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Review Article

Asian society of gynecologic oncology workshop 2010

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This workshop was held on July 31-August 1, 2010 and was organized to promote the academic environment and to enhance the communication among Asian countries prior to the 2nd biennial meeting of Australian Society of Gynaecologic Oncologists (ASGO), which will be held on November 3-5, 2011. We summarized the whole contents presented at the workshop. Regarding cervical cancer screening in Asia, particularly in low resource settings, and an update on human papillomavirus (HPV) vaccination was described for prevention and radical surgery overview, fertility sparing and less radical surgery, nerve sparing radical surgery and primary chemoradiotherapy in locally advanced cervical cancer, were discussed for management. As to surgical techniques, nerve sparing radical hysterectomy, optimal staging in early ovarian cancer, laparoscopic radical hysterectomy, one-port surgery and robotic surgery were introduced. After three topics of endometrial cancer, laparoscopic surgery versus open surgery, role of lymphadenectomy and fertility sparing treatment, there was a special additional time for clinical trials in Asia. Finally, chemotherapy including neo-adjuvant chemotherapy, optimal surgical management, and the basis of targeted therapy in ovarian cancer were presented.

Key Words: ASGO, Workshop, Cervical caner, Endometrial cancer, Ovarian cancer, Clinical trials

PREVENTION OF CERVICAL CANCER

1. Cervical cancer screening in Asia, Mohamad Farid Aziz

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 cancers.[1]

Southeastern Asia are less developed regions, the estimated age-standardized incidence and mortality rates per 100,000 are higher than those of Eastern Asia. Thailand has the highest incidence and mortality among the southeastern countries, while Singapore is the lowest. In Eastern countries, Hong Kong is the lowest in incidence. Prevalence of human papillomavirus (HPV) infection is slightly different, but HPV 16 is consistent in southeastern and eastern Asia. Contributing factors to the development of cervical cancer in general are young age at first intercourse, high parity, and multiple sexual partners. Cervical cancer screening programs that are fully supported by their governments in these regions are very few, especially in the Southeastern regions. The methods are Pap smear, colposcopy, and in less developed countries, visual in-

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spection with acetic acid followed by cryotherapy is more favored. The last procedure is known as "See and Treat." Targeted age-groups and interval of screening are slightly different in each country.

2. Screening in low resource setting, Uma K. Devi

Cervical cancer is the most common cancer among women in developing countries. 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 & Southeast Asia, Sub-Saharan Africa, and South & Central America.[2] Unfortunately, these low resource countries have access to less than 5% of the global cancer treatment resources.[3] Estimated age-adjusted mortality rates due to cancer of the 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.

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. Cytology screening has been largely responsible for the significant decline in the burden of cervical cancer in developed countries in the last five decades, and has reduced invasive cervical cancer rates by 74%.

The Pap test 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. The apparent lack of impact of cervical cytology program and difficulties in organizing such programs 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. However, WHO has suggested low intensity cytology/Pap test once a lifetime after 35 years at 10 year intervals, and simple visual inspection of the cervix to organize cytology for the control of cervical cancer in developing countries. As this method of visual inspection did not detect microscopic disease, it was considered inadequate.[4-6]

Hence, various strategies have been devised as an alternative to appropriate technologies in cervical cancer screening for low resource settings, for example, visual inspection with acetic acid (VIA),[7,8] visual inspection with Lugol's iodine (VILI), combination of VIA and VILI, cervicography, "See & Treat" techniques using diathermy, cryosurgery, and the HPV test.[9-11]

Although the sensitivity of VIA ranged between 66% and 96%, and specificity between 64% and 98% in a low resource setting, it is difficult to ensure screening at regular intervals, so a single screening test will be a good option, or a HPV test at a ten year interval is another alternative proposal.

In conclusion, attempts to screen in low resource settings 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 settings require further exploration, and until then VIA and HPV testing may be considered as another option.

3. Update on HPV vaccination, Hextan Y. S. Ngan

Cervical cancer vaccines are prophylactic vaccines preventing infection of HPV types 16 and 18 which are associated with about 70% of cervical cancer worldwide. So far, 100% and more than 90% efficacy in preventing CIN2/3 was shown by both the bivalent and quadrivalent vaccines in their phase II and III studies, respectively.[12,13] Also, a decrease in abnormal cytology, need for colposcopy referral or treatment were shown in the phase III trial. No excessive serious adverse events over controls were 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 which showed there was evidence of cross-protection to other non-targeted HPV types; the apparent waning of antibody levels in HPV 18 in the quadrivalent vaccine, the antibody assay using the 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 HPV 31 for both vaccines, 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, the 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 the current vaccines.

Long term follow-up of antibody levels for HPV 16 and 18 after 8.4 years still showed more than 10- fold levels above the baseline in the bivalent vaccine.[14] For the monovalent HPV16 vaccine, high levels were seen after more than 9 years. 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 levels showed significantly higher antibody levels after bivalent than quadrivalent vaccines, which may be due to the new adjuvant ASO4 in the bivalent vaccine.[15] However, both vaccines showed substantially high levels of antibody response over natural infection. Based on mathematical models of the decline of the antibody over the years, boosters may not be needed for at least 20 years.

Since registration data was based on efficacy trials in 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.[12,16] The quadrivalent vaccine trial in 24-45 year old women showed 83% efficacy in preventing persistent infection, CIN or external genital lesion (EGL).[17] The bivalent vaccine trial in 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 the sub-group analysis, women who were HPV negative but seropositive showed significantly lower persistent infection and CIN rates in the vaccinated arm when compared to the control arm.[18] 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.[12] Though the incidence of infection is decreasing with increasing age, new infections were 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.[19] 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.

NEW TRENDS IN CERVICAL CANCER MANAGEMENT

1. Radical surgery overview, Jong Hyeok Kim/Joo-Hyun Nam

Radical hysterectomy is a well established standard surgical management for early stage cervical cancer. This operation yields 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, Sharma et al.[20] introduced radical extirpation of the parametria with a vaginal approach in the management of early stage cervical cancer. And then, Wertheim developed the abdominal radical hysterectomy, and this led to the near abandonment of the vaginal radical hysterectomy.[20] 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 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, the Meigs procedure became the standard of care in western countries.

Besides the Meigs procedure, the Wertheim's operation has been modified many times by several surgeons to improve both anatomic detail and radicality. Among 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.[21] 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 to be 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.[20] 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.[22] The major merit of these operations is to improve the functional outcome and quality of life.

2. Fertility sparing and less radical surgery, Seung Cheol Kim

In the past, a diagnosis of early stage invasive cervical cancer would usually lead to infertility because of the recommended treatment, a radical hysterectomy with bilateral pelvic lymphadenectomy for stage IA2-IB1 cervical cancer. This sometimes includes 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.[23] 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%.[24] 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 Kim et al.[25] in 2010.

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.[26] 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.[27]

Neoadjuvant chemotherapy (NACT) can reduce the tumor size prior to fertility-sparing surgery.[28] 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 may be detrimental to ovarian follicles, and less gonadotoxic 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 $\leq$2 cm, negative pelvic nodes, and depth of invasion $\leq$10 mm is only 0.6%.[29] 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 a feasible procedure for this patient population, with low morbidity, recurrence, and mortality rates.[30] As more experience 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 NACT. 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.

3. Myths and facts about nerve-sparing radical hysterectomy, Tomoyasu Kato

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.[31] Though it is only recent that nerve-sparing radical hysterectomy has been introduced to western as well as to Asian countries, the concept of preservation of autonomic nerves during radical hysterectomy has now become the standard in many onco-gynecological centers in the world.

Pelvic organ function is organized by both the central and peripheral nervous system. For instance, the lower urinary tract is innervated by 3 sets of peripheral nerves involving the parasympathetic nerves from the sacral plexus, sympathetic nerves from the lumbar plexus, and somatic nervous systems such as the pudendal nerves. These nerves contain afferent sensory as well as efferent motor axons. Multiple reflex pathways organized in the brain and spinal cord mediate coordination between the urinary bladder and urethra.

These autonomic nerves can be dissected during the different phases of radical hysterectomy.[22] 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 a high quality of life. Simple and modified radical hysterectomy may obtain non-touch preservation of autonomic nerves, however they compromise radicality. To achieve a good balance between radicality and retaining pelvic function, we perform exposure or partial preservation of these autonomic nerves 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 corresponds to the anterior renal fascia, which includes the HGN and the pelvic plexus (PP).

2) Preserving the parasympathetic nerve (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 pelvic plexus (PP)

The HGN entered the PP at the anterosuperior corner. The 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 case of a 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 during 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 involve them and be cut.

Through 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 vulnerable to damage due to pressure from surgical retarctors, extension stress with taping, thermal injury by an energy source 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 quality of life (QOL) after nerve-sparing radical hysterectomy.

4. Primary CCRT in locally advanced cervical cancer, Hee Sug Ryu

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).

After Fu[32] proposed the enhanced effect of the radiotherapy acting as a radiosensitizer, and the systemic effect of preventing distant metastasis of the cervical cancer, the results of 5 randomized prospective studies regarding the role of CCRT in cervical cancer patients were published between 1999 and 2000, 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.[33-36]

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.

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 the Korean Gynecology Oncology Group (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.[37] This report concluded that survival rates were the best among patients who underwent postoperative adjuvant CCRT, while the worst in radiotherapy only. Since 2005, the 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 disease free survival between the weekly and monthly chemotherapy regimens for locoregionally advanced stage IIb-Iva cervical cancer, but there was a tendency for improved survival in patients who received monthly chemotherapy.

SURGICAL TECHNIQUE

1. Nerve sparing radical hysterectomy, Shingo Fujii

Since Ernst Wertheim introduced radical hysterectomy in 1911, several different types of modifications have been made on radical hysterectomy. In western countries, radical hysterectomy classified by Piver, Rutledge and Smith as the class III is believed as the standard procedure of radical hysterectomy. However, in eastern countries, particularly in Japan, the Okabayashi method 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, the 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 have 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 forms 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.[38]

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 have recently reported how to identify the inferior hypogastric plexus.[22,38] As well as these papers, the paper on the anatomy of the vesico-uterine ligament (anterior/posterior) that we previously published shall be helpful for the understanding of the whole anatomy of the inferior hypogastric plexus.

2. Optimal staging in early ovarian cancer, Dae Gy Hong/ Yoon Soon Lee

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, otherwise abdominal hysterectomy and bilateral salpingo-oophorectomy are appropriate therapy.[39]

The uterus and the contralateral ovary can be preserved 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.[40] In 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 have been 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.[41] 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.[42]

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.[42]

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.

3. Laparoscopic radical hysterectomy, Jong Hyeok Kim

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.[43] 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.[44] 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 equiv-

alent 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 (RCT), such a study is nearly impossible nowadays because patients will refuse to participate in the study if they were randomized to the 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.[45]

During the last 13 years, LRH has been performed in over 500 patients with early cervical cancer 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 early cervical cancer, and gynecologic oncologic surgeons should do their best to improve laparoscopic surgical techniques.

4. One-port surgery, Tae-Joong Kim

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 cosmetic results and less postoperative pain are documented,[46] 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.[47]

However, there are few reports on the use of SPA laparoscopy in gynecologic cancers. For now, SPA is considered for risk-reducing salpingo-oophorectomy, total hysterectomy for precancerous lesions, and staging operation for early stage ovarian/endometrial cancer. Fader et al. reported the feasibility of SPA in treating a variety of disease processes.[48] Of thirteen patients who had SPA surgery performed, 9 were done laparoscopically and four robotically. Procedures included endometrial cancer staging (n=1), ovarian cancer staging (n=1), retroperitoneal pelvic lymph node dissection (PLND, n=1), risk-reducing extrafascial hysterectomy/bilateral salpingo-oophorectomy (BSO, n=2) and BSO alone (n=5), and an ovarian cystectomy (n=1) and BSO (n=2) for complex adnexal masses. All procedures were successfully performed via a single incision and no post-operative complications occurred.

We have two cases of SPA laparoscopic staging operations in the video clips - one was BSO, laparoscopy-assisted vaginal hysterectomy (LAVH), bilateral PLND, infracolic omentectomy, and washing cytology in borderline ovarian tumor, and the other was LAVH, BSO, PLND with washing cytology in endometrial cancer (video clip available at the ASGO homepage). The number of harvested pelvic lymph nodes were 23 and 19, respectively, and there were no intraoperative or postoperative complications. SPA laparoscopic staging may be performed in selected patients. The efficacy, safety, and potential benefits of this technique should be evaluated in further trial.

5. Robotic surgery, Young Tae Kim

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.[49-51] The shortcomings of conventional laparoscopy have led to the development of a robotic surgical system and the 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 provided improved imaging and instrumentation, the absence of tactile feedback and the high cost of the technology remain as limitations. New generations of 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.

ENDOMETRIAL CANCER

1. Laparoscopic surgery versus open surgery in endometrial cancer, Kung-Liahng Wang

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,[52] feasibility of ovarian preservation[53] and the necessity of high para-aortic lymph node dissection.[54] Alternatively, laparoscopic management of gynecologic malignancy has received much attention and given rise to considerable debates in the past decade.[44,55,56] 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.[57]

The results of several clinical trials and retrospective studies unanimously demonstrated the safety, effectiveness and

short-term advantages of laparoscopy over laparotomy. A large Gynecologic Oncology Group (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.[58] Quality of life and physical functioning were significantly improved 6 weeks post-operatively following laparoscopy. The estimated 3-year overall survivals were 89.8% and 89.9% for patients randomized to laparoscopy and laparotomy, respectively. It concluded that laparoscopic surgical staging for uterine cancer does not result in an inferior outcome for recurrence or survival; and should be considered as a standard of care for endometrial cancer. Another large randomized trial "Laparoscopic Approach to Cancer of the Endometrium (LACE)001" is still ongoing. Meta-analysis of four other RCT 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.[59]

Until mature data from the LACE trial become available and demonstrate otherwise, the application of laparoscopic surgical staging operation is considered a good alternative to laparotomy for endometrial cancer.

2. Role of lymphadenectomy in endometrial cancer, Taek Sang Lee

The lack of consensus for primary surgical treatment of endometrial cancer, the most common gynecological cancer, is deplorable. Whether lymphadenectomy should be done together with hysterectomy has been debated at length and passionately. To avoid unnecessary lymph node (LN) dissection and related surgical morbidity, imaging modalities have been suggested for prediction of LN metastasis.[60] Sensitivity and negative predictive value of MRI for LN metastasis were reported as 45% to 78% and 91% to 95%, respectively. Because of this uncertainty, MRI does not seem to be able to replace surgical staging in the prediction of LN metastasis.

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% to 90%) and negative predictive value (83% to 94%) of MRI in the detection of deep myometrial invasion was not satisfactory.

In 1987, Creasman et al.[61] reported a large scaled study of the patterns of spread in endometrial cancer. This study introduced the concept of surgical staging and specific factors including tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), positive peritoneal cytology, adnexal involvement, and other evidence of extra-uterine disease to predict for nodal metastases.

Trimble et al.[62] 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, P¼0.011).

The recently published ASTEC surgical trial randomized just over 1400 women with endometrial carcinoma, preoperatively thought to be confined to the uterine corpus, and asserted that routine systematic lymphadenectomy was not recommended 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.[63] Recently, Todo et al.[64] reported in SEPAL study 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 to 0.64; $p < 0.0001$).[64]

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 overall survival improved only in high-risk patients.

Therefore, we suggest that systematic lymphadenectomy 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.

3. Fertility sparing treatment for endometrial cancer, Kimio Ushijima

As the number of younger women with endometrial carcinoma has increased, fertility-sparing treatment has received much attention.[53,65] 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.[66]

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 600 mg 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. Complete response (CR) 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 stage 1a 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 collaboration between the gynecologic oncologist and the reproductive endocrinologist is indispensable for patient safety and goal achievement in fertility-sparing treatment.

CLINICAL TRIALS IN ASIA

1. Asian role in global clinical drug development, Sang-Goo Shin

Asia has been globalized in clinical trials just since the International Conference of Harmonization (ICH) started in early 1990s. Few Southeast Asian countries appeared to be involved in the US initiated multinational trials during the 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 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 in the 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 have been recognized for excellence in clinical trial activity, especially in the late phases with their large treatment-naive patient populations and relatively low study cost with a 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 III 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 a number of phase III clinical trials in which it is participating (again listed in clinicaltrials.gov) surge by 30.9% from 2005 to 2008. However early phase 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, a new trend has emerged especially among large companies such as Pfizer and GSK, who are 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 pharmacologists and experienced clinical investigators. In 2008, around 35% out of 216 multinational trials approved by Korean Food & Drug Administration (KFDA) were early phases clinical trials. That was the result of government initiatives to foster a 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 trials, but it is attracting lots of international interest in the early phase research, because the country's Biomedical Sciences initiative has been encouraging, and is enabling international companies to set up dedicated Phase I centers in Singapore and Korea. Early phase clinical research in Asian Region can also reduce the drug-lag for patient access to new innovative drugs 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, there are still challenges in this region in conducting early phase trials which include slow clinical trial authorization and lack of public awareness of early phase clinical trials.

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

OVARIAN CANCER

1. First line chemotherapy: overview of trends, Yin Nin Chia

The accidental discovery of Melphan as a chemotherapeutic

agent during World War II has revolutionized the treatment of epithelial ovarian cancers. Since then, 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 further improving the outcome. By the late 1990s and early 2000s, the combination of platinum and taxane has become 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.[67]

The Japanese GOG in a recently published a RCT in Lancet 2009 showed an improvement in overall progression free survival (PFS) with dose dense chemotherapy using weekly paclitaxel in combination with 3 weekly platinum *ie*, 28.0 months versus 17.2 months in the traditional 3 weekly regimen.[68]

Most recently, a phase III trial by GOG of Bevacizumab presented in American Society of Clinical Oncology (ASCO) 2010 showed a PFS of 14.1 months (carbo/paclitaxol/bevacizumab +maintenance 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.

2. Neo-adjuvant chemotherapy (NACT) in ovarian cancer, Sarikapan Wilailak

Bulky scattered disease in difficult sites precludes 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.

NACT is the administration of cytotoxic chemotherapy before attempting aggressive cytoreductive surgery for treating women with advanced-stage epithelial ovarian cancer.[69] 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 NACT for patients who were too medically infirmed to tolerate aggressive cytoreductive surgery. A decade after its use in that regard, NACT was then offered to the patients who, by CT criteria, were unlikely to be optimally surgically cytoreduced.

A meta-analysis of Bristow et al.[70] which included 6,885 patients with stages III and IV ovarian cancer, reported an optimal cytoreduction rate (<2 cm residual disease) of 42%. Also, only a small fraction of patients were cytoreduced to microscopic disease. A recent 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.[71] 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 <1 cm or no gross residual is vital. NACT would be beneficial in terms of having patients in a better preoperative status (*ie*, 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.

To date, two meta-analyses have been published.[72,73] The first in 2006 by Bristow and Chi[72] reviewed 22 cohorts of patients with stages III and IV ovarian cancer (835 patients) who received NACT with a platinum-based regimen prior to surgery. The authors concluded that NACT survival outcomes are overall infusion compared to conventional primary surgery. More recently in 2009, Kang and Nam[73] 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 NACT affords greater optimal cytoreduction rates. Interestingly, they found a trend for increased median overall survival in the NACT group. However, this was not significant.

Only one well controlled randomized trial comparing NACT with primary cytoreductive surgery has been completed and two trials are currently underway. The European Organisation for Research and Treatment of Cancer (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. Lastly, the Japanese Clinical Oncology Group (JCOG) is randomizing 300 patients to either the NACT or primary cytoreductive arm.

NACT 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 NACT. The proper number of cycles given prior to surgery is to be defined. Significant benefits of NACT will be lost if the patient is not operated on promptly or if less than optimal surgical cytoreduction is performed.

3. Optimal surgical management for ovarian cancer, Sang Yoon Park

Among several prognostic factors, postoperative residual tumor size is the only changeable factor when physicians man-

age the patients. We should keep in mind that the morbidity of surgery should not interrupt postoperative adjuvant chemotherapy because chemosensitivity is one of the most important prognostic factors.

Not only advanced ovarian cancer but also early ovarian cancer is confirmed after pathologic examination from extensive surgery in the current FIGO staging system: hysterectomy, BSO, omentectomy, lymph node dissection, peritoneal biopsy, and washing cytology are essential surgical procedures for optimal staging. 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.[74] Endometriosis mimics ovarian cancer clinically. Complete excision of suspicious lesion for endometriosis or ovarian cancer may be important in the surgical management of ovarian cancer because intra-operative differentiation of endometriosis from ovarian cancer is difficult.

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 EOC is to accurately establish a diagnosis and leave little or no residual disease. Although there are no RCT supporting cytoreductive surgery, nearly every retrospective and prospective study has demonstrated an inverse relationship between residual tumor diameter and patient survival.[75]

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/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.

In addition to conventional optimal staging surgery, splenectomy, distal pancreatectomy, liver resection, resection of tumor from the porta hepatis, cholecystectomy, total colectomy, pelvic peritonectomy, diaphragmatic stripping and/or resection should be tried to attain minimum residual disease as an extensive surgery. Sometimes video assisted thoracosocpic surgery (VATS), wedge resection of the stomach, pelvic bone resection, and abdominal wall resection may be needed.

Although clinical CR can be achieved in many patients with advanced EOC 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. Surgery for recurrent EOC 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 central nervous system (CNS) lesions also seems to afford a similar survival advantage for the affected patients.

4. Research targets in targeted therapy, Hidetaka Katabuchi

While advances in chemotherapy have certainly improved the prognosis for ovarian cancer patients, survival rates and the long-term prognosis remains 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. Recently, clinical trials of chemotherapy combined with molecular targets developed for other diseases, particularly anti-angiogenic drugs, have been conducted to ovarian cancer, but the anticipated results have not always been obtained. In this lecture, we extracted keywords from ovarian cancer research and, based on these as starting points, discuss the outlook for the development of novel therapeutic strategies for ovarian cancer.

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.[76,77] 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.

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.[76] 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.

With the discovery of the *BRCA1/2* gene in the breast-ovarian cancer syndrome, and the abnormal mismatched repair gene in the Lynch syndrome, a 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 β-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,[78-80] 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 may pave the way for the development of novel treatments for ovarian cancer.

ADDENDUM

During break times, approaching meeting schedules and a few promotions of other societies were introduced. A promotion slide of the ASGO online homepage was presented to encourage Asian gynecologic oncologists to sign up for the membership of the ASGO. In addition, the interim meeting of Asia Oceania research organisation on Genital Infections (AOGIN) scheduled for March 17-19, 2011 at Bali, Indonesia before the 5th biennial meeting of the year of 2012. On April 2-3 of next year, the International Gynecologic Cancer Society (IGCS) regional meeting on gynecologic cancers will be held in New Delhi, India. Finally, the 2nd biennial meeting of ASGO will be held November 4-5, 2011 in Seoul, Korea.

Thanks to all the speakers, the slides and video clips are available at the ASGO homepage, asiansgo.org with permissions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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