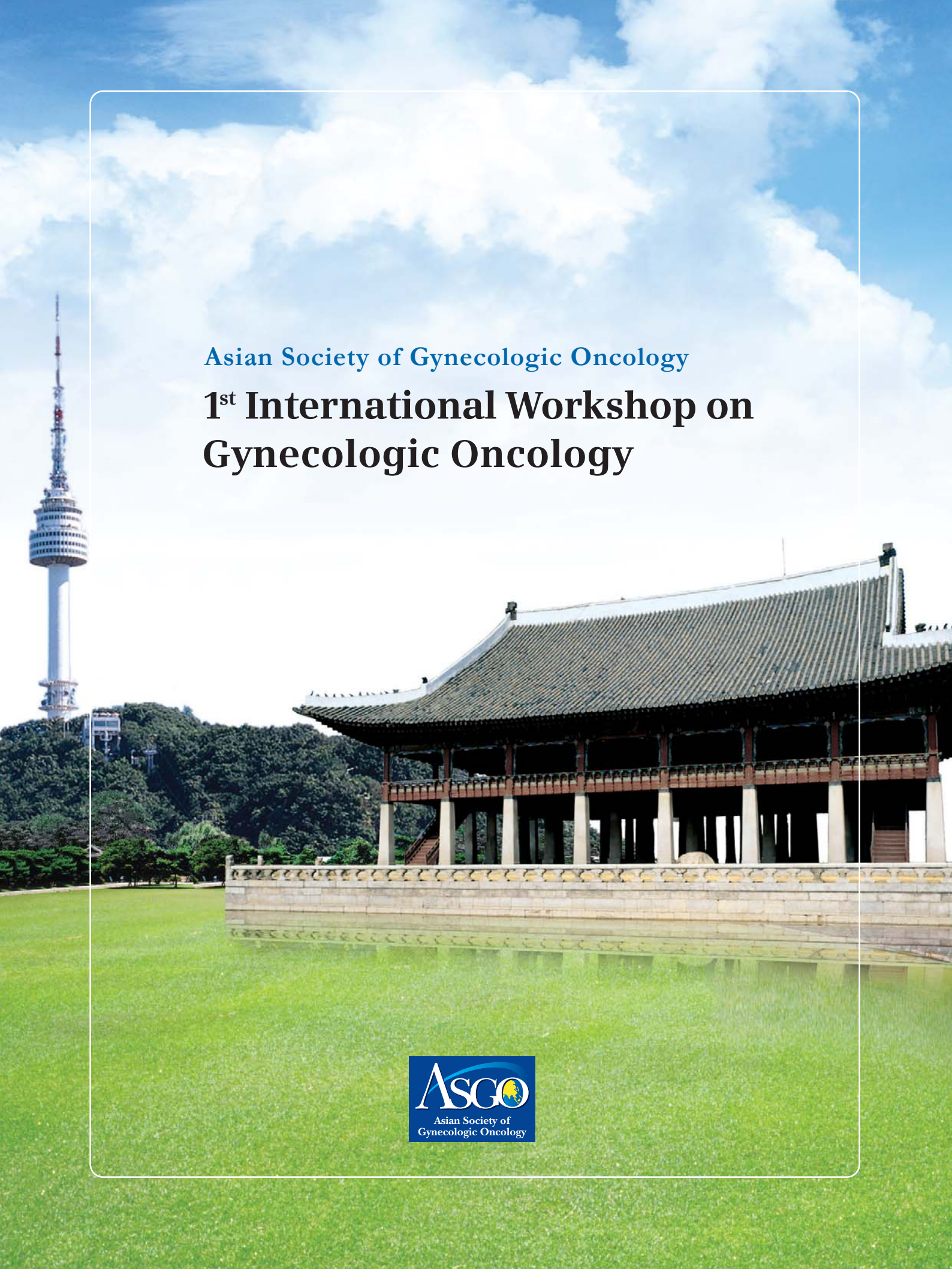

Asian Society of Gynecologic Oncology

1st International Workshop on Gynecologic Oncology

ASGO
Asian Society of Gynecologic Oncology

1st International Workshop on Gynecologic Oncology

Contents

Welcome Message

On behalf of the Asian Society of Gynecologic Oncology, I would like to cordially invite you to the 1st International Workshop on Gynecologic Oncology to be held in Seoul, Korea from 31 July to 1 August, 2010.

This workshop is organized to promote the academic environment and to enhance the communication among Asian countries prior to the 2nd Biennial meeting, which will be held in November, 2011.

ASGO was founded in November, 2008 in accordance with a resolution adopted in the 7th Korea-Japan Gynecologic Oncology Joint Meeting and it has council members from 10 asian countries nominated from asian gynecologic oncologists.
ASGO has achieved stability in such a swift manner that it stands shoulder to shoulder with European Society of Gynecological Oncology and Society of Gynecologic Oncologists (SGO). The 1st Biennial Meeting of ASGO was successfully held in Tokyo, Japan in November, 2009.

I firmly believe that the 1st International Workshop on Gynecologic Oncology will be a great opportunity for Asian young doctors to enhance their knowledge in this field and also for every participant to have a wider perspective on the Gynecologic Oncology as renowned speakers will present their recent studies on Gynecologic Oncology.
I hope Asian Society of Gynecologic Oncology will play a leading role to establish systematic studies and educational environment and to care Asian patients who are suffered from gynecologic tumor.

I wish this Workshop would be a memorable one to all participants and welcome you in Seoul upcoming July.

Soon Beom Kang, M.D., Ph.D.
President, Asian Society of
Gynecologic Oncology
Seoul National University, Korea

Toshiharu Kamura, M.D., Ph.D.
President Elect, Asian Society of
Gynecologic Oncology
Kurume University, Japan

Program

Asian Society of Gynecologic Oncology
1st International Workshop on Gyecologic Oncology

Day 1 31st July (Saturday)

08:20-08:45	**Registration**	
08:45-09:00	**Opening remark**	**Soon Beom Kang,** President of ASGO
	Congratulatory remark	**Shingo Fujii,** President Elect of IGCS, Japan
		Eung Soo Lee, President of KSGOC, Korea
		Yong Won Park, Chairman of KSOG, Korea

Session I Prevention of Cervical Cancer

Chairman : Noriyuki Inaba, Japan / Seung Jo Kim, Korea

09:00-09:20	**Cervical cancer screening in Asia**	**Mohamad F. Aziz,** Indonesia
09:20-09:40	**Screening in low resource setting**	**Uma Devi,** India
09:40-10:00	**Update on HPV vaccination**	**Hextan Y. S. Ngan,** Hong Kong
10:00-10:10	**Q & A**	
10:10-10:30	**Break**	

Session II New Trends in Cervical Cancer Management

Chairman : Zeyi Cao, China / Jae Wook Kim, Korea

10:30-10:50	**Radical surgery overview**	**Jong Hyeok Kim / Joo Hyun Nam,** Korea
10:50-11:10	**Fertility sparing & less radical surgery**	**Seung Cheol Kim,** Korea
11:10-11:30	**Myths & facts about nerve sparing radical surgery**	**Tomoyasu Kato,** Japan
11:30-11:50	**Primary chemo-radiotherapy in LACC**	**Hee Sug Ryu,** Korea
11:50-12:00	**Q & A**	

Luncheon seminar - MSD

Chairman : Joon Mo Lee, Korea

12:00-12:20	**Implementation of HPV vaccination with policy priorities to reduce societal burdens**	**Young Tak Kim,** Korea
12:20-13:30	**Lunch**	

Session III Surgical technique: film session

Chairman : Sung Eun Namkoong, Korea / Kyu Wan Lee, Korea

13:30-14:00	**Nerve sparing radical hysterectomy**	**Shingo Fujii,** Japan
14:00-15:00	**Optimal staging in early ovarian cancer**	**Dae Gy Hong / Yoon Soon Lee,** Korea
	Laparoscopic radical hysterectomy	**Jong Hyeok Kim,** Korea
	One-port surgery	**Tae Joong Kim,** Korea
	Robotic surgery	**Young Tae Kim,** Korea
	Q & A	
15:00-15:20	**Break**	

Session IV Endometrial Cancer

Chairman : Yasuhiro Udagawa, Japan / Hyo Pyo Lee, Korea

15:20-15:40	**Laparoscopic surgery vs. open surgery**	**Kung Liahng Wang,** Taiwan
15:40-16:00	**Role of lymphadenectomy**	**Taek Sang Lee,** Korea
16:00-16:20	**Fertility sparing treatment for endometrial cancer**	**Kimio Ushijima,** Japan
16:20-16:30	**Q & A**	
19:00-21:00	**Dinner**	

Day 2 1st August (Sunday)

Special lecture

Chairman : Jung Eun Mok, Korea

09:00-09:30	**Clinical trials in Asia**	**Sang-Goo Shin,** Korea
09:30-09:40	**Q & A**	
09:40-10:00	**Break**	

Session V Ovarian Cancer

Chairman : Kazunori Ochiai, Japan / KyungTai Kim, Korea

10:00-10:20	**First line chemotherapy: overview of trends**	**Yin Nin Chia,** Singapore
10:20-10:40	**Neo-adjuvant chemotherapy in ovarian cancer**	**Sarikapan Wilailak,** Thailand
10:40-11:00	**Optimal surgical management for ovarian cancer**	**Sang Yoon Park,** Korea
11:00-11:20	**Targeted therapy**	**Hidetaka Katabuchi,** Japan
11:20-11:30	**Q & A**	
11:30-11:35	**Introduction of 2nd ASGO meeting**	**Joo Hyun Nam,** Korea
11:35-11:40	**Closing remark**	**Toshiharu Kamura,** President Elect Of ASGO, Japan
	Adjourn	

1st International Workshop on Gynecologic Oncology

Session I

Prevention of Cervical Cancer

Chairman : Noriyuki Inaba, Japan **/ Seung Jo Kim,** Korea

- Cervical cancer screening in Asia
  Mohamad F. Aziz, Indonesia

- Screening in low resource setting
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- Update on HPV vaccination
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Cervical cancer screening in Asia

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Abstract

Cervical cancer is the third most common cancer in women, and the seventh overall, with an estimated 529,000 new cases in 2008. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancer.

South Eastern Asia is less developed regions, the estimated age-standardised incidence and mortality rates per 100,000 is higher than in Eastern Asia regions. The highest estimated age-standardised incidence rates in Eastern Asia is Mongolia (28.38) and the lowest is Democratic Republic of Korea (6.64), while in South Eastern Asia regions, the highest is Cambodia (27.4) and the lowest is Singapore (6.83). The high risk HPV type 16 and 18 are consistently identified in cervical cancer regardless of countries or regions. Contributing factors to the developement of cervical cancer in general are young age at first intercourse, high parity and multiple sexual partners. Cervical cancer screening program that have fully support by their governments in these regions is very few especially in South Eastern regions the methods are Pap smear, colposcopy and in less developed countries visual inspection with acetic acid (VIA) and followed by cryotherapi is more favourable. The last procedure is known as see and treat. Targeted age-groups and interval of screening are slightly different in each countries.

Key words: cervical cancer, incidence, mortality, contributing factors, screening, south eastern regions, eastern regions

Screening in low resource setting

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Introduction :

Cervical Cancer is the most common cancer among women in developing countries. Cancer of uterine cervix is a major cause of morbidity and mortality in females. Cancer registries have also highlighted that more than 80% of cases in females occur in the age group of 35-64, thereby suggesting the impact of cancer as a major public health problem in the most productive age group. Cervical cancer accounted for 493,000 newly diagnosed cases, 1.4 million prevalent cases and 273,000 deaths worldwide in the year 2002. Of these more than 80% occurred in the low – and medium – resource countries in South & South-East Asia, sub-saharan Africa, and south & central America.[1]

Unfortunately these low resource countries that have access to less than 5% of global cancer treatment resources.[2]

The magnitude & mortality of cervical cancer

There is an eight fold variation in the incidence rates of cervical cancer world -wide and age-standarized incidence rates about 25 per 100,000 women are observed in many developing countries as opposed to rates lower than 10 per 100,000 in most developed counties and lower than 7 per 100,000 in the middle eastern countries.

Estimated age-adjusted mortality rates due to cancer of uterine cervix exceed 10 per 100,000 women in most developing countries with rates exceeding 25 per 100,000 in East African countries as opposed to less than 5 per 100,000 women in most developed countries.

Indian scenario-cervical cancer

From the population based cancer registries in India, there were 135,000 new cases of cancer of uterine cervix of which 75,000 patients die of this disease annually. There were 26 population based cancer registry and 5 hospital cancer registry, covering 1/3 of

population of the country, India alone accounts for more than 1/5 of cervical cancer to the global burden.

India, a country of more than one billion people, lacks organized national screening program for cervical cancer and screening has not reached the vast majority of women in need. The mortality is due to advanced clinical stage at presentation and to the fact that significant proportion of patients do not have facility to avail, afford, access or complaint to the prescribed treatment .

Screening in low resource setting

The purpose of cervical cancer screening is to decrease the morbidity and mortality associated with a specific disease through early detection. This aim is achieved through the performance of cost effective tests applied to an asymptomatic population that is at significant risk for the disease. The screen is not diagnostic of the disease itself, but identifies a population that requires more specific testing to determine if treatment is required.

The ideal screening test is inexpensive and is not associated with significant discomfort or inconvinience to the patient. The yield per test is expected to be low unless that of diagnostic test.

Cytology screening has been largely responsible for the significant decline in the burden of cervical cancer in developed countries in the last five decades[1] & has reduced invasive cervical cancer rates by 74%.[4] Organized screening with systematic call, recall, follow up and surveillance system have shown the greatest effect at scandanivian countries (Finland, Iceland). Cervical cancer incidence has been reduced by as much as 80% where cytology screening quality, coverage and follow up of women are high.

PAP test(cytology screening) is yet to be effectively implemented in many developing countries or has failed to reduce cervical cancer burden to an appreciable extent in some developing countries. However, several studies at meta analysis, of cytologic screening has revealed that it has low sensitivity of 50%,[5] although it has specificity of 86 - 100%.[5, 6]

The apparent lack of impact of cervical cytology program and difficulties in organizing such program in low - and- medium resource countries have prompted the search for and evaluation of alternative screening tests and paradigms that require one single or two visits, to complete the screening and diagnosis / treatment processes.[7]

However, who has suggested low intensity cytology/pap test once in a life time after 35 years or at 10 year intervals and simple **Visual Inspection** [VI] of cervix to organized

cytology for the control of cervical cancer in developing countries.[8, 9] As this method of visual inspection did not detect microscopic disease, it was considered inadequate .[10,11,12,13]

Hence a various strategies has been devised as an alternative to appropriate technologies in cervical cancer screening for low resource settings:

* Visual Inspection with Acetic Acid **(VIA)**[14, 15]
* Visual Inspection with Lugol's Iodine **(VILI)**[16]
* **Combination of VIA &VILI**
* **Cervicography**
* The **"See & Treat"** technique using diathermy, cryosurgery
* **HPV test** [17, 18, 19, 20]

Although the sensitivity of VIA ranged between 66 & 96% and specificity between 64 & 98% and in low resource setting it is difficult to ensure screening at regular intervals, so a single time screening test will be a good option or HPV test at ten years interval from the age-standarized rate of invasive cancer among screen negative women is another alternative proposal. The association of gynaecologic oncologists of India has proposed a simple C [3] program at a systematic level to implement at level 1 (Primary Health Unit) to level 4 (at tertiary referral centre) with intention of early detection & treatment protocol referral system.

Conclusion :

Cervical cancer remain the deadliest gynaecological malignancy in developing countries and the poor prognosis is largely attributable to the advanced stage at diagnosis for the majority of patients. Attempts to screen at low resource setting have yet to determine the optimal screening strategy or to demonstrate a significant reduction in mortality due to these efforts. The impact of future screening strategy at low resource setting require further exploration until then VIA & HPV care test can be considered as another option.

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Update on HPV vaccination

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Cervical cancer vaccines are prophylactic vaccines preventing infection of Human Papillomavirus types 16 and 18. These 2 types are associated with about 70% of cervical cancer worldwide. So far, 100% efficacy in preventing CIN2/3 was shown by both the bivalent and quadrivalent vaccines in their Phase II studies. Both showed more than 90% efficacy in Phase III trial. Also, a decrease in abnormal cytology, need for colposcopy referral or treatment were shown on Phase III trial. No excessive serious adverse event over control was seen in both vaccines. Post-marketing surveillance showed that for both vaccines were safe.

Several issues arise on further analysis of trial data or new trials showed there was evidence of cross-protection to other non-targeted HPV types; the apparent waning of antibody level in HPV 18 in the quadrivalent vaccine, the antibody assay using same method on both vaccines, efficacy in adult women and apparent efficacy in women previously infected by HPV.

Sub-group analysis showed 68-70% efficacy in preventing CIN caused by HPV31 in both vaccine and almost 100% for HPV 45 in bivalent vaccines. Since the trial was not powered or designed for assessment of efficacy to non HPV 16 and 18, these results had to be interpreted with care. Since the protection is not complete and the duration of protection is yet to be determined, exact benefit of cross-protection is difficult to define. However, the theoretical advantage of significant prevention of HPV 45 is in the prevention of adenocarcinoma which is not easy to detect by conventional cytology screening. A properly designed randomized control trial is needed to determine the impact of cross-protection on adenocarcinoma. The new development of multivalent vaccines may provide more protection than current vaccines.

Long term follow-up of antibody level for HPV 16 and 18 after 8.4 years still showed more than 10 folds above the baseline in bivalent vaccine. For the monovalent HPV16 vaccine, high level was seen more than 9 years. No breakthrough CIN was found in

both the bivalent and quadrivalent vaccines Phase II cohort and hence no immune-correlation of the minimal antibody level required in maintaining efficacy can be determined. While the antibody of HPV18 seems to have declined to the level of natural infection in the quadrivalent vaccine, it could be due to the method of assay based on one epitope only. One study using same method, pseudovirion- based neutralizing assay, in monitoring antibody level showed significantly higher antibody levels after bivalent than quadrivalent vaccines which could be due to the new adjuvant ASO4 in the bivalent vaccine. However, both vaccines showed substantially high level of antibody response over natural infection. Based on mathematical model of the decline of the antibody over the years, booster may not be needed for at least 20 years.

Since registration data was based on efficacy trials on 16-26 years of age and bridging immunological response study of adolescence, efficacy on adult women was performed for data in supporting registration up to 45 years of age. Quadrivalent vaccine trial on 24-45 years old women showed 83% efficacy in preventing persistent infection, CIN or EGL. Bivalent vaccines trial on women 24-45 years showed efficacy in preventing persistent infection. Both studies showed no increase in SAE. Thus, vaccinating adult women is effective and safe.

In sub-group analysis, women who were HPV negative but seropositive showed significantly lower persistent infection and CIN rate in vaccinated arm when compared to control arm. Though again this observation was not in the original design of the trial, the high antibody response after vaccination in previously infected women with a low natural infection antibody titre seems to be effective in preventing HPV re-infection. Though the incidence of infection is decreasing with increasing age, new infection was still found in older women and these women may benefit from vaccine protection. Furthermore,recent epidemiology studies showed that in some regions of the world, a second peak of HPV infection was found in women suggesting that there is certain benefit in vaccinating sexually active adult women. However, it is difficult to predict the degree of protection in these women.

To conclude, evidence so far showed that both the bivalent and quadrivalent vaccines are effective and safe and should be considered for population vaccination of girls/adolescence before sexual exposure. Vaccination of adult women may have some benefits that need individual counseling. Cervical cancer screening is still required as the protection after vaccination is not complete.

1st International Workshop on Gynecologic Oncology

Session II

New Trends in Cervical Cancer Management

Chairman : Zeyi Cao, China / **Jae Wook Kim,** Korea

- Radical surgery overview
  Jong Hyeok Kim / Joo Hyun Nam, Korea
- Fertility sparing & less radical surgery
  Seung Cheol Kim, Korea
- Myths & facts about nerve sparing radical surgery
  Tomoyasu Kato, Japan
- Primary chemo-radiotherapy in LACC
  Hee Sug Ryu, Korea

Radical surgery overview

Jong Hyeok Kim / Joo-Hyun Nam

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Radical hysterectomy is a well established standard surgical management for early stage cervical cancer. This operation yield 5-year survival rates of 75-90% in most cases. After its introduction in the management of early stage cervical cancer over 100 years ago, surgical technique, anatomic detail, and classification of this surgery are continuously evolving. For the first time, Schauta introduced radical extirpation of the parametria with a vaginal approach in the management of early stage cervical cancer. And then, Wertheim developed abdominal radical hysterectomy, and this led to the near abandonment of the vaginal radical hysterectomy. However, the mortality rate after abdominal radical hysterectomy was as high as 40% at that time. Therefore, the use of abdominal radical hysterectomy decreased with the introduction of radiation therapy in the management of cervical cancer. In the 1940s, Meigs reintroduced the Wertheim's abdominal radical hysterectomy, combining it with a complete pelvic lymph node dissection to increase its therapeutic efficacy. In addition, the advances in antibiotics, anesthetic techniques, and surgical techniques reduced morbidity and mortality associated with abdominal radical hysterectomy to acceptable levels. Therefore, Meigs procedure became the standard of care in western country. Besides Meigs procedure, the Wertheim's operation has been modified many times by several surgeons to improve both anatomic detail and radicality. Of them, Okabayahi in Japan sought to improve the technique by developing a more radical removal of tissue than advocated by Wertheim. Okabayashi's method is characterized by wide extirpation of parametrial tissue and a rather novel separation of the posterior leaf of the vesicouterine ligament. The techniques employed, and the results of Okabayashi's radical hysterectomy, were first reported in 1921, and this method became standard for radical hysterectomy in Japan. In the 1950s, Mitra used an extraperitoneal pelvic lymph node dissection and Dargent introduced laparoscopic pelvic lymph node dissection in combination with radical vaginal hysterectomy, and this made vaginal radical hysterectomy looked at with renewed interest. Recently, with the advances in the laparoscopic surgical techniques

and instruments, total laparoscopic radical hysterectomy has been a minimally invasive alternative to the abdominal radical hysterectomy. Robotic radical hysterectomy is more widely accepted in the management of early stage cervical cancer. Other recent advances in the surgical management of early stage cervical cancer include nerve-sparing radical hysterectomy and fertility-sparing radical trachelectomy. The major merit of these operations is to improve the functional outcome and quality of life. In this lecture, the author aimed to present the overview of radical surgery in patients with early stage cervical cancer in historical and anatomical perspectives.

Fertility Sparing and Less Radical Surgery

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Cervical cancer is the second most common female cancer. In developed countries, cervical cancer accounts for 3.6% of new cancers, and the incidence is 14 cases per 100,000 women per year. In the past, a diagnosis of early stage invasive cervical cancer would usually lead to infertility because of the recommended treatment necessary to cure the cancer. The recommended surgical treatment for stage IA2-IB1 cervical cancer is a radical hysterectomy with bilateral pelvic lymphadenectomy. This includes removal of the uterus and cervix, radical resection of the parametrial tissue and upper vagina, and complete pelvic lymphadenectomy and sometimes radiation therapy and/or chemotherapy. Over the past decade, there has been an increased focus towards fertility preservation in the treatment of cervical cancer since about 15% of all cervical cancers and 45% of surgically treated stage IB cancers occur in women under 40 years of age. These women represent the subset of patients who are candidates for fertility preservation if they are identified as having a low risk of recurrence and a low risk of lymph-node involvement.

The majority of experience with fertility sparing in cervical cancer has been with radical vaginal trachelectomies(RVT). RVT with laparoscopic pelvic lymphadenectomy is a fertility-preserving procedure that has recently gained worldwide acceptance as a method of surgically treating small invasive cancers of the cervix. Since the original description of RVT by Daniel Dargent in 1994, over 500 cases of utilization of this technique have been reported in the literature, with over 100 live births reported following this procedure. The morbidity associated with RVT is low, with a tumor recurrence rate of 5% and a mortality rate of 3%. The current literature indicates no difference in the rate of recurrence with this technique compared with radical hysterectomy when proper selection criteria are used. In Korea, there is a recent study showing that laparoscopic radical trachelectomy is a safe and useful alternative to radical hysterectomy by Nam et al. in 2010. Combining RVT with laparoscopic sentinel lymph-node biopsy can further reduce the duration, extent, and complications of surgery.

The radical abdominal trachelectomy(RAT) is very similar to the radical hysterectomy (RH), making it a more accessible procedure for surgeons trained in radical pelvic surgery. Experience with RAT has been limited in comparison to RVT but does offer another fertility-sparing option for young women with cervical cancer. The similar approach of this technique to RH makes it more accessible to surgeons who are not well trained with radical vaginal surgery, and additionally can be used with larger tumors, or with vaginal anatomy that prohibits the applicability of the RVT.
Neoadjuvant chemotherapy (NACT) can reduce the tumor size prior to fertility-sparing surgery. NACT combined with conization and pelvic lymphadenectomy has also led to successful pregnancies. It should be noted that alkylating agents such as ifosfamide and cisplatin can be detrimental to ovarian follicles, and less gonado toxic regimens should be evaluated in the future.

Approximately 65% of patients do not have any residual cancer in the trachelectomy specimen after a diagnostic cone. Additionally, the rate of parametrial involvement in patients with tumor size ≤ 2cm, negative pelvic nodes, and depth of invasion ≤ 10mm is only 0.6%. This highlights the question as to whether less aggressive surgery provides similar effectiveness to RVT. Large conization or simple trachelectomy with pelvic lymphadenectomy might be an alternative for early stage low volume disease. The use of simple trachelectomy or cone biopsies for fertility sparing also warrants further investigation, which can be combined with NACT, as previously described. This will obviously require strict selection criteria to avoid recurrences and deaths in this group of highly curable patients.

The treatment of cervical cancer has evolved over the past 10 years, with gradual abandonment of radical surgery in favor of more conservative techniques for young women wishing to preserve fertility. RVT is now well established as a safe and feasible procedure for this patient population, with low morbidity, recurrence, and mortality rates. As more experiences with this procedure help to further delineate patient selection criteria and prognostic factors for adjuvant treatment, other additional fertility-sparing options continue to evolve. The use of RAT in selected patients has increased, in addition to more conservative methods of fertility sparing such as simple trachelectomy or cone biopsy, with or without neoadjuvant chemotherapy. Continued research in these areas will determine the safety and feasibility of these potential procedures, which will help give more treatment options for young women with early stage cervical cancers.

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Myths & facts about nerve sparing radical surgery

Tomoyasu Kato

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Autonomic nerve damage during surgery is thought to play a crucial role in the etiology of bladder dysfunction, sexual dysfunction and colorectal motility disorders that are seen in patients after radical hysterectomy. In order to prevent these complications, Japanese gynecologists introduced a surgical technique with preservation of the pelvic autonomic nerves in 1961. In the 1988 the first English paper was published. It is only recently that nerve-sparing radical hysterectomy has been introduced to Western as well as to Asian countries. Nowadays the concept of preservation of autonomic nerves during radical hysterectomy has become standard in many oncogynecological centers in the world.

Pelvic organ function is organized by both central and peripheral nerve system. For instance, the lower urinary tract is innervated by 3 sets of peripheral nerves involving the parasympathetic, sympathetic, and somatic nervous systems. Pelvic parasympathetic nerves (PSN) arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra. Lumbar sympathetic nerves inhibit the bladder body and excite the bladder base and urethra. Pudendal nerves excite the external urethral sphincter. These nerves contain afferent sensory as well as efferent motor axons. Multiple reflex pathways organized in the brain and spinal cord mediate coordination between urinary bladder and urethra.

These autonomic nerves can be dissected during the different phases of radical hysterectomy. A level of nerve preservation is classified into 4 levels: non-touch, exposure, partial preservation and dissection. From a point of view on nerve preservation, non-touch preservation provides high quality of life. Simple and modified radical hysterectomy can obtain non-touch preservation of autonomic nerves, however they compromise radicality. To achieve a good balance between radicality and retaining pelvic function, we conducted to perform exposure or partial preservation of these

autonomic nerves. Our method consists of four parts as follows.

1. Preserving the hypogastric nerves (HGN): Developing the pararectal space between the ureter and the internal iliac vessels, HGN running along the rectum is to be identified. The ureter is separated from the retroperitoneum and this tissue plane is kept facing downwards. This tissue plane is corresponded to the anterior renal fascia, which includes the HGN and the pelvic plexus (PP).

2. Preserving the PSN: The cardinal ligament (CL) is dissected immediately above the middle rectal artery as close as possible to the pelvic sidewall. The PSN originating from S3 run to the PP dorsal to the middle rectal artery.

3. Preserving the PP: The HGN entered the PP at the anterosuperior corner. Deep uterine vein is located below the HGN. The HGN and the PP were frequently damaged during dissection of the uterosacral ligaments (USL). To diminish these nerve injuries, the medial stump of the CL should be fully mobilized above the HGN before dissecting the USL. In the case of the tumor with deep myometrial or parametrial invasion, we dissect the USL just below the medial stump of the CL. Then the PP is preserved partially.

4. Preserving the bladder branches: The bladder branches ventral to the ureter are more likely to be injured in dissection of the posterior leaf of the vesicouterine ligament for wide resection of the paracolpium and the vagina. In order to maximize preservation of the bladder branches dorsal to the ureter, the rectovaginal ligaments should be clamped using right angle forceps not to involved them and be cut.

According to our method, even patients with partial preservation showed recovery to a postvoid residual urine volume less than 50 ml at a median of 24 days postoperatively.

Autonomic nerves are liable to damage due to pressure from surgical retarctors, extension stress with taping, thermal injury by an energy sauce and/or direct injury with electrical scarpels. Both an understanding of the precise neuroanatomy and a gentle handling of the autonomic nerves are important to obtain a good balance between oncologic outcome and QOL after nerve-sparing radical hysterectomy.

Primary chemo-radiotherapy in LACC

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While radiotherapy has been established as the primary mode of therapy, it has been shown that radiotherapy alone is accompanied by a high failure rate in patients with large-sized lesions, or in patients at risk for recurrent disease after surgical treatment. These findings have led to the development of combination radiotherapy and chemotherapy, the presently widely employed concurrent chemoradiotherapy (CCRT).

In 1985, Fu et al.[1] proposed the theory that combination radiotherapy and chemotherapy resulted in a reduction in tumor size, an enhanced effect of the radiotherapy acting as a radiosensitizer, and that the systemic effect prevented distant metastasis of the cervical cancer. With this theory as a basis, studies were initiated which investigated the therapeutic effect of CCRT in patients with squamous cancers of the head and neck, lung, and esophagus, as well as vulvar cancer in women.[2-5]

Between 1999 and 2000, the results of 5 randomized prospective studies regarding the role of CCRT in cervical cancer patients were published, and all 5 studies showed that platinum-based (cisplatin) CCRT decreased local and distant metastasis rates, and thus increased survival by 30% to 50%. It was also concluded that CCRT increased survival by approximately 40% compared to radiotherapy alone.[6-10]

Since then, CCRT has become the mainstay treatment modality for all cervical cancer patients requiring radiotherapy, and CCRT is provided largely for the following two groups of patients: 1) primary CCRT without surgery for patients with large-sized stage Ib tumors and stage IIb–IVa locally advanced disease, and 2) postoperative adjuvant CCRT for patients at high risk of treatment failure after radical hysterectomy. This review will focus on the first group.

One of the first randomized prospective studies on CCRT was the Radiation Therapy Oncology Group (RTOG) #9001.[7] This study was conducted between 1986 and 1990 and enrolled patients with locally advanced disease and negative para-aortic lymph nodes; RTOG #9001 showed that the administration of CCRT resulted in significantly improved disease-free survival (DFS) compared to radiotherapy alone.[7]

The next large scale study was the Gynecology Oncology Group (GOG) #120,[9] in

which a comparative analysis was performed between cervical cancer patients who received weekly cisplatin, monthly cisplatin+5-FU+hydroxyurea (HFC), and hydroxyurea. The results were similar to the results of RTOG #9001, i.e., patients showed increased survival rates after cisplatin-based CCRT compared with hydroxyurea alone, and weekly cisplatin regimen was more tolerable than HFC.[9] Yoon et al.[11] also showed results similar to the GOG #120 in a large scale retrospective study of CCRT and its related toxicities in Korea. They observed that the 5-year overall survival (OS) rates in patients who received definitive CCRT without surgery were enhanced to a favorable 70% to 84%. Although there was no statistical difference in OS among the three CCRT regimens between weekly cisplatin, monthly cisplatin+5 FU at 3 week intervals, and a paclitaxel based regimen as primary therapy in the study, the paclitaxel based regimen had a significantly lower DFS than weekly cisplatin and monthly cisplatin+5-FU regimen. Therefore, they recommend that further studies focusing on the indications and determining the efficacy of paclitaxel-based CCRT regimens should be performed.[11]

In 2007, regarding the efficacy of CCRT for the controversy of the treatment of stage Ib2 cervical cancer, the results of a multicenter study which was performed by KGOG was published which retrospectively investigated the survival rates of various modes of therapy for stage Ib2 cervical cancer patients during the past 10 years in Korea.[12] This report concluded that survival rates were the best among patients who underwent postoperative adjuvant CCRT, while survival was worst in patients who received postoperative radiotherapy only. Yoon et al.[11] also showed adjuvant CCRT for cervical cancer afforded a very favorable 5-year OS rate of 82% to 95%, and in particular, combination chemotherapy with the paclitaxel+cisplatin/carboplatin regimen resulted in a 5-year OS rate as high as 95.6%. Therefore, they suggested that further prospective studies be conducted to confirm their results.[11] Since 2005, the Korean Gynecology Oncology Group (KGOG) has been conducting a prospective study in an attempt to ascertain the effectiveness of paclitaxel and carboplatin as a CCRT regimen for patients with high risk factors for recurrent disease after radical hysterectomy. We have to wait until the study will mature.

We have found in this review that CCRT is a widely used regimen in the treatment of patients with cervical cancer, and that it is effective. While combination chemotherapy is associated with increased toxicity, the toxicities are generally easily manageable. The weekly regimen containing cisplatin was associated with the least toxicity of all the regimens reviewed. We did not find any significant difference in DFS between the weekly and monthly chemotherapy regimens for loco-regionally advanced stage IIb-IVa cervical cancer, but there was a tendency for improved survival in patients who received monthly chemotherapy.

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1st International Workshop on Gynecologic Oncology

Luncheon seminar - MSD

Chairman : Joon Mo Lee, Korea

- Implementation of HPV vaccination with policy priorities to reduce societal burdens
  Young Tak Kim, Korea

Implementation of HPV vaccination with policy priorities to reduce societal burdens

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Worldwide each year, an estimated 500,000 women are diagnosed with cervical cancer and 250,000 die of the disease.[1] Cervical cancer is the second most common cancer among women globally.[1]

HPV can also lead to other significant consequences. Cervical, vulvar, and vaginal intraepithelial neoplasia are the abnormal growth of cells on the cervix, vulva, or vagina, respectively. They are considered precancerous conditions. There are an estimated 10 million cases of high-grade cervical dysplasia (cervical intraepithelial neoplasia [CIN] 2/3) and 30 million cases of low-grade cervical dysplasia (CIN 1) related to HPV each year worldwide.[2] HPV Types 16 and 18 are found in approximately 76% and 64% of vulvar intraepithelial neoplasia [VIN] 2/3 and vaginal intraepithelial neoplasia [VaIN] 2/3 cases.3 Lastly, HPV is related to 30 million new cases of genital warts worldwide each year.4

HPV-associated diseases cause significant economic burden.

Estimates of national health expenditures have demonstrated that the costs incurred by HPV-related diseases can be substantial. In addition to the costs of managing cervical cancer cases, the economic burden of HPV-associated diseases includes costs related to genital warts, management of abnormal Pap smears, and cervical intraepithelial neoplasia (CIN 1–3).

A review of the literature found that the annual burden of all cervical HPV-related disease in the United States ranged from $2.35 to $4.6 billion (2005 US dollars), of which $181.5 to $393 million was related to cervical cancer cases.5 The 2004 estimated economic burden of newly diagnosed genital warts was $760 per 1,000 individuals in the general population, with the estimated total exceeding $220 million.[6]

In 2003, estimated direct medical costs associated with detection and management of cervical cancer, cervical dysplasia, and treatment of genital warts in the United Kingdom were £208 million (ranging between £186.9 and £214 million based upon

sensitivity analyses), of which £46.7 million was related to incident and prevalent cervical cancer cases.[7] The cost of treatment and management of all genital warts (including "first time,
recurrent, and persistent patients) contributed £22.4 million to the total estimated cost of HPV disease.[7]

Global, national, and regional public health authorities recommend HPV vaccination.

WHO recommends routine HPV vaccination if prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered.8 When introduction of HPV vaccines is considered, WHO suggests identifying the primary target population based on the age of initiation of sexual activity and feasibility of reaching adolescent girls through schools, health care facilities, or community-based settings.[8] WHO estimates that the primary target population is likely to be girls between 9 or 10 and 13 years of age.[8] WHO also supports vaccination of secondary target populations including older adolescents or young women if it is "feasible, affordable, cost-effective, does not divert resources from vaccinating the primary target population or effective cervical cancer screening programs, and if a significant proportion of the secondary target population is likely to be naïve to the vaccine-related HPV types." [8]
National public health authorities recommend HPV vaccination in many countries, including Australia, Canada, several European countries, New Zealand, and United States.[9,10,11] Primary target populations vary globally; however, they fall within the range estimated by WHO.[12,13,14] HPV vaccination is recommended for secondary target populations in Australia, Canada, Denmark, France, Greece, Luxemburg, Netherlands, New Zealand, Norway, Portugal, Sweden, Switzerland, United Kingdom, and the United States.[12,13,14]

Vaccination with Quadrivalent HPV Vaccine is a cost-effective health intervention.

Systematic reviews of the literature on health economic modeling of HPV vaccination have concluded that HPV vaccination can be cost-effective.[15,16] As mentioned earlier, the results of mathematical models may be sensitive to the following assumptions: duration of vaccine-induced immunity, vaccine efficacy, vaccine coverage rates, and vaccine price. Appendix B presents the key assumptions utilized in the models reviewed in this section.

Many analyses examining the cost-effectiveness of quadrivalent vaccination have demonstrated that routine HPV vaccination of a primary cohort of young adolescent females is generally cost-effective.[17–27] Some analyses have also demonstrated that routine vaccination of a primary cohort of girls by age 12 combined with a temporary catch-up program for a secondary cohort of girls between age 12 and 24 is also cost-effective.[17-19, 28-29] In some instances, a vaccination strategy that includes both a primary cohort and catch-up cohort "dominated" the single cohort vaccination strategy from a cost-effectiveness perspective.[17,19,28,29] Dominant vaccination strategies are more effective and efficient than the other strategies with which they are compared.[32]

Studies indicate that HPV Types 6 and 11 in the quadrivalent vaccine add substantially to the cost-effectiveness of HPV vaccination.[28-32] For example, no protection against HPV 6/11 infection and related disease is assumed, the incremental cost-effectiveness ratio of 12-year-old females with a temporary catch-up program for 12- to 24-year-old females in the United States increased to $11,254/QALY.[17] In Taiwan, the cost-effectiveness ratio increased approximately 40% to NT$575,437 per QALY gained in the absence of any reductions in HPV 6– and 11–related genital warts.[28]

Many government bodies around the world have made the decision to allocate budget and resources for HPV vaccination because they see it as being an important health intervention in improving the lives of women. As an expert group, ASGO should contribute in building a consensus to urge inclusion of HPV vaccination in National Immunization Programs. It will help save lives and improve QOL for women in Asian Countries.

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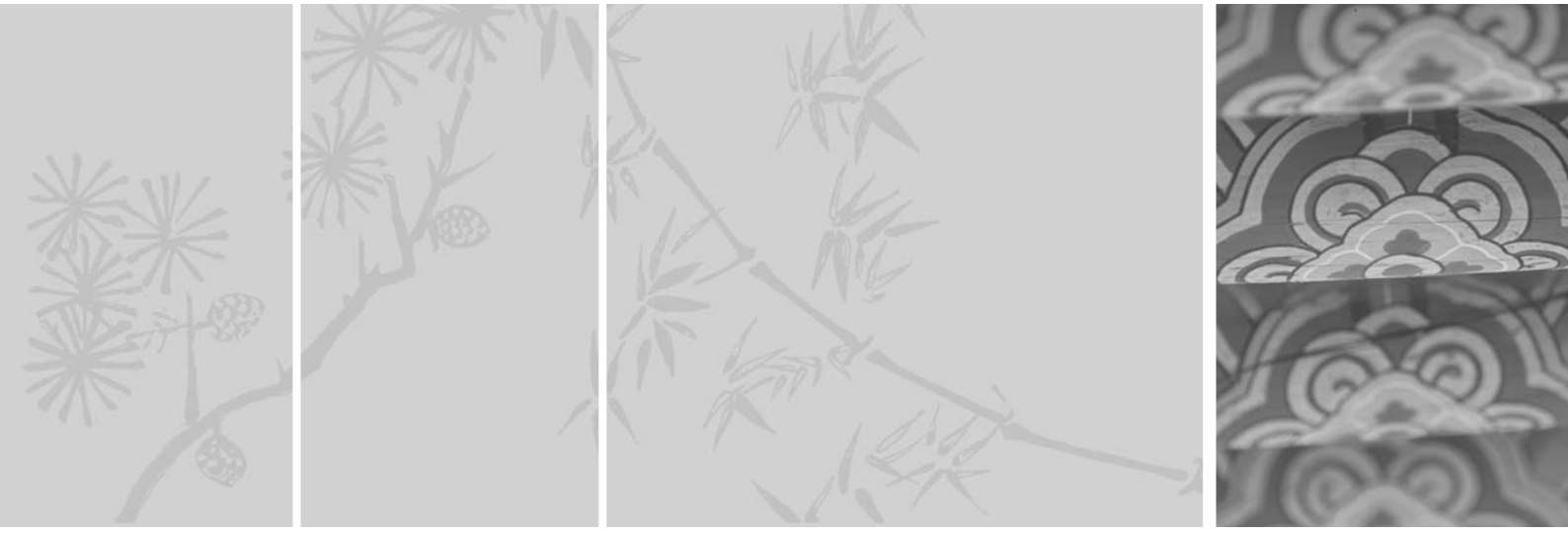

Session III

Surgical technique: film session

Chairman : Sung Eun Namkoong, Korea / **Kyu Wan Lee,** Korea

- Nerve sparing radical hysterectomy
  Shingo Fujii, Japan

- Optimal staging in early ovarian cancer
  Dae Gy Hong / Yoon Soon Lee, Korea

- Laparoscopic radical hysterectomy
  Jong Hyeok Kim, Korea

- One-port surgery
  Tae Joong Kim, Korea

- Robotic surgery
  Young Tae Kim, Korea

Nerve sparing radical hysterectomy

Shingo Fujii

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Since Ernst Wertheim introduced radical hysterectomy in 1911,[1] several different types of modification had been made on radical hysterectomy. In western countries, radical hysterectomy classified by Piver, Rutledge and Smith[2] as the class III is believed as the standard procedure of radical hysterectomy. However, in eastern countries, particularly in Japan, the Okabayashi method[3] is the standard procedure of radical hysterectomy. Both methods separate the anterior leaf of the vesico-uterine ligament, but there is a different concept on the separation of the posterior leaf of the vesicouterine ligament. The class III method divides the paravaginal tissues together with the posterior leaf of the vesicouterine ligament and the paracolpium (vaginal blood vessels). In contrast Okabayashi method separates and divides the posterior leaf of the vesicouterine ligament intentionally and then the paracolpium is isolated and divided, respectively. The latter procedure enables the surgeon to separate the bladder with the ureter completely away from the lateral side of the cervix and vagina and allows easy resection of any vaginal length deemed appropriate for the optimization of the radical hysterectomy. However, both types of radical hysterectomy had been often associated with severe bladder dysfunction and colorectal motility disorders.

The uterus, vagina, urinary bladder and rectum are innervated by a motor and sensory autonomic nerve supply, both of sympathetic and parasympathetic origin. The sympathetic fibers come from T11-L2 which form the superior hypogastric plexus. The parasympathetic fibers come from S2, 3 and 4 at the pelvic wall as the pelvic splanchnic nerve. These fibers merge and form the inferior hypogastric plexus which branch to innvervate the uterus and the urinary bladder. It has been reported that during radical hysterectomy the hypogastric nerve is often sacrificed when the surgeon divides the uterosacral ligament and rectovaginal ligament, the pelvic splanchnic nerve when the surgeon divides the deep uterine vein in the cardinal ligament, and the bladder branch of the pelvic nerves when the surgeon ligates and divides the paracolpium.[4, 5]

However, the anatomy of the inferior hypogastric plexus encompassing the hypogastric nerve, the pelvic splanchnic nerve and the bladder branch/the uterine branch from this plexus is complicated and is not easy to appreciate during the surgery. In order to accomplish nerve-sparing radical hysterectomy, it is absolutely necessary for us to reveal the inferior hypogastric plexus and to transect only the uterine branch from the inferior hypogastric plexus. By this procedure we can preserve the hypogastric nerve, the pelvic splanchnic nerve and the bladder branch from the inferior hypogastric plexus.

We recently reported how to identify the inferior hypogastric plexus using.[4, 5] As well as this paper, the paper on the anatomy of the vesico-uterine ligament (anterior/ posterior) that we previously published[6] shall be helpful for the understanding of the whole anatomy of the inferior hypogastric plexus.

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Optimal staging in early ovarian cancer

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The primary treatment for early stage epithelial ovarian cancer is surgical and patients should undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging.

Fertility preservation operation in early stage ovarian cancer is recommended for patients who have undergone a through staging operation and for whom there is no evidence of spread beyond the ovary, abdominal hysterectomy and bilateral salpingo-oophorectomy are appropriate therapy.

The uterus and the contralateral ovary can be preserve in women with stage Ia, grade 1 to 2 disease who desire to preserve fertility. For patients whose disease is more poorly differentiated or in whom there are malignant cells either in ascitic fluid or in peritoneal washings, complete surgical staging must be performed.

Despite the prognostic relevance of lymph node metastasis, there is a great debate about the role of pelvic and para-aortic lymph node dissection. In the early ovarian cancer, lymph node dissection is required to make an accurate clinical stage according to the FIGO classification and to select adequate adjuvant therapy. But the survival benefit of pelvic and para-aortic lymph node dissection in early ovarian cancer is controversial.

There are no randomized trials published to date to compare the laparoscopic surgical staging of presumed early ovarian cancer with conventional open staging. Now the feasibility and safety of laparoscopic staging early ovarian carcinoma have been established. The tumor control and survival of minimal access surgery in early ovarian cancer have not been compared with conventional open procedures by randomized study. Impaired survival compared with conventional open treatment has not been demonstrated for any laparoscopically treated malignancy.

Although ongoing surveillance, attention to technique, and appropriate management of port sites are mandatory, the laparoscopic management of early ovarian cancer seems to be justified by the significant reduction in morbidity, hospital stay, and recovery time that result from this surgical approach and by lack of any solid evidence that if used

properly by qualified individuals it does not harm.

In conclusion, primary surgical staging is the standard procedure in early ovarian cancer but some considerations must be given to the variable situations. Although laparoscopic staging for ovarian cancer is controversial, it may be an alternative approach for early ovarian cancer.

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Laparoscopic radical hysterectomy

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Laparoscopic surgery has many benefits over conventional abdominal approach. These include less postoperative pain, improved cosmetics, less blood loss, shorter recovery time, shorter length of hospital stay, and shorter time interval to adjuvant therapy without increase in complications or morbidity. In addition, it appears that the risk of cancer recurrence does not increase with a laparoscopic approach. With advances of laparoscopic instruments and surgical skills, laparoscopic surgery also has been adopted in the surgical management of early cervical cancers.

Laparoscopic radical hysterectomy (LRH) for the treatment of patients with early cervical cancer was first described in the early 1990s, but the acceptance of LRH has been slower than other laparoscopic oncologic surgical techniques and the use of LRH was limited to the patients with small tumor because of its technical difficulty and diversity of surgical techniques. However, with increasing experience, standardization of technique, and advances of laparoscopic instruments, the indication of LRH is extending to almost all patients with early cervical cancer and LRH is becoming a dominant paradigm in the surgical management of early cervical cancer. According to the currently existing data in the literature reported by several expert surgical teams through the world, there is no doubt that LRH is feasible and safe both surgically and oncologically. The rate of conversion to laparotomy was extremely low and the surgical safety profile was comparable to that of abdominal radical hysterectomy(ARH). The surgical outcomes were even more favorable in terms of operating time, estimated blood loss, transfusion requirement, postoperative complication rate, postoperative recovery, cosmetic results, and patients' satisfaction. The local radicality and lymph node yield were also similar to those of ARH, and the recurrence rate and survival rate after LRH were also equivalent to those of ARH. Although the best way to evaluate the feasibility and safety of LRH is to compare LRH with ARH in a randomized controlled trial, such study is nearly impossible nowadays because patients will refuse to participate in the

study if they were randomized to open surgery group. Many gynecologic oncologic surgeons believe that LRH can be safely performed in almost all patients with early cervical cancer without decrease in survival of patients and the surgical outcomes are superior to conventional open surgery if the surgery is performed by an experienced laparoscopic surgical team. During the last 13 years, LRH has been performed in over 500 patients with early cervical cancers in our department. We have found that the surgical and oncologic outcomes were similar or even better compared to ARH. We strongly believe that laparoscopic surgery should be the preferred standard surgical management for earl cervical cancer and gynecologic oncologic surgeons should do their best to improve laparoscopic surgical techniques.

The aim of this video was to introduce our detailed surgical techniques of LRH for patients with early cervical cancer.

One-port surgery

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Abstract

Single-port access (SPA) laparoscopic surgery is evolving as new instruments become available. The advantages over traditional multi-port laparoscopic surgery with regard to morbidity, good cosmesis and less postoperative pain are documented, but these advantages should be evaluated in well-designed prospective trials. There are some published reports of SPA laparoscopy utilized to treat benign gynecologic disorders. However, there are few reports on the use of SPA laparoscopy in gynecologic cancer.

We performed a single port access (SPA) laparoscopy staging - bilateral salpingo-oophorectomy, laparoscopy-assisted vaginal hysterectomy, bilateral pelvic lymphadnectomy, infracolic omentectomy, and washing cytology - in borderline ovarian tumor. The number of harvested pelvic lymph node was twenty-three and there were no intraoperative or postoperative complications. SPA laparoscopic staging can be performed in selected patients. The efficacy, safety, and potential benefits of this technique should be evaluated in further trial. 1. Kim TJ, Lee YY, Kim MJ, Kim CJ, Kang H,

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Robotic surgery

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Abstract

Operative laparoscopy was initially developed in the field of gynecology earlier on and the advent of laparoscopic surgery led to advances in general surgery as well. In the last few years, a number of articles have been published on the performance of surgical procedures using the robot-assisted laparoscopy. The shortcomings of conventional laparoscopy have led to the development of robotic surgical system and future of telerobotic surgery is not far away, enabling a surgeon to operate at a distance from the operating table.

The complete loss of tactile sensation is often quoted as a big disadvantage of working with robotic systems. Although the first generation da Vinci Robotic surgical system provides improved imaging and instrumentation, the absence of tactile feedback and the high cost of the technology remain as limitations. New generations of the robotic surgical systems have been developed, allowing visualization of preoperative imaging during the operation. Though the introduction of robotics is very recent, the potential for robotics in several specialties is significant. However, the benefit to patients must be carefully evaluated and proven before this technology can become widely accepted in the gynecologic surgery.

Key words: Robotics; Uterine cervical neoplasm; Hysterectomy

1st International Workshop on Gynecologic Oncology

Session IV

Endometrial Cancer

Chairman : Yasuhiro Udagawa, Japan / **Hyo Pyo Lee,** Korea

- Laparoscopic surgery vs. open surgery
  Kung Liahng Wang, Taiwan

- Role of lymphadenectomy
  Taek Sang Lee, Korea

- Fertility sparing treatment for endometrial cancer
  Kimio Ushijima, Japan

Laparoscopic surgery vs. open surgery

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Surgery has been the primary treatment of choice for endometrial cancer since the adaptation of FIGO surgical staging in 1988. However, the extent of operation depends not only on various disease characteristics, but also on the surgeon's specialties as well as the guideline of respective institutes. Several issues still remain to be clarified, including the option of radical hysterectomy, feasibility of ovarian preservation and the necessity of high para-aortic lymph node dissection. Alternatively, laparoscopic management of gynecologic malignancy has received much attention and given rise to considerable debates in the past decade. Of these tumors, early endometrial cancer is probably the one with the least concern in terms of technical feasibility and disease spreading pattern. The advantages of laparoscopy have been well documented in lessening the morbidity of laparotomy, providing better visualization for delicate tissue dissection of lymph nodes, and expediting the post-operative recovery of the patients. On the other hand, important considerations such as the expertise of the surgeon, impact of positive peritoneal cytology by laparoscopy, and its performance in obese patients might limit the routine use of this procedure in endometrial cancer.

The results of several clinical trials and retrospective studies unanimously demonstrated the safety, effectiveness and short-term advantages of laparoscopy over laparotomy. A large GOG LAP2 phase III randomized study comparing laparoscopy versus laparotomy in endometrial cancer revealed that laparoscopic surgical staging could be performed in 76.3% of cases. Quality of life and physical functioning were significantly improved 6 weeks post-operatively following laparoscopy. The long-term data in recurrence and survival of this trial has yet to be reported. Another large randomized trial "Laparoscopic Approach to Cancer of the Endometrium" LACE001 is still ongoing. Meta-analysis of four other randomized controlled trials showed that longer operative time, lower intra-operative blood loss, and fewer post-operative complications were associated with laparoscopy, when comparing to laparotomy. There are no differences in the overall, progression-free and cancer-related survivals. In brief, the application of laparoscopic surgical staging operation in selected patients appears to be a good alternative to laparotomy. Until mature data from GOG and LACE trials become available, the role of laparoscopy as a standard treatment for endometrial cancer is still debatable.

Role of lymphadenectomy

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The lack of consensus for primary surgical treatment of endometrial cancer, the most common gynaecological cancer, is deplorable. Whether lymphadenectomy should be done together with hysterectomy has been debated at length and passionately. This review is the current issues surrounding lymphadenectomy in the management of endometrial cancer.

Prediction of lymph node metastasis

To avoid unnecessary LN dissection and related surgical morbidity, imaging modalities, such as CT, MRI, PET/CT have been suggested for prediction of LN metastasis.[1-3] Considering the clinical significance of LN metastasis, the tests to predict LN metastasis should have a high sensitivity and negative predictive value. According to on systematic review, the sensitivity and negative predictive value of MRI for LN metastasis were reported as 45%-78% and 91%-95%, respectively.[3] This uncertainty might be caused by difficulty in differentiating metastatic nodes from hyperplastic nodes. Thus, we suggest that MRI shows unsatisfactory results in prediction of LN metastasis and cannot replace surgical staging.

Additionally, LN metastasis is highly correlated with the depth of myometrial invasion (MMI) and prediction of MMI is crucial in decisions as to whether conservative treatment should be administered to uterine corpus cancer patients. However, the sensitivity (36%-90%) and negative predictive value (83%-94%) of MRI in the detection of deep myometrial invasion was not satisfactory.

As a result, previous results for the prediction of LN metastasis and myometrial invasion are not sufficiently reliable, thus leaving room for further study. Though imaging may play a role in pre-operative assessment of individual endometrial cancer patients, there is currently no imaging modality sufficiently reliable that it can take the place of surgical staging in the management of endometrial cancer patients at risk for nodal metastases.

Benefit of lymphadenectomy in endometrial cancer

In 1987, Creasman et al.[4] reported a large scaled study of the patterns of spread in endometrial cancer. This study introduced the concept that hysterectomy and bilateral salpingo-oophorectomy was insufficient in the management of endometrial cancer and led to a change in the staging of endometrial cancer from a clinically based protocol to surgical staging. They showed results of 621 cases of endometrial cancer treated with TAH, BSO, selective pelvic and para-aortic lymphadenectomy and peritoneal cytology. Two major conclusions were drawn from this study. First, surgical staging is necessary to accurately determine the extent of disease and should be incorporated in the treatment of endometrial cancer. Secondly, specific factors including tumor grade, depth of myometrial invasion, Lymohvascular space invasion (LVSI), positive peritoneal cytology, adnexal involvement, and other evidence of extra-uterine disease predict for nodal metastases. Despite the mounting evidence that surgical staging is an important factor in the management of endometrial cancer, practice around the world has not consistently incorporated surgical staging. Trimble et al.[5] addressed survival in 9,185 endometrial cancer patients in the National Cancer Institute Surveillance, Epidemiology and End Results program (SEER) database. They compared patients who did and did not undergo lymphadenectomy at surgery. For stage I endometrial cancer, 5-year survival was not significantly different between the two groups. It was only in grade 3 patients that there was a significant survival difference in favor of lymphadenectomy (0.89 vs. 0.81, P_0.011). The resently published ASTEC surgical trial randomized just over 1400 women with endometrial carcinoma, preoperatively thought to be confined to the uterine corpus, and asserted that systematic lymphadenectomy was not recommended as a routine procedure for therapeutic purposes in patients with stage I disease. However, The negative results from this trial was criticized in some points that all histologic subtypes were included, para-aortic LN dissection was optional and inconsistently harvested, an inadequate number of LNs was retrieved in 1/3 of patients, and most patients were in the low-risk group.[6]

Recently, Yukiharu Todo and colleagues report results from their comparative cohort study (SEPAL), 10 in which they avoided most of the pitfalls that have plagued previous investigations of lymphadenectomy. Although retrospective, by comparison of two practice standards that differed mainly in the use of para-aortic lymphadenectomy, bias was kept to a minimum. The authors report that the addition of paraaortic lymphadenectomy to hysterectomy and pelvic lymphadenectomy reduced the risk of death, with a hazard ratio of 0·44 (95% CI 0·30–0·64, p<0·0001).[7]

A Korean multi-center retrospective study involving 758 patients surgically treated for early-stage
endometrioid uterine cancer, with a median follow-up of 35 months, reported that systematic lymphadenectomy did not provide a therapeutic benefit in terms of overall survival in all of the patients, while the systematic lymphadenectomy group showed improved overall survival in high-risk patients.[8,9]

Therefore, we suggest that systematic lymphadenctomy is effective in detecting micro or occult LN metastasis, and thus improve surgical staging and make it possible to accurately predict the prognosis at least in patients with high risk uterine corpus cancer. The greatest challenge should be continued to define and accurately detect low-risk disease.

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Fertility sparing treatment for endometrial cancer

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As the number of younger women with endometrial carcinoma has increased, fertility-sparing treatment has received much attention. Progestin has played a major role in this treatment. Nevertheless, the clinical benefit of fertility sparing treatment with progestin is still uncertain. To clarify the efficacy of fertility-sparing treatment using medroxyprogesterone acetate (MPA) for endometrial carcinoma (EC) and atypical hyperplasia (AH) in young women, we conducted a multicenter prospective study for this issue at 16 institutions in Japan.

Twenty-eight patients having EC at presumed stage Ia and 17 patients with AH at less than 40 years of age were enrolled. All patients were given a daily oral dose of 600mg MPA with low dose aspirin. This treatment continued for 26 weeks, as long as the patients responded. Either estrogen-progestin therapy or fertility treatment was provided for the responders after MPA therapy. CR (complete response) was found in 55% of EC cases and 82% of AH cases. The overall CR rate was 67%. Neither therapeutic death nor irreversible toxicities were observed. During the 5-year follow-up period, among 20 patients hoping to conceive a child, fifteen pregnancies in 12 patients and 9 normal deliveries were achieved after MPA therapy. Eleven of 15 pregnancies were brought about by fertility treatment, and 8 of them were achieved by in-vitro fertilization and embryo-transfer program. Fifteen recurrences were found between 7 and 58 months including 9 of 14 EC (64%) and 6 of 16 AH (38%). Recurrence was seen in 72% of patients having a treatment free period and in 86% of patients without conception in spite of fertility treatment.

Four cases of ovarian malignancies (10.2%) were found in this study. In EC patients at our institution, there was a higher incidence of ovarian cancer in EC patients of less than 40 years of age (15.0%) than in patients more than 40 years of age (6.6%). Also, a high incidence of clonality difference between endometrial cancer tissue and ovarian

cancer tissue was found in younger patients.

In conclusion, the efficacy of fertility-sparing treatment by high- dose MPA for EC and AH has been proven by this first prospective trial. The indication of MPA therapy should be restricted to stage1a disease. Even in responders, close follow up with continuous Estrogen-Progesterone administration or immediate infertility treatment is required due to the substantial recurrence rate. Longer-term hormonal treatment or ovarian preservation at hysterectomy is not recommended, because these patients have a high incidence of synchronous ovarian cancer. Close communication and corroboration between the gynecologic oncologist and the reproductive endocrinologist is indispensable for patient safety and goal achievement in fertility-sparing treatment.

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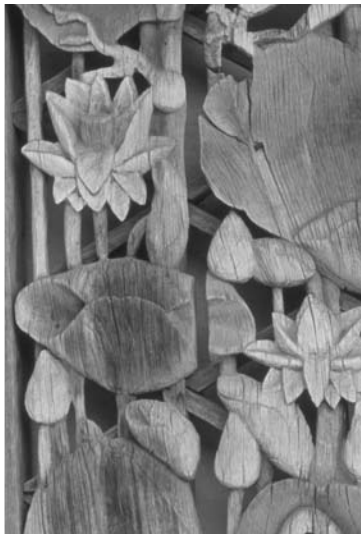

Special lecture

Chairman : Jung Eun Mok, Korea

- Clinical trials in Asia
  Sang-Goo Shin, Korea

Clinical Trials in Asia

Sang-Goo Shin

Seoul National University College of Medicine
Korea National Enterprise for Clinical Trials (KoNECT)

Asia has been globalized in clinical trials just since International Conference of Harmonization (ICH) started in early 1990s. Few of Southeast Asian countries appeared to be involved in US initiated multinational trials during mid-1990s. However, after consolidation of ICH-E5 (Ethnic factors in the acceptability of foreign clinical data) and ICH-E6 (Good Clinical Practice) guidelines, many of Asian countries started to change their drug regulatory environment to be compatible with western countries. From late 1990s to early 2000s, several northeast Asian countries have been eager to participate to global trial, but far later than east European and South American countries. In spite of their late harmonization in drug regulations and trial environments, several Asian countries has been recognized for excellence in clinical trial activity, especially in the late phases with its large treatment-naive patient populations and relatively low study cost with track record of faster patient recruitment.

According to a November 25, 2009 analysis by PAREXEL Consulting and KoNECT, East Asian countries (Korea, Taiwan, China, Hong Kong, and Japan) were participating in 15.7% of all Phase 3 clinical trials listed in the www.ClinicalTrials.gov database in 2008 and 18.2% in 20091H, up from just 9.6% in 2005. Meanwhile, the region has seen the number of Phase 3 clinical trials in which it is participating (again listed in ClinicalTrials.gov) surge by 30.9% from 2005 to 2008. However early phases research in Asia has been fairly limited and mainly consists of bridging studies providing local pharmacokinetics, pharmacodynamics, efficacy and safety data for registration of foreign-developed drugs in each country.

Recently, new trend has been emerged especially among large companies such as Pfizer and GSK, conducting global trials with more and more Asian sites starting to be involved in early-phase studies. This trend is the result of increased confidence in quality and speed in Asian sites that have been built through late phase clinical trials in

the region, especially in Singapore, South Korea and Taiwan including Japan. There are many sites with excellent facilities suitable for early proof of concept studies including phase 1 studies for normal volunteer or patient-based PK-PD studies, with trained clinical research personnel including clinical pharmacologist and experienced clinical investigators. In 2008, around 35% out of 216 multinational trials approved by KFDA in Korea were early phases clinical trials. That was the result of government initiatives to foster clinical trial infrastructure including Regional Clinical Research Centers and the collaboration among government, academia and industry. Singapore has a very small population, which is not suitable for large scale clinical trial but it is attracting lots of international interest in the early phase research, because the country's Biomedical Sciences initiative has been encouraging and enabling international companies to set up dedicated Phase I centers in Singapore. Early phases clinical research in Asian Region can also reduce the drug-lag for patient access to new innovative drug and phase lag in clinical development in the region. For pharmaceutical companies, it increases market access to the huge Asia markets including South Korea, China, and especially Japan.

However still there are challenges in this region to conduct early phase trials including slow clinical trial authorization and lack of public awareness in early phase clinical trials.

This presentation will highlights past historical experience of globalization and current status of clinical trials especially in northeast Asian countries, and also will discuss the opportunities and challenges of Asian countries in simultaneous global trials environment.

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Session V

Ovarian Cancer

Chairman : Kazunori Ochiai, Japan / **KyungTai Kim,** Korea

- First line chemotherapy: overview of trends
  Yin Nin Chia, Singapore

- Neo-adjuvant chemotherapy in ovarian cancer
  Sarikapan Wilailak, Thailand

- Optimal surgical management for ovarian cancer
  Sang Yoon Park, Korea

- Targeted therapy
  Hidetaka Katabuchi, Japan

First Line Chemotherapy: Overview of Trends

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Abstract

The accidental discovery of Melphan as a chemotherapeutic agent in world war II has revoluntionized the treatment of epithelial ovarian cancers. Since, many new chemotherapeutic agents have emerged and have dramatically improved the survival of an otherwise fatal disease. In the 1990s, the discovery of platinum was a great milestone forward in improving the outcome further. By the late 1990s and early 2000s, the combination of platinum and taxane has became the new standard of care in the first line management of epithelial ovarian cancers. In recent years, attempts have been made both in terms of new agents as well as the route/dose of administration to further improve upon this current standard. Docetaxel may be considered as an alternative to paclitaxel in those in whom peripheral neuropathy is a concern. GOG 172 trial of IP-IV chemotherapy in 2006 found an impressive improvement in median overall survival of 16 months resulting in a NCI alert in 2006 to support a first line regimen containing IP cisplatin and IV/IP taxane in women with optimally debulked stage III epithelial ovarian cancers. The Japanese GOG in a recently published a RCT in Lancet 2009 showed an improvement in overall progression free survival with dose dense chemotherapy using weekly paclitaxel in combination with 3 weekly platinum i.e. 28.0 months versus 17.2 months in the traditional 3 weekly regimen. Most recently, a phase III trial by GOG of Bevacizumab presented in ASCO 2010 showed a PFS of 14.1 months (carbo/paclitaxol/bevacizumab + maintainence bevaxizumb versus 11.2 months (carbo/paclitaxol/bevacizumab) versus 10.3 months (control arm carbo/paclitaxol only). Recognizing that epithelial ovarian cancers are a heterogeneous group of diseases, there is also a trend towards immunotherapy in the management of epithelial ovarian cancers.

Neo-adjuvant chemotherapy in ovarian cancer

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Ovarian cancer has the highest fatality to case ratio among all gynecologic malignancies. Advanced-stage ovarian cancer, in particular, has even worse prognosis. In fighting against ovarian cancer, we have 2 major weapons which are surgery and chemotherapy. In early-stage ovarian cancer, conventional therapy –ie, aggressive cytoreductive surgery followed by chemotherapy are recognized as being effective. Whereas in advanced-stage ovarian cancer, both modalities of treatment are not rather effective. Bulky disease in difficult sites preclude optimal cytoreductive surgery. With regard to chemotherapy, ovarian cancer is moderately sensitive to chemotherapy and it is difficult for bulky disease to be completely diminished by chemotherapy

Definition and History

Neoadjuvant chemotherapy is the administration of cytotoxic chemotherapy before attempting aggressive cytoreductive surgery for treating women with advanced-stage epithelial ovarian cancer. This approach was first used at Yale University in 1979. The diagnosis of ovarian cancer was based on cytologic or histologic specimens and diagnostic imaging findings consistent with ovarian cancer. The initial approach used at Yale University was to reserve neoadjuvant chemotherapy for patients who were too medically infirmed to tolerate aggressive cytoreductive surgery. A decade after its use in that regard, neoadjuvant chemotherapy was then offered to the patients who, by CT criteria, were unlikely to be optimally surgically cytoreduced.

Rationale

A meta-analysis of Bristow et al. which included 6,885 patients with stages III and IV ovarian cancer, reported an optimal cytoreduction rate (< 2cm. residual disease) of 42%. And only a small fraction of patients were cytoreduced to microscopic disease. A recent Gynecologic Oncology Group (GOG) study reported that only 23% of 1,895 stage III patients and only 8% of 360 stage IV patients were cytoreduced to microscopic disease. One of the most important prognostic factors of ovarian cancer is residual disease after surgery. Therefore, to reduce residual disease after surgery to the level of < 1cm. or no

gross residual is vital. Neoadjuvant chemotherapy would be beneficial in terms of having patients in a better preoperative status (i.e. nutritional status, ascites, pleural effusion), having a higher rate of surgical cytoreduction to no visible disease and less operative morbidity including shorter time, less blood loss and shorter hospitalization.

Meta-analysis

To date, two meta-analyses have been published. The first in 2006 by Bristow et al. reviewed 22 cohorts of patients with stages III and IV ovarian cancer (835 patients) who received neoadjuvant chemotherapy with a platinum - based regimen prior to surgery. The authors concluded that neoadjuvant chemotherapy survival outcomes are overall infusion compared to conventional primary surgery. More recently in 2009, Kang and Nam performed a meta - analysis using a random - effects model to perform statistical analysis that accounts for the sample heterogenicity and retrospective nature of the studies in order to obtain more reliable results. Twenty - one studies were reviewed. Their results agree with Bristow et al. in that neoadjuvant affords greater optimal cytoreduction rates. Interestingly, they found a trend for increased median overall survival in the neoadjuvant group. However, this was not significant.

Prospective Randomized Trials

Only one well controlled randomized trial comparing neoadjuvant chemotherapy with primary cytoreductive surgery has been completed and two trials are currently underway. The EORTC completed randomized trial of 718 patients revealed the same over-all survival, whereas the complication rates were higher in the primary cytoreductive group. In the United Kingdom, recruiting patients for a trial of chemotherapy or upfront surgery (CHORUS) is underway, with a goal of 550 patients. And lastly, the Japanese Clinical Oncology Group (JCOG) is randomizing 300 patients to either neoadjuvant or primary cytoreductive arm.

Conclusions

Neoadjuvant chemotherapy followed by surgery is best suited for patients with medical co - morbidities not able to undergo aggressive cytoreductive surgeries and for patients deemed to have unresectable disease. However, the ability to predict unresectable disease remains limited and this in itself remains a major factor in selecting patients who would be appropriate candidates for neoadjuvant chemotherapy. The proper number of cycles given prior to surgery is to be defined. And significant benefits of neoadjuvant chemotherapy will be lost if the patient is not operated on promptly or if less than optimal surgical cytoreduction is performed.

Optimal surgical management for the management of ovarian cancer

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There are several prognostic factors such as stage, age, ascites, performance status, pathologic type, genetic alteration, chemosensitivity, and postoperative residual tumor size in the management of ovarian cancer. These factors are unchangeable except postoperative residual tumor size when physicians manage the patients. Chemosensitivity is one of the most important prognostic factor. We should keep in mind that the morbidity of surgery should not interrupt postoperative adjuvant chemotherapy.

Early-Stage Epithelial Ovarian Cancer

At diagnosis, approximately one third of patients with epithelial ovarian cancer have early-stage disease that is confined to the ovary or pelvis. The extensive surgical procedures and outcomes which have been investigated have mainly focused on advanced ovarian cancer. Not only advanced ovarian cancer, but also early ovarian cancer, is also confirmed after pathologic examination from extensive surgery in the current FIGO staging system: hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymph node dissection, peritoneal biopsy, and washing cytology are essential surgical procedures for optimal staging. For complete removal of all suspicious metastatic lesions and adequate surgical staging, an extensive surgical procedure is important, even in early ovarian cancer. In early ovarian cancer, unique characteristics, such as a higher incidence of non-serous histology and co-existence of endometriosis, have been identified. Ovarian carcinogenesis from endometriosis has been reported. On the other hand, endometriosis mimics ovarian cancer clinically. Bowel excision is sometimes required for complete excision of pelvic endometriosis. Complete excision of suspicious lesion for endometriosis or ovarian cancer may be more important in the surgical management of ovarian cancer because intra-operative differentiation of endometriosis from ovarian cancer is difficult and endometriosis has been suggested to be a possible precursor lesion of ovarian cancer. Such observations

beg the following questions. Which surgical procedures are required to remove all suspicious lesions in early ovarian cancer? What are the pathologic outcomes in such patients? To answer these questions, we reviewed our experiences with cytoreductive surgery as a part of the primary cytoreductive surgery for early ovarian cancer with respect to operative procedures and pathologic outcomes.

Advanced-Stage Epithelial Ovarian Cancer

Advanced epithelial ovarian cancer typically presents with widely disseminated intra-abdominal disease. The standard treatment of advanced epithelial ovarian cancer (EOC) includes primary cytoreductive surgery followed by adjuvant systemic chemotherapy. The goal of primary surgery for advanced epithelial ovarian cancer is to accurately establish a diagnosis and leave little or no residual disease. Although there are no randomized controlled trials supporting cytoreductive surgery, nearly every retrospective and prospective study has demonstrated an inverse relationship between residual tumor diameter and patient survival, including a recent meta-analysis by Bristow and colleagues, which showed that each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival.

Procedures of Surgical Cytoreduction

A substantial number of patients with advanced-stage ovarian cancer present with bulky upper abdominal disease, malignant pleural effusions, or even intraparenchymal liver disease and may require diaphragmatic or intestinal procedures, splenectomy with or without a distal pancreatectomy, and peritoneal stripping to achieve an optimal cytoreduction. Recent data demonstrate the technical feasibility of ultra-radical surgery and the significant survival advantage afforded by optimal tumor removal even in stage IV patients.

Surgery for ovarian cancer requires that the abdominal incision be adequate to explore the entire abdominal cavity and allow safe cytoreductive surgery. Any ascites or free peritoneal fluid should be collected for cytology. If no free peritoneal fluid is present, separate peritoneal washings can be obtained from the pelvis, paracolic gutters, and infradiaphragmatic area. Patients with stage III or IV disease do not require cytologic assessment. All peritoneal surfaces including the surface of both diaphragms and the serosa and mesentery of the entire gastrointestinal tract should be visualized and palpated for evidence of metastatic disease with careful inspection of the omentum and removal, if possible.

TAH, BSO, lower anterior resection, omentectomy, PLND, PALND, multiple peritoneal biopsy should be performed as a conventional surgery, and splenectomy, distal pancreatectomy, liver resection, resection of tumor from perta hepatis, cholecystectomy, total colectomy, pelvic peritonectomy, diaphragmatic stripping and/or resection should be tried to attain minimum residual disease as a extensive surgery. Sometimes VATS (video assisted thoracosocpic surgery), wedge resection of stomach, pelvic bone resection, abdominal wall resection may be needed.

I would like to present our experiences with cytoreductive surgery as a part of the primary cytoreductive surgery for advanced ovarian cancer with respect to operative procedures and clinical outcomes.

Recurrent Epithelial Ovarian Cancer

Although complete clinical remission can be achieved in many patients with advanced epithelial ovarian cancer using a combination of cytoreductive surgery and chemotherapy, the disease will likely recur and require further intervention. Complete resection of the tumor recurrence was one of the most powerful determinants of prolonged survival. Good performance status, early FIGO stage initially, no residual tumor after first surgery, and the absence of ascites could predict complete resection. A longer disease-free interval has also been associated with an improved survival outcome. Surgery for recurrent epithelial ovarian carcinoma should therefore be considered for patients with a localized recurrence, an extended disease-free interval of at least 6 to 12 months, and a good performance status. The resection of isolated hepatic and extra-abdominal disease such as solitary lung or CNS lesions also seems to afford a similar survival advantage for the affected patients.

I would like to present our experiences with secondary cytoreductive surgery for recurrent ovarian cancer with respect to operative procedures and clinical outcomes if time allows.

Targeted therapy

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Worldwide, ovarian cancer, 204,000 cases and 125,000 deaths per year, is the sixth most common cancer (4.2%) and the seventh cause of death from cancer (4.0%) in women. While advances in chemotherapy have certainly improved the prognosis for ovarian cancer patients, survival rates and the long-term prognosis remain poor. Current clinical management of ovarian cancer exists against a background of insufficient information regarding precursor cells, risk factors and the mechanisms of carcinogenesis and dissemination, especially when compared to the knowledge held regarding endometrial and cervical cancers. Recently, clinical trials of chemotherapy combined with molecular targets developed for other diseases, particularly antiangiogenic drugs, have been conducted to ovarian cancer, but the anticipated results have not always been obtained. In this lecture, we extract keywords from ovarian cancer research and, based on these, discuss the outlook for the development of novel therapeutic strategies for ovarian cancer.

1. Putative precursor cells

The precursor cells of ovarian cancer have not yet been identified, and one of the major reasons underlying the dismal prognosis of this disease is that nearly 75% of cases are already at an advanced stage at diagnosis. Moreover, each of the four main cancer tissue types, serous, mucinous, endometrioid and clear cell adenocarcinoma, has different clinical features and, thus, the precursor cell type may be different for each of these tissues. Among the potential precursor cell types, ovarian surface epithelium and inclusion cysts are the most likely candidates. One basis for this supposition is the existence of de novo ovarian cancer, which is common among serous adenocarcinomas. For serous tissue types, we should also mention the adenoma-carcinoma sequence progressing from an adenoma/borderline malignancy through a micropapillary variant to a carcinoma. Furthermore, recent studies of women with BRCA1/2 mutations undergoing risk-reducing salpingo-oophorectomy have highlighted the distal fallopian tube as a common (80%) site of tumor origin. Additional studies of unselected women with pelvic serous carcinoma have demonstrated that serous tubal intraepithelial

carcinoma may precede a significant percentage of these pelvic tumors. On the other hand, in some mucinous, endometrioid, and clear cell adenocarcinomas, there is a process of malignant alteration of the respective benign adenoma or of endometriosis. Among these malignant alterations are borderline malignancy and atypical endometriosis.

2. Risk factors

Epidemiology provides an important basis for considering cancer risk factors. Human papilloma virus in cervical cancer and estrogens in endometrial cancer are classic examples of cancer risk factors. The development of ovarian cancer is influenced by lifetime ovulation frequency and incessant ovulation is still considered a leading risk factor. Meanwhile, the peak age for ovarian cancer corresponds to the physiologic rise in pituitary gonadotropins seen during perimenopause and the prevalent expression of gonadotropin receptors by many ovarian cancers suggests that these hormones are an important factor in carcinogenesis. The possible connection between chemical substances, such as talc, and cancer also requires further attention as the peritoneal cavity of women is linked to the external environment via the fallopian tubes and the incidence of ovarian cancer is high in advanced countries, which tend to have higher levels of environmental pollution.

3. Molecular mechanisms of carcinogenesis

With the discovery of the BRCA1/2 gene in breast-ovarian cancer syndrome and the abnormal mismatched repair gene in Lynch syndrome, part of the ovarian cancer carcinogenesis process has also been clarified. Specific gene abnormalities in each type of ovarian cancer have also been identified, including KRAS in mucinous adenocarcinoma, PTEN and b-catenin in endometrioid adenocarcinoma, and KRAS in clear cell adenocarcinoma. Moreover, from studies of carcinogenesis at the molecular level, serous adenocarcinomas have been classified as low-grade based on BRAF and KRAS abnormalities and as high-grade based on p53, HER2/neu, and AKT2 abnormalities.

In recent studies involving the transfer of abnormal candidate genes using immortalized ovarian surface epithelium, the tumor formation stage has been reached, but differentiation to ovarian cancer-specific tissue types has not been achieved. Further elucidation of ovarian cancer-specific precursor cells, risk factors, and the mechanisms of carcinogenesis is needed. Based on such findings, a change in our current perspective can pave the way for the development of novel treatments for ovarian cancer.

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