



Salvage therapy of epithelial ovarian cancer: What is the appropriate setting for Asian situation?

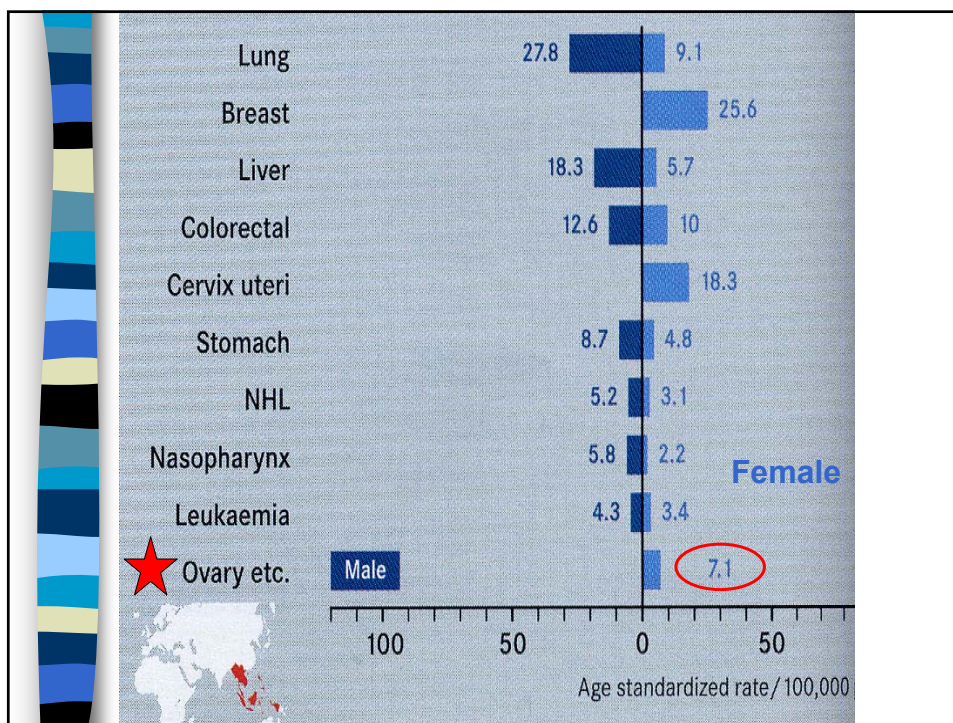


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Content

- Persistent/recurrent EOC
- Choices of salvage therapy in EOC
- Asian countries
- Appropriate setting for Asian situation
 - Supportive care
 - Surgery
 - Chemotherapy
 - Etc.





New cases and death of cancers in the world

Facts :

- 70% responses to first-line therapy
- 60 – 80% of these patients have been found to experience persistence/recurrence and finally die of the disease.

Magnitude of the Problem

Recurrence

Initial disease	Frequency (%)	Recurrence (%)
Stage I-II, favorable	10	10
Stage I-II, unfavorable	15	20
Stage III, residual < 2 cm.	30	60-70
Stage III-IV, residual	45	80-85
Overall	100*	62

AJR Am J Roentgenol 1979;133:221

Clin Radiol 1984;35:465

Recurrent EOC cases per year in the world

- New cases per year of ovarian cancer are **192,000** cases.
- **85%** is EOC(ACOG data).
- **62%** has recurrence.
- Recurrent EOC cases per year are $192,000 \times 0.85 \times 0.62 = 101,184$ cases.

Cancer in Thai Women'2003

Cancer	Incidence*	New cases/yr
Cervix	19.5	6268
Breast	17.2	5592
Liver	16.0	4696
Lung	10.0	2964
Colorectal	7.3	2215
Ovary	5.2	1655

* Age-standardized incidence rate/100,000 person-years

Source : Cancer in Thailand. Vol. III, 2003

	ACOG 1994 %	IARC* 1993 %	RAMA 1990-94 %
Epithelial Ovarian Cancer	85	65.2	83.3
Malignant Germ Cell Tumor	10	6.6	11.6
Sex cord – Stromal Tumor	5	3.1	0.9
not specified/unclassified		21.4	2.2

* IARC : International Agency for Research on Cancer
RAMA : Ramathibodi Hospital, Bangkok, Thailand
Ovarian Cancer : Distribution by histological type

Recurrent EOC cases per year in Thailand

- Recurrent cases per year of EOC in Thailand are $1,655 \times 0.833 \times 0.62 =$

855 cases.

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Staging Classifications and Clinical Practice Guidelines for Gynaecological Cancers

A collaboration between FIGO and IGCS

Third Edition

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Ovarian Cancer

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OVARIAN CANCER
PRACTICE GUIDELINE



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อนุกรมการศึกษามะเร็งอวัยวะสืบพันธุ์
ราชวิทยาลัยสูตินรีแพทย์แห่งประเทศไทย

Patients after first-line therapy

Patients with a treatment-free interval of ≤ 6 months were designated as **platinum refractory** and those > 6 months as **platinum sensitive**.

- Clinically low-volume or focal recurrence after disease-free interval $> 6-12$ mo
→ consider **secondary cytoreductive surgery** then carboplatin+paclitaxel or carboplatin+gemcitabine or recurrence regimen

■ For patients who are considered platinum sensitive, a combination of carboplatin and paclitaxel is suggested.

■ Platinum-refractory → supportive care or recurrence regimen

Choices of salvage therapy in EOC

- Supportive care

- Surgery

- Chemotherapy

(Usually, the response rate to salvage chemotherapy of any regimen is rarely more than 30 %)

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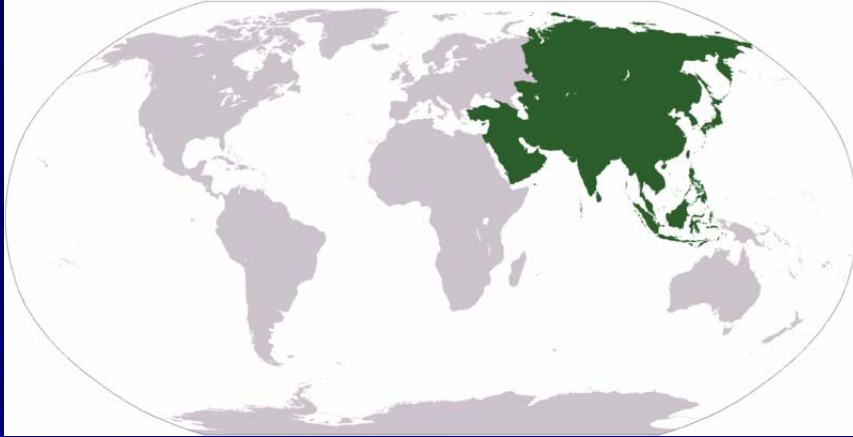
 - Supportive care

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Map of Asia



Asia

- 49,703,948 km²
- 4,001,377,185 people
- 57 countries
- 6 developed countries
51 developing countries

- **Developed country Definition** – “a country that has reached a stage of economic development characterised by the growth of industrialisation. In developed countries, the amount of money made by the population (national income) is enough to pay for schools, hospitals and other services. Population growth in developed countries is usually slower than in developing countries.”

UN definition

- **Developing country Definition** - “a country that has not reached the stage of economic development characterised by the growth of industrialisation. In developing countries, the amount of money made (national income) is less than the amount of money needed to pay for schools, hospitals and other services (domestic savings). Often these countries also have big populations, which are growing very fast. This means that there is very little money to build new factories and increase the national income. Developing countries find it hard to break this cycle of poverty.”

UN definition

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Policy of treating EOC

- Usually, the national policy of developing countries in treating EOC stresses on first-line therapy due to its cost-effectiveness, while salvage therapy is not.

First-line treatment of ovarian cancer: Thailand scenario

Thailand

- Thailand is a developing country.
- Thailand's GDP per capita is US\$ 8,542 which ranks 19th in Asia and 72nd in the world .

FIGO Annual Report

Carcinoma of the Ovary: 5-yr Survival Rates

YEAR	PATIENTS	SURVIVAL %
1958-62	2,320	26.8
1963-68	4,588	27.3
1969-72	4,892	30.1
1973-75	5,268	30.5
1976-78	6,724	29.8
1979-81	8,082	30.9
1982-86	10,912	35.0
1987-89	2,942	39.1
1990-92	7,059	41.6
1993-95	3,409	48.4
1996-98	4,116	46.4
1999-2001	4,911	49.7
	56,196	

- The median overall survival of ovarian cancer is 5 yr (60 mo).

Epithelial ovarian cancer treated by platinum or platinum analogue with cyclophosphamide: experience in Ramathibodi Hospital.

Linasmita V, Wilailak S, Srisupundit S, Tangtrakul S, Bullangpoti S, Israngura N.

J Med Assoc Thai. 1998 Jan;81(1):10-6. Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital

Cost Effectiveness Analysis of First-line Therapy

- **Treatment CP:** Drug cost = US\$ 100/cycle
 - Number of cycles are 6 times
 - Therefore, total drug cost of treatment is equal to 6xUS\$ 100
 - US\$ 600
- **Treatment TP:** Drug cost = US\$ 1,120/cycle
 - Number of cycles are 6 times
 - Therefore, total drug cost of treatment is equal to 6xUS\$ 1,120
 - US\$ 6,720

Cost Effectiveness Analysis of First-line Therapy (continued)

- Overall survival time = 60 months
- Cost/Effectiveness Ratio: Cost of Treatment / Overall survival time
 - Treatment CP: $\text{US\$}600/60 \text{ mo.} = 10(\text{US\$/mo.})$
 - Treatment TP: $\text{US\$}6,720/60 \text{ mo.} = 112(\text{US\$/mo.})$

Salvage therapy of EOC: Thailand scenario

Secondary cytoreductive surgery

The DESKTOP–OVAR study

**Descriptive Evaluation Selection KriTeria
for Operability in recurrent OVARian cancer**
(Dubois A, et al. Int J Gynecol Cancer 2005;15 (suppl2):78)

Objective : To evaluate the criteria for **cytoreductive surgery (CRS) in recurrent ovarian cancer (ROC) patients**

Methods : 267 patients, retrospective multicenter(25)

ECOG : PS 0=53%, 1/2= 39%/8%

FIGO stage : I/II =31% , III/IV = 69%

Residual 1st Sx : 0 mm = 58%, >0 = 42%

Platinum based after Sx = 55%

The DESKTOP-OVAR study

Residual	Median survival	HR (95%CI)	P
No	45.2 mo.	Reference	-
1-10	19.6 mo.	4.17(2.42-7.16)	<0.001
>10	19.7 mo.	3.31(1.86-5.88)	<0.001

Cost Effectiveness Analysis of Secondary Cytoreductive Surgery

- Cost of cytoreductive surgery = 300 US\$

Cost Effectiveness Analysis of Secondary Cytoreductive Surgery (continued)

- No residual: overall survival time = 45 months (Dubois)
- Residual : overall survival time = 20 months (Dubois)
- Cost / Effectiveness Ratio: Cost of Treatment / Overall survival time
 - No residual : US\$ 300/45 mo. = 6.7(US\$/mo.)
 - Residual : US\$ 300/20 mo.= 15 (US\$/mo.)
- C/E No residual < C/E residual
- No residual is more cost effective than residual.

Chemotherapy **TP** in **platinum-sensitive** EOC

Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in the treatment of relapsed ovarian cancer: the ICON4 / AGO-OVAR-2.2 trial

**Jonathan A Ledermann,
on behalf of all ICON and AGO Collaborators**

ICON 4 Trial design

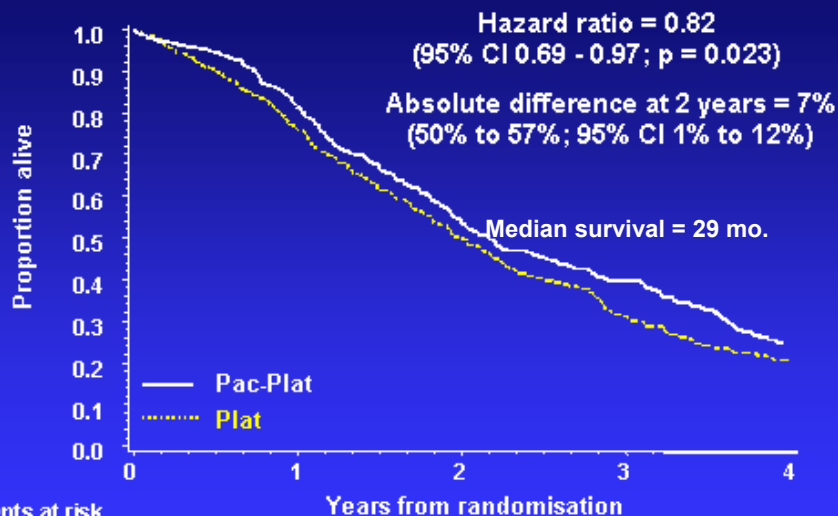
- Relapsed ovarian or primary peritoneal (serous type) carcinoma, requiring chemotherapy
- Previous platinum-based chemotherapy
- TFI ≥ 6 months MRC/AGO, ≥ 12 months IRFMN

RANDOMISE

Conventional platinum-based chemotherapy

Paclitaxel plus platinum chemotherapy

Overall survival (OS)



Cost Effectiveness Analysis of TP Regimen in Platinum-sensitive EOC

- **Treatment TP:** Drug cost = US\$ 1,120/cycle
 - Number of cycles are 6 times
 - Therefore, total drug cost of treatment is equal to 6xUS\$1,120
 - **US\$ 6,720**

Cost Effectiveness Analysis of TP Regimen in Platinum-sensitive EOC (continued)

- **Overall survival time** = 29 months (ICON4)
- **Cost /Effectiveness Ratio:** Cost of Treatment / Overall survival time
 - **Treatment TP:** US\$ 6,720/29 mo.= 232(US\$/mo.)

Liposomal doxorubicin in platinum-refractory EOC

A study of pegylated liposomal Doxorubicin in platinum-refractory epithelial ovarian cancer.

**Wilailak S,
Linasmitta V.**

**Department of Obstetrics and Gynaecology,
Faculty of Medicine, Ramathibodi Hospital, Bangkok,
Thailand. Oncology. 2004;67(3-4):183-6.**

Using a dose of **40 mg/m²** given every 3 weeks, in the treatment of platinum-refractory epithelial ovarian cancer. The response rate in 14 patients was **23%**.

The median survival was **14.5 mo.**

Cost Effectiveness Analysis of Liposomal Doxorubicin in Platinum-Refractory EOC

- Liposomal doxorubicin: Drug cost = US\$ 1,600/cycle
 - Number of cycles are 5 times
 - Therefore, total drug cost of treatment is equal to 5xUS\$ 1,600
- US\$ 8,000

Cost Effectiveness Analysis of Liposomal Doxorubicin in Platinum-Refractory EOC (continued)

- Overall survival time = 14.5 months (Wilailak)
- Cost / Effectiveness Ratio: Cost of Treatment / Overall survival time
 - Treatment liposomal doxorubicin: US\$ 8,000/14.5 mo. = 552(US\$/mo.)

Megestrol Acetate in platinum-refractory EOC

Phase II study of high-dose megestrol acetate in platinum-refractory epithelial ovarian cancer.

Wilailak S, Linasmita V, Srisupundit S. Anticancer Drugs. 2001 Oct;12(9):719-24.

Department of Obstetrics & Gynaecology, Ramathibodi Hospital, Mahidol University

Patients with platinum-resistant epithelial ovarian cancer were treated with megestrol acetate (800 mg/day) orally for 28 days and then 400 mg/day for a minimum of 28 days before being assessed ready for evaluation of response to therapy. Thirty-six patients were enrolled. Response was observed in seven of 36 patients (three CR and four PR). The response rate was 19.4% (95% CI 9-36). The majority of patients gained weight and had a fair quality of life score during treatment. The overall survival time was 6 months.

Cost Effectiveness Analysis of Megestrol acetate in Platinum- Refractory EOC

- Megestrol acetate: Drug cost = US\$ 200/cycle
 - Number of cycles are 4 times
 - Therefore, total drug cost of treatment is equal to 4xUS\$ 200
 - US\$ 800

Cost Effectiveness Analysis of Megestrol acetate in Platinum- Refractory EOC (continued)

- Overall survival time = 6 months (Wilailak)
- Cost /Effectiveness Ratio: Cost of Treatment / Overall survival time
 - Treatment megestrol acetate: US\$800/6 mo.= 133(US\$/mo.)

Supportive care

Historical Treatment of Ovarian Cancer

Year	Event	Medial Survival for
1960-1970	Use of whole-abdominal irradiation	12 Mo.
1970-1990	Improved understanding of importance of surgery	
1970-1980	Single-agent alkylating agent chemotherapy	12 Mo.
1980-1995	Platinum combination chemotherapy	24 Mo.
1995-	Platinum/Taxol chemotherapy	36 Mo.

Cost Effectiveness Analysis of Supportive care after first-line therapy

- Hospital cost for supportive care = US\$ 2,500

Cost Effectiveness Analysis of Supportive care after first-line therapy (continued)

- Overall survival time = 36 months
Cost/Effectiveness Ratio: Cost of Treatment /Overall survival time
 - Supportive care: US\$ 2,500/36 mo.= 70(US\$/mo.)

Patients receiving salvage therapy

- Supportive care
- Platinum-sensitive EOC
- Platinum-refractory EOC

Cost effectiveness of

- Supportive care = 70(US\$/mo.)

Cost effectiveness

Platinum-sensitive EOC

- Surgery: no residual+TP+supportive care
= $6.7+232+70=308.7$ (US\$/mo.)
- Surgery: with residual+TP+supportive care
= $15.8+232+70=317.8$ (US\$/mo.)
- TP+supportive care = $232+70 = 302$
(US\$/mo.)

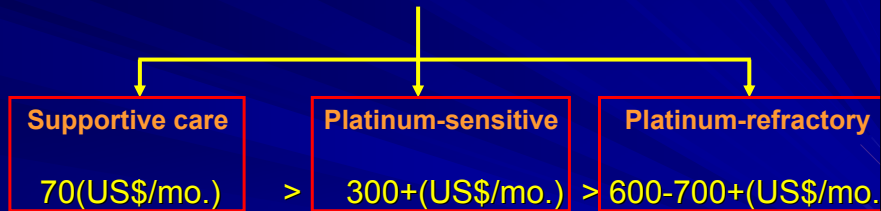
Cost effectiveness

Platinum-refractory EOC

- Liposomal doxorubicin+supportive care =
 $552+70 = 662$ (US\$/mo.)
- Liposomal doxorubicin+megestrol
acetate+supportive care = $552+113+70 =$
 735 (US\$/mo.)
- Megestrol acetate+supportive care = $113+70 =$
 183 (US\$/mo.)

Cost effectiveness

Salvage therapy



The appropriate setting in Asian countries?

For the national policy on salvage therapy of EOC, supportive care and/or additional surgery/chemotherapy is reasonable. This depends on the affordability of each country.

The use of investigational/expensive agents is individualized.

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