval: 54.9-65.6%) and 39.6%, respectively. Chemotherapies were given to most patients (86.8%). Five-year survival rates and recurrence free survival rates were 42.2% and 26.8%. Overall survival rate was significantly lower in the non-standard group (adjusted hazard ratio = 1.42, 95% confidence interval: 1.01-2.02, p = 0.046).

Conclusion: National guidelines on treatment of epithelial ovarian cancers should be followed, because of poorer outcomes in the non-standard groups.

Keywords: treatments, oncological outcomes, epithelial ovarian cancers, national guideline recommended therapy.

วิธีและผลการรักษาของโรคมะเร็งเยื่อบุโพรงมดลูกในโรงพยาบาลศรีนครินทร์

จิรภิญญา ชุมวรธาชัย, บัณฑิต ชุมวรธาชัย, สงวนโชค ล้วนรัตนากร, อมรรัตน์ เต็มธนะกิจไพศาล, นราทัศน์พล ลิขิตดี, ยุวดี อธิรัตน์

บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบวิธีการรักษามะเร็งเยื่อบุโพรงมดลูก (รวมถึงมะเร็งท่อนำไข่และมะเร็งเยื่อบุช่องท้องปฐมภูมิ) กับแนวทางการรักษามาตรฐาน และผลการรักษามะเร็งเหล่านี้ ระหว่างกลุ่มที่ได้รับวิธีการรักษามาตรฐานกับวิธีการรักษาที่มีไม่มาตรฐาน

วัตถุประสงค์และวิธีการ: ทบทวนและเก็บข้อมูลจากที่มีบันทึกอยู่ในเวชระเบียนของผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเยื่อบุโพรงมดลูก มะเร็งท่อนำไข่และมะเร็งเยื่อบุช่องท้องปฐมภูมิ ($n = 318$) ในสาขาวิชาสูติศาสตร์และนรีเวชวิทยา โรงพยาบาลศรีนครินทร์ ระหว่างวันที่ 1 มกราคม 2557 ถึงวันที่ 31 ธันวาคม 2561 เปรียบเทียบวิธีการรักษาด้วยการผ่าตัดและการรักษาเสริมด้วยยาเคมีบำบัดกับแนวทางการรักษามาตรฐาน และเปรียบเทียบผลการรักษามะเร็งระหว่างกลุ่มที่ได้รับวิธีการรักษามาตรฐานกับวิธีการรักษาที่มีไม่มาตรฐาน ใช้การวิเคราะห์ถดถอยเอกนามและพหุนามเพื่อปัจจัยในการได้รับการรักษามาตรฐาน วิเคราะห์อัตราการอยู่รอดด้วยวิธี Kaplan-Meier และวิเคราะห์เพื่อเปรียบเทียบและบ่งชี้ปัจจัยในการอยู่รอดได้นานกว่าในระหว่างกลุ่มด้วยวิธี Cox-regression

ผลการศึกษา: มีผู้ป่วยที่เข้าเกณฑ์ในการศึกษาได้ทั้งหมด 318 ราย ผู้ป่วยส่วนใหญ่ได้รับการวินิจฉัยเป็นมะเร็งเยื่อบุโพรงมดลูก (ร้อยละ 89.9) ผลการตรวจทางพยาธิวิทยาส่วนใหญ่เป็นชนิด high grade serous (ร้อยละ 53.8) ผู้ป่วยส่วนใหญ่ได้รับการผ่าตัด (ร้อยละ 92.1) ชนิด primary cytoreductive surgery (ร้อยละ 72.4) และชนิด complete surgical staging (ร้อยละ 80.5) มีก้อนมะเร็งหลงเหลืออยู่ขนาดใหญ่กว่า 5 มม. ร้อยละ 42.3 อัตราการได้รับการรักษามาตรฐานและที่ไม่ใช่มาตรฐาน (ทั้งน้อยกว่าและมากกว่า) พบได้ร้อยละ 60.4 (ช่วงความเชื่อมั่นร้อยละ 95: ร้อยละ 54.9-65.6) และร้อยละ 39.6 ตามลำดับ ผู้ป่วยส่วนใหญ่ได้รับยาเคมีบำบัด (ร้อยละ 86.8) อัตราการอยู่รอดที่ 5 ปี และอัตราการอยู่รอดปลอดโรค เท่ากับร้อยละ 42.2 และ 26.8 อัตราการอยู่รอดโดยรวมในกลุ่มที่ได้รับการรักษาไม่ตรงตามมาตรฐาน ต่ำกว่ากลุ่มที่ได้รับการรักษาตามมาตรฐานอย่างมีนัยสำคัญ (adjusted hazard ratio = 1.42, ช่วงความเชื่อมั่นร้อยละ 95: 1.01-2.02, $p = 0.046$)

สรุป: การรักษามะเร็งเยื่อบุโพรงมดลูก ควรปฏิบัติตามแนวทางการรักษามาตรฐาน เพราะอัตราการอยู่รอดโดยรวมในกลุ่มที่ได้รับการรักษาไม่ตรงตามมาตรฐาน ต่ำกว่ากลุ่มที่ได้รับการรักษาตรงตามมาตรฐานอย่างมีนัยสำคัญ

คำสำคัญ: การรักษามะเร็ง, ผลการรักษามะเร็ง, มะเร็งเยื่อบุโพรงมดลูก, แนวทางเวชปฏิบัติ

Introduction

Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in general population, accounting for more deaths than any other cancer of the female reproductive system⁽¹⁾. Globally, the incident rate of new cases of ovarian cancer was 10.6 per 100,000 women per year. The estimated death in 2021 was 13,700, accounting for 2.3% of all cancer death. Approximately 1.1 percent of women will be diagnosed with ovarian cancer at some point during their lifetime⁽²⁾. In Thailand, breast cancer was the most common cancer in women (age-standardized incidence rate (ASR) = 34.2), and ovarian cancer was the third most common gynecologic cancers (under cervical cancer and endometrial cancer) with ASR = 6.0 leading to 53% deaths⁽³⁾.

About half of the women who are diagnosed with ovarian cancer are elderly patients. Most of the cases are diagnosed in an advanced stage, which leads to poor outcomes of this disease. Ovarian cancer is often called the silent killer because the symptoms such as bloating, early satiety or bowel habits changes, are subtle. These could also be confused with other illnesses⁽⁴⁾.

Two versions of national guidelines of epithelial ovarian cancer have been used in Thailand, which are NHSO (National Health Security Organization) 2018's⁽⁵⁾ and TGCS (Thai Gynecological Cancer Society) 2019's⁽⁶⁾. Adjuvant treatments have been mainly consisted of systemic chemotherapy (CMT), being considered from International Federation of Gynecology and Obstetrics (FIGO) stage and histologic grade. There was a study already done in Thailand⁽⁷⁾ but only aspects of outcomes were evaluated in patients who underwent incomplete surgical staging, not any about the standard treatments' comparison.

Treatments of ovarian cancer might vary depending on the stage of the disease, histology, the performance status of the patient, expert opinion of the surgeon and patients' choice and their related outcomes are also depending on these factors. In the

past, several studies in many countries had been done about the treatment that patients had been received compared with standard treatment according to the national guidelines⁽⁸⁻¹⁰⁾. The results were shown that many factors were associated with the lower rate of standard treatment, especially in elderly patients^(8,9).

Treatments and their related outcomes had also never been evaluated in Srinagarind Hospital. Therefore, the objectives of this study were to compare treatments with national guidelines and oncological outcomes between standard and non-standard groups in real-life practice at Srinagarind Hospital.

Materials and Methods

This study was a retrospective descriptive analytical study conducted at Srinagarind Hospital, a tertiary hospital in Khon Kaen, Thailand. Study protocol was approved by Office of the Khon Kaen University Ethics Committee in Human Research on 14 June 2021 (HE641117). After then, this retrospective study was conducted.

The study was conducted in ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma patients diagnosed in Srinagarind Hospital from January 2014 to December 2019 by retrieving data from out-patient department (OPD) cards and health object (HO), the program to collect patients' data in electronics' pool. These data were then entered into a computerized database for subsequent analysis.

Inclusion criteria were all patients aged 18 years old or more who diagnosed as malignant neoplasms of ovary, fallopian tube, peritoneum during that period at Srinagarind hospital. Exclusion criteria were as follows; 1) surgeries were not done at Srinagarind Hospital, 2) final diagnoses were benign disease, 3) final diagnoses were borderline ovarian tumor, 4) final diagnoses were other primary origin or ovarian metastasis, 5) final diagnosis were germ cell, sex cord stromal, sarcoma, spindle cell and undifferentiated tumor, and 6) incomplete data recorded such as missed operative note.

The definition of “standard therapy” was that patients having surgery and/or chemotherapy as recommended in Thai national guidelines^(5,6) based on the stage, histology and grade of the cancer. The definition of “non-standard therapy” was that patients not having “standard therapy”. Only one deviation of the guideline would be interpreted as non-standard. However, pelvic without para-aortic lymphadenectomy could still be considered as standard therapy, as this was not mentioned in NHSO guideline⁽⁵⁾. Cessation of chemotherapy due to severe complication was considered as non-standard because the treatment was inadequate.

The rate of standard therapy rate was 80.0% from a previous study, with 95% confidence level and an error margin of 5%, the estimated sample size was at least 250. Table 1 shows the definition of standard treatment according to Thai national

guideline recommended therapy.

Descriptive statistics were used to describe the demographic baseline characteristics. Numerical data were expressed as mean, standard deviation, percentages and 95% confidence interval (CI) to demonstrate the precision of the data. Categorical variables were expressed as percentages. Univariate and multivariate logistic regression was used to analyze odds ratio and adjusted odds ratio (adj OR), respectively. A p value of < 0.05 was considered statistically significant. Survival rate was analyzed by Kaplan-Meier method and overall survivals were compared. Factors for longer survival were analyzed by Cox-proportional hazards model. All data analyses were performed using IBM SPSS statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Table 1. The definition of standard treatment according to Thai national guideline.

FIGO stage	Histology	Surgery (Primary cytoreductive surgery (PCS)/ Interval debulking surgery(IDS))	Chemotherapy	
			Number of Neoadjuvant cycles (PCS/IDS)	Number of Adjuvant cycles (PCS/IDS)
IA/IB	Low grade*, except clear cell carcinoma	PCS/IDS	None/2-4	None
	Clear cell carcinoma	PCS/IDS	None/2-4	3-8/3-6
	High grade**	PCS/IDS	None/2-4	3-8/3-6
IC	Any of above	PCS/IDS	None/2-4	3-8/3-6
II	Any of above	PCS/IDS	None/2-4	3-8/3-6
III	Any of above	PCS/IDS	None/2-4	3-8/3-6
IV	Any of above	PCS/IDS	None/2-4	3-8/3-6

* Endometrioid grade 1-2, low grade serous grade 1, mucinous carcinoma

** High grade serous grade 2-3, high grade endometrioid

Results

A total of 1,551 patients were recruited between January 1, 2014 and December 31, 2019. Not all were analyzed, due to 1,233 of them being excluded by the criteria mentioned above. Details of these exclusions were described in Fig. 1. Finally, there were 318 fully retrieved datasets for analyses.

Mean follow-up time was 5 years (range 2-8 years, from January 2014 to December 2021). Overall survival rates at 1-, 3- and 5-year were 81.3%, 56.3%, and 42.2%, respectively. There were 166 recurrences (52.2%) in the whole cohort, therefore, the 5-year recurrence free survival rate was 26.8%. Median overall survival time was 3.6 years and

median recurrence free survival time was 0.83 years. Fig. 2 and 3 show overall survival times (OS)

and recurrence free survival times (RFS) compared between standard and non-standard treatment.

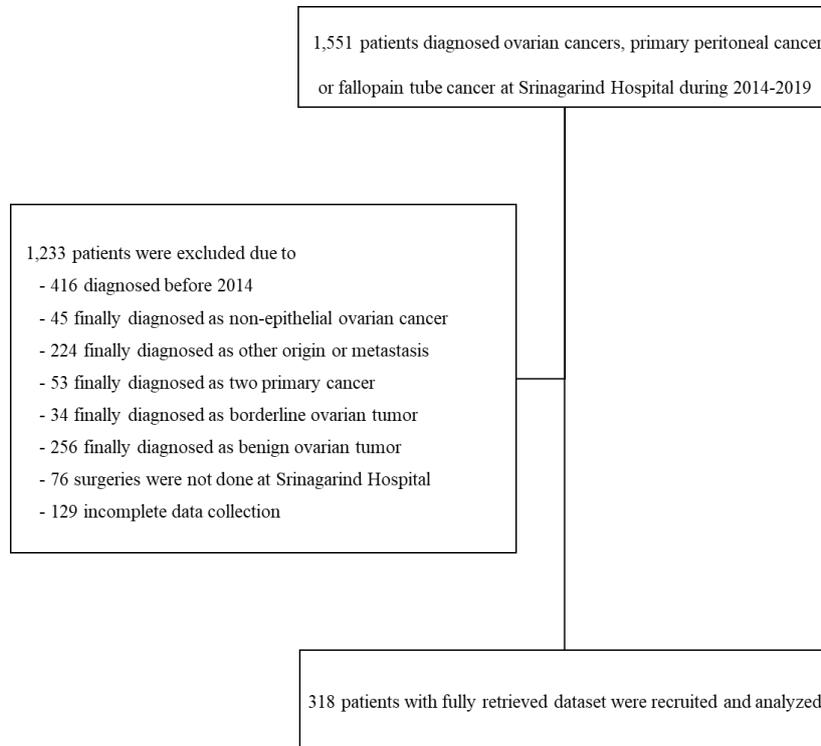


Fig. 1. Participants flow diagram.

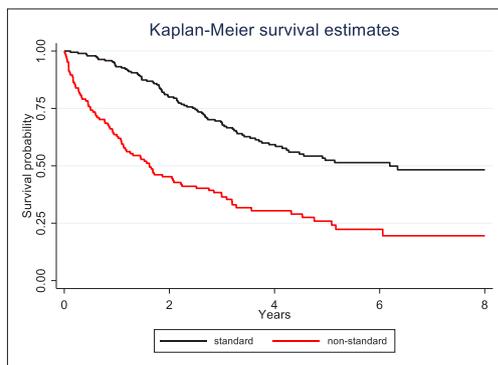


Fig. 2. Overall survival times (OS) compared between standard and non-standard treatment.

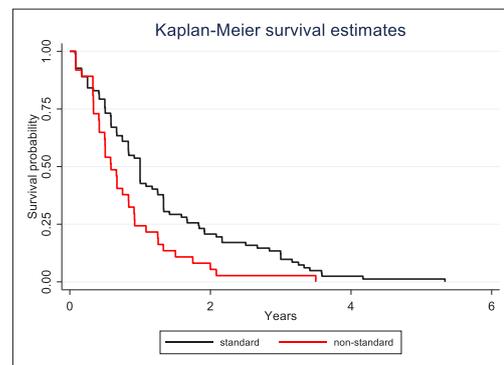


Fig. 3. Recurrence free survival times (RFS) compared between standard non-standard treatment.

Baseline characteristics were demonstrated in Table 2. Among 318 women diagnosed with ovarian cancers, fallopian tube cancers, and primary

peritoneal adenocarcinoma, 104 were elderly (> 60 years old). The mean age was 55.3 years. One third (28.6%) were nulliparity, and two third were post-

menopausal (73.9%). Most of them were married (78.0%) and had universal coverage (UC) and civil servant medical benefit scheme (CSMBC) as their health insurances (53.8% and 38.7%, consecutively). Mean body mass index (BMI) was 22.4 kg/m². Half

of them had normal weight (53.8%), and at least 1 underlying disease (47.8%). Almost all (88.1%) of them were in class 0 of Eastern Cooperative Oncology Group (ECOG) performance status. Some of them had previous abdominal surgeries (14.8%).

Table 2. Baseline characteristics/ demographic data of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

Baseline characteristics/ demographic data	n (%)
Age (years)	55.3
Parity	
- 0	91 (28.6%)
- 1	41 (12.9%)
- ≥ 2	186 (58.5%)
Menopausal status	
- Premenopausal status	83 (26.1%)
- Post-menopausal status	235 (73.9%)
Status	
- Single	65 (20.4%)
- Married	248 (78.0%)
- Divorced	5 (1.6%)
Health insurance	
- Universal coverage (UC)	171 (53.8%)
- Civil servant medical benefit scheme (CSMBC)	123 (38.7%)
- Social security scheme (SSS)	24 (7.5%)
- Self-pay	0 (0%)
Body mass index (BMI) categories	
- Underweight (BMI < 18.5)	45 (14.2%)
- Normal (BMI 18.5 - 22.9)	171 (53.8%)
- Overweight (BMI 23.0 - 24.9)	40 (12.6%)
- Obese (BMI > 25)	62 (19.5%)
Underlying disease	
- No	166 (52.2%)
- Yes	152 (47.8%)
Previous abdominal surgeries	
- No	271 (85.2%)
- Yes	47 (14.8%)
ECOG performance status	
- ECOG 0	280 (88.1%)
- ECOG 1	32 (10.1%)
- ECOG 2	3 (0.9%)
- ECOG 3	3 (0.9%)

ECOG: Eastern Cooperative Oncology Group

Pathological features were shown in Table 3. Most patients were diagnosed with epithelial ovarian cancer (89.9%), fallopian tube cancer and primary peritoneal adenocarcinoma were found in only 2.5% and 7.5%,

consecutively. Over half of them were presented with advanced stage of disease (61.0%), 28.0% in stage IIIC and 21.1% in stage IVB. The majority of pathology was high grade serous adenocarcinoma (53.8%).

Table 3. Pathological features of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma cancers (n = 318).

Pathological features	Number	Application of guidelines-recommended therapy	
		Standard treatment	Non-standard treatment
Diagnosis			
- Ovarian cancer	286	176 (61.5%)	110 (38.5%)
- Fallopian tube cancer	8	7 (87.5%)	1 (12.5%)
- Primary peritoneal adenocarcinoma	24	9 (37.5%)	15 (62.5%)
Stages			
- IA	31	24 (77.4%)	7 (22.6%)
- IB	2	1 (50%)	1 (50%)
- IC	52	39 (75%)	13 (25%)
- IIA	6	6 (100%)	0 (0.0%)
- IIB	33	27 (81.8%)	6 (18.2%)
- IIIA	7	1 (14.3%)	6 (85.7%)
- IIIB	27	19 (70.4%)	8 (29.6%)
- IIIC	89	51 (57.3%)	38 (42.7%)
- IVA	4	2 (50%)	2 (50%)
- IVB	67	22 (32.8%)	45 (67.2%)
Histology			
- Low grade serous	8	7 (87.5%)	1 (12.5%)
- High grade serous	171	99 (57.9%)	72 (42.1%)
- Endometrioid	33	27 (81.8%)	6 (18.2%)
- Mucinous	23	15 (65.2%)	8 (34.8%)
- Clear cell	61	44 (72.1%)	17 (27.9%)
- Others/Unknown	22	0 (0.0%)	22 (100%)

Table 4 shows surgical treatment procedures. Surgeries were done in almost all of them (92.1%). Most surgical procedures were primary cytoreductive surgery (72.4%) and complete surgical staging (80.5%). Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) were done in most patients (90.4% and 93.5%, consecutively). Unilateral SO was performed in selected cases where the patients had fertility needed (4.8%). Omentectomies were done in

92.5%. Peritoneal cytology was done in 11.6%. Only some patients underwent bilateral pelvic node dissection or sampling (BPND/S) and para-aortic node dissection or sampling (PAND/S) (16.0% and 2.7%, consecutively). Residual tumors were left in 42.3% (suboptimal surgery). There was only 1 case that residual disease was not mentioned in the operative note. Other procedures such as appendectomy were performed in some cases (14.7%).

Table 4. Surgical treatments related procedures of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

Surgical Treatments Related Procedures	n (%)
Surgery was not done	25 (7.9)
Surgery was done	293 (92.1%)
Surgery type	
- Primary cytoreductive surgery	212 (72.4%)
- Interval debulking surgery	81 (27.6%)
Surgery type	
- Fertility sparing surgery	16 (5.5%)
- Complete surgical staging	236 (80.5%)
- Incomplete surgical staging	41 (14.0%)
Residual disease	
- Optimal	169 (57.7%)
- Suboptimal	124 (42.3%)
Total hysterectomy (TH)	265 (90.4%)
Unilateral salpingo-oophorectomy (Unilateral SO)	14 (4.8%)
Bilateral salpingo-oophorectomy (BSO)	274 (93.5%)
Omentectomy	271 (92.5%)
Peritoneal cytology	34 (11.6%)
Bilateral pelvic node dissection or sampling (BPND/S)	47 (16.0%)
Para-aortic node dissection or sampling (PAND/S)	8 (2.7%)
Other procedures (adhesiolysis, appendectomy, peritoneal biopsy, random biopsy, etc.)	43 (14.7%)

Adjuvant treatments were classified in Table 5. Chemotherapies were given to most patients (86.8%), in which 34.4% were neo-adjuvant. Almost all (98.9%) were platinum-based with an average number of 4.1

courses. A total of 266 patients received adjuvant therapies (96.4%). Most of them (98.9%) received platinum-based chemotherapies with an average number of 5.5 courses.

Table 5. Chemotherapy treatments related procedures of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

No chemotherapy	42 (13.2%)
Chemotherapy	276 (86.8)
Neoadjuvant chemotherapy	
- Platinum based regimen (cases)	94
- Others regimen (cases)	1
- Mean of chemotherapy cycle (cycles)	4.1
Adjuvant chemotherapy	
- Platinum based regimen (cases)	263
- Others regimen (cases)	3
- Mean of chemotherapy cycle (cycles)	5.5

Treatments were classified in Table 6 depending on stages following FIGO staging in epithelial ovarian neoplasms. Application of guideline recommended therapy was found in 192 of 318 cases (60.4%), comparing with national treatment guidelines^(5, 6). In stage IA, there were 7 case (22.6%) that had non-standard treatment; including 5 cases that denied surgeries (3 cases due to advanced age and 2 cases due to fertility need), and 2 cases with incomplete

staging. In stage IB, there was 1 patient (50%) receiving non-standard treatment due to adjuvant chemotherapy cessation after cycle 3 from severe neutropenia. In stage IC, there were 13 patients (25.0%) received non-standard treatment (10 cases due to incomplete surgical staging, and 3 cases due to adjuvant chemotherapy cessation from complications, which were severe neutropenia and hepatitis).

Table 6. Adjuvant treatments of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

Stages	Number	Chemotherapy			Surgeries			Application of guidelines-recommended therapy		Recurrent
		No	NACT	Adj CMT	No	Primary cytoreductive surgery	IDS	Yes	No	
IA	31	13	0	18	0	31	0	24 (77.4%)	7 (22.6%)	4 (12.9%)
IB	2	0	0	2	0	1	1	1 (50%)	1 (50%)	0 (0%)
IC	52	2	4	50	0	48	4	39 (75%)	13 (25%)	9 (17.3%)
IIA	6	0	0	6	0	6	0	6 (100%)	0 (0%)	1 (16.7%)
IIB	33	0	7	33	0	27	6	27 (81.8%)	6 (18.2%)	10 (30.3%)
IIIA	7	3	1	4	2	4	1	1 (14.3%)	6 (85.7%)	5 (71.4%)
IIIB	27	0	16	27	0	13	14	19 (70.4%)	8 (29.6%)	19 (70.4%)
IIIC	89	1	46	86	0	47	42	51 (57.3%)	38 (74.5%)	67 (75.3%)
IVA	4	4	2	4	0	2	2	2 (50%)	2 (50%)	2 (50%)
IVB	67	19	18	35	23	33	11	22 (32.8%)	45 (67.2%)	49 (73.1%)
Total	318	42	276 (86.8%)	25	293 (92.1%)	192 (60.4%)	126 (39.6%)			166 (52.2%)

All patients in stage IIA had standard treatments according to standard guidelines. In stage IIB, there were 6 patients (18.2%) received non-standard treatments due to incomplete surgical staging. In stage IIIA, there were 6 patients (85.7%) received non-standard treatments due to denial for receiving surgery, denial for receiving chemotherapy, incomplete surgical staging, and others due to loss follow-up. In stage IIIB, there were 8 patients (29.6%) received non-standard treatments due to incomplete surgical staging. In stage IIIC, there were 38 patients (74.5%) received non-standard treatments due to incomplete surgical staging (19 cases), complication

from chemotherapy (11 cases), and progressive disease during treatment (9 cases).

In stage IVA, there were 2 patients (50%) received non-standard treatment due to incomplete surgical staging. In stage IVB, there were 45 patients (67.2%) received non-standard treatments; 20 denied surgeries or chemotherapy due to advanced age and underlying disease, 3 had surgical complications (death), 14 had incomplete surgical staging, and 8 had progressive diseases during treatment.

Table 7 lists the factors associated with application of guidelines-recommended therapy. After the univariate and multivariate analyses were

performed by univariate and multivariate logistic regression, respectively. Age < 60-years-old (OR = 1.78, 95%CI: 1.11 to 2.87, p = 0.017, but adj OR = 1.69,

95%CI: 0.98 to 2.91, p = 0.06) and optimal surgery (adj OR = 4.64, 95%CI: 2.76 to 7.80, p < 0.001) were associated with received standard treatment.

Table 7. Factors associated with application of guidelines-recommended therapy.

Factors	Standard treatment applied = No		Standard treatment applied = Yes		OR (95%CI) p value	Adj OR* (95%CI) p value
	n	%	n	%		
Age						
≤ 60 years	75	59.52	139	72.4	1.78 (1.11 to 2.87) 0.017	1.69 (0.98 to 2.91) 0.06
> 60 years	51	40.48	53	27.6	1	-
Diagnosis						
Ovarian cancer	110	87.3	176	91.67	1	-
Fallopian tube cancer	1	0.79	7	3.65	4.38 (0.53 to 36.04) 0.17	-
Primary peritoneal adenocarcinoma	15	11.9	9	4.69	0.38 (0.16 to 0.89) 0.025	-
Stage	26	20.8	97	50.52	3.89 (2.32 to 6.52) < 0.001	-
Early (I-II)	26	20.8	97	50.52	3.89 (2.32 to 6.52) < 0.001	-
Advance (III-IV)	99	79.2	95	49.48	1	-
Histology						
Low grade (G1-2)	13	10.32	45	23.44	2.66 (1.37 to 5.17) 0.004	-
High grade (G3, Clear cell)	113	89.68	147	76.56	1	-
Residual disease						
Optimal,	34	33.66	135	70.31	4.67 (2.79 to 7.82) < 0.001	4.64 (2.76 to 7.8) < 0.001
Suboptimal	67	66.34	57	29.69	1	-
Underlying disease						
No	66	52.38	100	52.08	1	-
Yes	60	47.62	92	47.92	1.01 (0.65 to 1.59) 0.959	-
Previous abdominal surgery						
No	105	83.33	166	86.46	1.28 (0.68 to 2.39) 0.443	-
Yes	21	16.67	26	13.54	1	-

* Multivariate logistic regression analysis
OR: odds ratio, CI: confidence interval

Survival of patients according to clinical and pathological features was shown in Table 8. Multivariate Cox-proportional hazards models were

fit for each covariate with both survivals. There were 4 and 2 statistically significant prognostic factors for overall survival time (OS) and recurrence free

survival time (RFS), consecutively, which consisted of advanced stages at diagnosis, received non-standard treatment (for both OS and RFS), suboptimal surgeries, and at least one underlying diseases (for OS only). The oncological outcomes (overall

survival rate and recurrent free survival rate) were poorer in the non-standard group [adjusted hazard ratio (aHR) = 1.42 (95%CI: 1.01 to 2.02, p = 0.046) and aHR = 1.74 (95%CI: 1.14 to 2.61, p = 0.007), respectively].

Table 8. Survival of patients according to clinical and pathological factors.

Factors	Overall survival		Recurrence-free survival	
	HR (95%CI), p	aHR* (95%CI), p	HR (95%CI), p	aHR* (95%CI), p
Age				
≤ 60 years	1	-	1 (0.67 to 1.5), 0.988	-
> 60 years	1.45 (1.06 to 1.97), 0.018	-	1	-
Diagnosis				
Ovarian cancer	1	-	1	-
Fallopian tube cancer	0.76 (0.28 to 2.04), 0.581	-	2.09 (0.84 to 5.2), 0.113	-
Primary peritoneal adenocarcinoma	1.96 (1.2 to 3.19), 0.007	-	0.72 (0.36 to 1.44), 0.354	-
Stage				
Early (I-II)	1	1	1	1
Advance (III-IV)	5.7 (3.78 to 8.58), < 0.001	3.4 (2.17 to 5.32), < 0.001	1.66 (1.05 to 2.64), 0.031	1.66 (1.04 to 2.64), 0.033
Histology				
Low grade (G1-2)	1	-	1	-
High grade (G3, Clear cell)	2.51 (1.54 to 4.09), < 0.001	-	1.15 (0.66 to 2.01), 0.627	-
Residual disease				
Optimal,	1	1	1	-
Suboptimal	4.34 (3.08 to 6.1), < 0.001	2.38 (1.62 to 3.5), < 0.001	1.6 (1.1 to 2.31), 0.013	-
Underlying disease				
No	1	1	1	-
Yes	1.55 (1.15 to 2.1), 0.004	1.59 (1.15 to 2.2), 0.005	1.08 (0.75 to 1.56), 0.685	-
Previous abdominal surgery				
No	1.13 (0.73 to 1.76), 0.574	-	1.13 (0.67 to 1.92), 0.649	-
Yes	1	-	1	-
Therapy				
Standard	1	1	1	1
non-standard	2.72 (2.01 to 3.67), < 0.001	1.42 (1.01 to 2.02), 0.046	1.75 (1.17 to 2.6), 0.006	1.74 (1.17 to 2.61), 0.007

* Multivariate Cox-proportional hazards model. HR: hazard ratio, aHR: adjusted hazard ratio

Discussion

The aim of this retrospective study was to evaluate the treatment and outcomes in the patient diagnosed with epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma who received primary treatments at Srinagarind Hospital, one of the largest tertiary-care hospitals in Thailand. Authors clarified the types of treatment that epithelial ovarian cancer patients received in comparison between standard and non-standard according to national guidelines^(5,6).

Authors included 318 patients diagnosed with epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma in Srinagarind hospital during 2014-2019. Patients' baseline characteristics/demographic data were quite similar among each group including age, parity, number of underlying diseases, health insurance, stages of the disease, histology and ECOG performance status.

The rate of receiving standard treatments was 60.4% (95%CI: 54.9-65.6%), which was lower than expected (80%). This rate differed from Bun et al's (78.7%),⁽⁸⁾ but similar to Fourcardier et al's (63.3%).⁽⁹⁾ This might be due to the two last versions of Thai national guideline on recommended therapy were published in 2018 and 2019, but authors studied on treatments since 2014.

Factors that associated with standard treatment were lower age (defined by a cut-off of 60-year-old in this study) and optimal surgery (Table 7). The elderly patients received standard therapies significantly less than the younger patients. These findings were similar to the previous studies. Bun et al⁽⁸⁾ studied 244 patients with ovarian cancer stage I-IV in Japan and found that elderly patients (aged more than 70-year-old) received standard therapies less than younger patients (57.5% vs 81.2%). Fourcardier et al⁽⁹⁾ studied 1,151 patients with all stage of ovarian cancer in France, also found that the elderly group (aged more than 70 years old) received standard therapies less than the younger group (52.0% vs 69.8%). This might be due to more underlying diseases, advanced stage at diagnosis, and less tolerance to chemotherapeutic

toxicities in elderly patients.

In this study, authors also found that age (as defined by a cut-off of 60-year-old) was not a prognostic factor for either overall survival times and recurrence free survivals times, but the advanced stages of the disease at diagnosed and non-standard treatment were (Table 8). This was similar to another previous study. Yoshikawa et al⁽¹⁰⁾ studied 114 patients with all FIGO stage ovarian cancers in Osaka city university hospital and found that prognostic factor for overall survival times were FIGO stage and standard primary therapy in younger group and were only performance status in elderly groups (defined by a cut-off of 70-year-old). Supporting by the rationale above, this was the possible reason why age was not found to be a significant prognostic factor in this study. Noticeably, the cut-off value for elderly patients in Thailand that author used was slightly lower than other studies because Thai life expectancy (LE) is lower.

For treatment outcomes, 5-years overall survival rate (42.2%) was slightly lower than the Thai previous study (57.0%)⁽⁷⁾, but similar to worldwide reference (49.7%)⁽²⁾. In addition, this study's new findings to Thailand suggested that overall survival time and recurrent free survival time were poorer in the non-standard treatment with aHR = 1.42 (95%CI: 1.01 to 2.02, p = 0.046) and aHR = 1.74 (95%CI: 1.17 to 2.61, p = 0.007), respectively (Table 8).

The reason why non-standard treatment resulted in poorer survivals should be due to its less optimality. Optimal therapy means that patients had no residual disease after surgery and enough adjuvant platinum combination chemotherapy given in any appropriate cases. This is straightforward and was mentioned earlier in 2013 by Trilsch et al⁽¹¹⁾ as in their multivariate analysis, age itself was not a prognostic factor for PFS while the ECOG performance status had prognostic significance. In addition, these findings were supported later by many authors^(8-10, 12-14).

Authors concluded that our rate of receiving standard treatment was comparable with France's (63.3%), but lower than Japan's (78.7%) and our expectation (80%). National guidelines on treatment

of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal adenocarcinoma should be followed, because of poorer outcomes in the non-standard groups.

The strengths of this study were as follows; first it was the second study about epithelial ovarian cancer treatment in Thailand with more detailed and larger sample size. Second, this study had adequate follow-up time with mean of 5 years (range 2-8 years) coverage of all epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma cases in Srinagarind Hospital, one of the largest tertiary-care hospitals in Thailand. Third, the sample size was adequate to detect oncological outcomes' differences between standard and non-standard groups.

Nevertheless, this study had some limitations. The analysis did not take factors such as details of underlying disease into account. Furthermore, no definite information about the reasons for non-standard treatment was available in retrieved study's data. Finally, this study was retrospective in nature, some biases might have occurred.

For practice and future research implications, collecting the reason for non-standard treatment and underlying diseases should be done. In addition, the correctable reason for non-standard treatment must be managed to optimize the effectiveness of treatments. Prospective data collection should be used.

Conclusion

Thai national guidelines on treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal adenocarcinoma should be followed, because of poorer outcomes in the non-standard groups.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Arora T, Mullangi S, Lekkala MR. Ovarian cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK567760/>
2. National Institutes of Health. Cancer Stat Facts: Ovarian cancer [Internet]. 2022. Available from: <https://seer.cancer.gov/statfacts/html/ovary.html>
3. Rojanamatin J, Ukranun W, Supaattagorn P, Chiawiriyabunya I, Wongsena M, Chaiwerawattana A, et al. Cancer in Thailand Vol X, 2016-2018. Bangkok: National Cancer Institute 2021:1-171.
4. American Cancer Society. About ovarian cancer [Internet]. 2022. Available from: <https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html>
5. National Health Security Organization (NHSO). Adult cancer treatment guideline. Bangkok: Sahamit Printing and Publishing 2018:1-167.
6. Thai Gynecological Cancer Society (TGCS). Ovarian cancer treatment guideline. Nonthaburi: PCK Design 2019:1-114.
7. Panprom P, Lertkhachonsuk R. Outcome of ovarian cancer patients who underwent incomplete surgical staging. *J Med Assoc Thai* 2008;91:1323-30.
8. Bun S, Yunokawa M, Ebata T, Kato MK, Shimoi T, Kato T, et al. Feasibility of initial treatment in elderly patients with ovarian cancer in Japan: A retrospective study. *Int J Clin Oncol* 2019;24:1111-8.
9. Fourcadier E, Trétarre B, Gras-Aygon C, Ecartot F, Daurès J, Bessaoud F. Under-treatment of elderly patients with ovarian cancer: A population based study. *BMC Cancer* 2015;15:937.
10. Yoshikawa K, Fukuda T, Uemura R, Matsubara H, Wada T, Kawanishi M, et al. Age related differences in prognosis and prognostic factors among patients with epithelial ovarian cancer. *Mol Clin Oncol* 2018;9:329-34.
11. Trillsch F, Woelber L, Eulenburg C, Braicu I, Lambrechts S, Chakerov R, et al. Treatment reality in elderly patients with advanced ovarian cancer: a

- prospective analysis of the OVCAD consortium. *J Ovarian Res* 2013;6:42.
12. Sabatier R, Calderon B Jr, Lambaudie E, Chereau E, Provansal M, Cappiello MA, et al. Prognostic factors for ovarian epithelial cancer in the elderly: a case-control study. *Int J Gynecol Cancer* 2015;25:815-22.
 13. Rauh-Hain JA, Melamed A, Wright A, Gockley A, Clemmer JT, Schorge JO, et al. Overall survival following neoadjuvant chemotherapy vs primary cytoreductive surgery in women with epithelial ovarian cancer: analysis of the national cancer database. *JAMA Oncol* 2017;3:76-82.
 14. Schuurman MS, Kruitwagen RFPM, Portielje JEA, Roes EM, Lemmens VEPP, van der Aa MA. Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis. *Gynecol Oncol* 2018;149:270-4.