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Review Article

Major clinical research advances in gynecologic cancer 2008

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In this review, we summarized 14 major clinical advances in gynecology which occurred in 2008. For cervical cancer, clinical impact of HPV vaccine, prognostic value of imaging during radiotherapy, and oncologic/obstetric outcomes of fertility-sparing surgery were chosen. For uterine cancer, optimal method of adjuvant radiotherapy in intermediate-risk patients, extent of lymph node dissection, outcome of robot-assisted staging surgery, new standard chemotherapy regimen for leiomyosarcoma were selected. For ovarian cancer, recent changes in adjuvant therapy, feasibility of neoadjuvant chemotherapy, prediction of optimal secondary cytoreduction, studies on new biomarkers, advances in screening and treatment of women with BRCA mutations were included. For other cancers, the safety of sentinel lymph node dissection in vulvar cancer and chemotherapy regimens for low-risk gestational trophoblastic tumors were reviewed.

Key Words: Gynecology, Urogenital neoplasms, Biomedical research

INTRODUCTION

Like other medical sciences, gynecologic oncology is a rapidly progressing area. New technologies such as robot surgery or human papillomavirus (HPV) vaccines become a common practice and standard therapy is changing year by year. Sometimes, it is hard to keep up with these progresses. Therefore, among numerous articles and presentations which were released or presented in 2008, we arbitrarily chose and reviewed 14 topics which we thought major progresses in gynecologic oncology. We hope that readers feel this review interesting and informative.

MAJOR CLINICAL RESERAH ADVANCES

1. Impact of HPV vaccine

HPV vaccines remains one of the most active areas of research in 2008, although the results of efficacy trials on HPV vaccines had been already published. In efficacy trials, both quadri- and bivalent HPV vaccines showed quite impressive efficacies in preventing persistent HPV infections and precancerous lesions in HPV negative women.[1-5] However, the impact of HPV vaccines on clinical practice is still unclear. For example, whether infrequent Papanicolaou (Pap) tests are safe in women who have received HPV vaccines is still unknown.

In the American Society of Clinical Oncology (ASCO) annual meeting, follow-up results of 9,628 women who were enrolled in one of three efficacy trials on quadrivalent vaccine and were negative at Pap and HPV test at enrollment were presented.[6] Vaccine or placebo was given on 0, 2, 6 month schedule. Pap testing was performed initially and every 6-12 months for up to 48 months. Referral for colposcopy or definitive therapy was algorithm based and was generally in agreement with accepted standards of care. Reduced incidence of abnormal Pap tests and procedures were observed in women who received HPV vaccine. Specifically, the incidence of low grade squamous intraepithelial lesion (LSIL), atypical squamous cells-high grade squamous intraepithelial lesion (ASC-H), and high grade squamous intraepithelial lesion (HSIL) decreased by 16%, 35%, and 43%. In addition, the incidence of colposcopy, biopsy, and definitive therapy was also reduced by 19%, 22%, and 42%, respectively.

Follow-up data longer than 48 months would be helpful to elucidate the long-term impact of HPV vaccines on clinical practice and to establish the optimal screening guideline in the era of HPV vaccine.

2. Role of imaging during therapy in cervical cancer

Reliable and early evaluation of tumor response to therapy is one of the important issues in clinical oncology because early

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response evaluation would allow the development of individualized therapy. An individualized therapy would have immense clinical value because ineffective therapies could result in increased toxicity and morbidity as well as delays in potentially effective therapies.

In cervical cancer, there have been attempts to evaluate the tumor response to radiotherapy during the course of therapy.[7,8] Assessment of tumor response during therapy had some advantages over post-therapy assessment. For example, early modification of treatment is possible and a potentially more individualized therapy could be performed. For medical oncologists, early evaluation of tumor response could be used to alter the number of chemotherapy cycles. For radiation oncologists, this information would lead to optimization of radiation dose or volume.

In a study including 36 patients with 1B1 to 3B cervical cancer, six and 26 patients had a complete and partial metabolic response on fluorodeoxy-D-glucose positron emission tomography (FDG PET) images obtained during radiotherapy, respectively. The remaining four patients had stable or increased tumor metabolic activity. Three of four patients with stable or increased activity were alive with disease or dead of disease at the last follow-up.[8] In another study including 20 patients with advanced cervical cancer, the apparent diffusion coefficient (ADC) calculated from the diffusion data of diffusion-weighted magnetic resonance imaging (DWI) obtained during radiotherapy was associated with tumor response.[7] Similarly, a study suggesting that DWI and dynamic magnetic resonance imaging could be useful to predict tumor response in patients with advanced cervical cancer was presented at the ASCO annual meeting.[9]

At the International Gynecologic Cancer Society (IGCS) biennial meeting, early data of a prospective study on the value of FDG PET during chemoradiation in patients with cervical cancer was presented. Twenty-five patients with 1B2 to 4A cervical cancer underwent PET scans during cisplatin-based chemoradiation. Six and 14 patients showed complete and partial metabolic response, respectively. Five patients showed stable disease on the PET scan. During follow-up (median 20 months, range 9 to 40), none of the six patients with complete response had relapsed. Seven of 12 patients with partial response suffered a relapse or persistent disease. Three of five patients with stable disease died of disease within 16 months.[10]

The concept of therapy individualization based on imaging during therapy is quite attractive. Clinical trials verifying the benefit of imaging during therapy in advanced cervical cancer are eagerly awaited.

3. Fertility-sparing surgery in cervical cancer

Due to a trend toward late childbearing and emphasis on the quality of life, fertility-sparing has been the major issue in the management of cervical cancer. Historically, in the 1950s, a gynecologist named Aburel described a technique called subfundic radical hysterectomy for microcarcinoma and carcinoma in situ (CIS) of the cervix. In 1977, Burghardt and Holzer reported that removal of fundus was not required for small cervical cancers. Recently, Dargent popularized the procedure known as the radical vaginal trachelectomy.[11]

Recently, an excellent review on the oncologic and obstetric outcomes after radical trachelectomy was published. According to the review, a total of 520 patients had been reported to have undergone radical vaginal trachelectomy. The median age was 31 years. Histologic type was squamous cell carcinoma in 60% of patients and adenocarcinoma in 40% of patients. In 24% of patients, lymphovascular space invasion was present in preoperative biopsy specimens. The majority of patients (88%) had tumors less than 2 cm in size. The median time of surgery was 213 minutes. During follow-up (median 48 months, range 1 to 176), the overall recurrence rate was 4.2%, and the death rate from cervical cancer was 2.8%. Approximately 43% of patients who underwent radical trachelectomy attempted to conceive and 70% of these women succeeded in being pregnant. Of these, 21% had a miscarriage in the first trimester, 8% had a miscarriage in the second trimester, 21% gave birth in the third trimester before 36 weeks, and 50% gave birth after 36 weeks. Complications after radical trachelectomy included dysmenorrhea (24%), dysplastic Pap smears (24%), irregular or intermenstrual bleeding (17%), problems with cerclage sutures (14%), excessive vaginal discharge (14%), isthmic stenosis (10%), and amenorrhea (7%). Outcome after radical abdominal trachelectomy was comparable to that of radical vaginal trachelectomy.[12]

Considering the excellent oncologic and obstetric outcomes after radical trachelectomy, patients with cervical cancer who are interested in fertility-saving should be informed with this option.

4. Adjuvant radiotherapy for intermediate-risk endometrial cancer

Appropriate adjuvant therapy for intermediate-risk endometrial cancer (IREC) is one of the most controversial issues in gynecologic oncology. Historically, adjuvant radiotherapy has been performed for such patients. However, clinical trials on adjuvant radiotherapy for IREC consistently demonstrated that adjuvant radiotherapy reduced vaginal and pelvic recurrences without survival benefit.[13]

Analysis of recurrence pattern in patients with IREC who received no adjuvant therapy allows us to optimize the adjuvant therapy for IREC. In patients with IREC without adjuvant therapy, distant recurrences account for half of the total recurrences, and vaginal recurrences accounts for more than half of local recurrences.[14,15]

To reduce distant recurrences, chemotherapy was adopted into the treatment of IREC. In radiation therapy oncology group (RTOG) 9708, the adjuvant chemoradiation showed excellent local and distant control in patients with IREC.[16] Furthermore, in a phase 3 trial (NSGO-EC-9501/EORTC

55991) including patients with IREC, patients who received adjuvant chemoradiation showed better overall and progression-free survival (PFS) than patients who underwent adjuvant radiation.[17]

Because most local recurrences are vaginal recurrences, an idea that brachytherapy could be effective to reduce local recurrences is logical. This hypothesis was verified in the PORTEC-2 trial which were presented at the ASCO annual meeting. After surgery, 427 patients with IREC were randomized into pelvic external beam radiotherapy (EBRT) vs. vaginal brachytherapy (VBT). The primary endpoint was vaginal relapse. Patients in the EBRT arm received 46 Gy radiation in 23 fractions and those in the VBT arm underwent 21 Gy high-dose rate or 30 Gy low-dose rate radiation. At a median follow-up of 34 months, 3-year actuarial rates of vaginal relapse were 2.0% in the EBRT arm and 0.9% in the VBT arm (p=0.97). Pelvic relapse rates were slightly higher in the VBT arm (3.6%) than in the EBRT arm (0.7%). However, rates of distant metastasis, overall survival (OS) and relapse-free survival (RFS) were similar between the two arms and the quality of life was better in the VBT arm than in the EBRT arm.[18]

Based on these findings, we believe that a trial testing the feasibility and efficacy of chemoradiation consisting of chemotherapy and VBT should be conducted for patients with IREC.

5. Extent of lymph node dissection in endometrial cancer

Although surgical staging of endometrial cancer was recommended by the international federation of gynecology and obstetrics (FIGO) two decades ago, the indication and extent of surgical staging is still controversial. The most controversial issue regarding the surgical staging of endometrial cancer is the extent and therapeutic value of lymphadenectomy. Proponents insisted that pelvic and para-aortic lymph node dissection should be performed for all patients with endometrial cancer, but opponents argue that lymphadenectomy in early stage endometrial cancers increases morbidity without clear therapeutic benefits.[19] Recently, a study providing some guidelines on this issue was published. In a single institute over 36 months, 422 consecutive patients with endometrial cancer underwent predefined surgical staging procedures including para-aortic lymph node dissection up to the renal vessels. After excluding low-risk patients who did not need lymphadenectomy, a total 281 patients received surgical staging procedures. Sixty-three of 281 patients had lymph node metastasis: both pelvic and para-aortic in 51%, only pelvic in 33%, and only para-aortic in 16%. Therefore, 67% of patients with lymph node metastasis had para-aortic lymph node metastasis. Furthermore, 77% of patients with para-aortic lymph node metastasis had metastasis above the inferior mesenteric artery (IMA), whereas nodes in the ipsilateral para-aortic area below the IMA and ipsilateral common iliac artery area were negative in 60% and 71%, respectively.[20]

This strikingly high incidence of para-aortic lymph node metastasis, especially nodes above IMA, implies that the adequate extent of lymph node dissection in endometrial cancer should be up to renal vessels. In addition, the presence of solitary lymph nodes metastasis above IMA suggests that there could be direct connections between the corpus and the para-aortic node areas such as the lymphatic channels adjacent to the gonadal vessels within the infundibulopelvic ligament.[21] Re-confirmation of these findings and clinical trials verifying the therapeutic benefit of lymphadenectomy in endometrial cancer is necessary.

6. Robot surgery in endometrial cancer

As robot use is gaining popularity in gynecologic surgery, there were many reports that addressed the feasibility and efficacy of robot surgery in 2008. In the Society of Gynecologic Oncologists (SGO) annual meeting, two studies comparing robot surgery with conventional surgery in the staging of endometrial cancer were presented.

In one study, authors retrospectively compared robot surgery with laparoscopic surgery for surgical staging of obese patients with endometrial cancer. Forty-nine patients underwent surgery with the DaVinci robotic system (Intuitive Surgical, Inc., Sunnyvale, California, USA) and 33 patients received traditional laparoscopy. The results showed that robot surgery was associated with shorter operative time, less blood loss, increased lymph node retrieval, and shorter hospital stay. The authors concluded that robot surgery should be the preferred minimally invasive tool for the surgical staging of the obese patients with endometrial cancer.[22]

In the other study, intraoperative and perioperative variables were compared among robot surgery, laparatomy, and laparoscopy. The results showed that operative time was longer for robot surgery than for laparatomy, but the operative time was similar between robot surgery and laparoscopy. Estimated blood loss and complication rates were lowest for robot surgery. Lymph node retrieval was similar among the three methods. Average return to normal activity was shorter for robot surgery than for laparatomy or laparoscopy.[23]

Based on these favorable outcomes of robot surgery, the indications of robot surgery in gynecology are anticipated to expand. We believe that prospective trials comparing robot surgery with conventional surgery should be performed when it is possible. Once robot surgery is accepted as a standard method, prospective trials will be impossible to conduct.

7. Chemotherapy for leiomyosarcoma

Prognosis of patients with advanced or recurrent uterine leiomyosarcoma is poor. The median survival of patients with advanced disease is known to be less than one year.[24] This poor prognosis is partly due to the poor response rate of this tumor to chemotherapy. In phase 2 trials testing several single agents reported negligible activities of cisplatin, mitoxantrone, amonifide, oral/intravenous etoposide, diazoquone, topotecan, paclitaxel, thalidomide, and trimetrexate.[24] Single

agents with moderate activity were ifosfamide, doxorubicin, and gemcitabine. For combination chemotherapy regimens, doxorubicin plus ifosfamide is known to be the most effective regimen and is frequently employed as the first-line therapy for patients with advanced or recurrent leiomyosarcoma.[24] However, second-line therapy has not been established.

In 2002, a new regimen, gemcitabine plus docetaxel, was reported to be effective for leiomyosarcoma in a single-institution study.[25] Recently, the Gynecologic Oncology Group (GOG) finished two phase 2 trials testing gemcitabine plus docetaxel as a first- and second-line therapy for metastatic leiomyosarcoma. Patients received gemcitabine 900 mg/m^2 over 90 min on day 1 and 8 plus docetaxel 100 mg/m^2 on day 8 every three weeks. Granulocyte growth factor support was routinely used, and patients with prior pelvic radiation received lower doses. As a first-line therapy, gemcitabine plus docetaxel showed 36% response rate with 5% complete response rate. The median PFS was 4.4 months and median OS was 16 or more months.[26] As a second-line therapy, gemcitabine plus docetaxel demonstrated 27% response rate with 6% complete response rate. The median PFS was 5.6 or more months and median OS was 14.7 months.[24]

Although its superiority to current standard regimens should be confirmed in a phase 3 trial, gemcitabine plus docetaxel is thought to be the new standard chemotherapy for metastatic leiomyosarcoma based on its excellent response rates demonstrated at the phase 2 trial. The GOG will activate a prospective randomized trial adding an angiogenesis inhibitor to gemcitabine and docetaxel.

8. Adjuvant chemotherapy in ovarian cancer

Historically, the standard chemotherapy regimen for high-risk ovarian cancer has been changed. Since 1995, several trials tested the efficacy of taxanes plus platinum agents. Early trials demonstrated the efficacy of 24-hour paclitaxel infusion plus platinum.[27,28] However, a randomized trial showed that 3- and 24-hour paclitaxel infusions had similar response rates and that the 3-hour infusion produced more neurotoxicity, but less myelosuppression.[29] Nowadays, 3-hour infusion schedules are more commonly used because it is more convenient. In an Italian trial, 502 previously untreated patients with advanced ovarian cancer were randomly assigned to six cycles of carboplatin (AUC 6) plus paclitaxel 175 or 225 mg/m^2. There were no significant differences in the response rate, 4-year PFS, OS between the groups receiving the higher and lower paclitaxel doses.[30] Therefore, although it is still controversial, 3-hour paclitaxel 175 mg/m^2 plus carboplatin AUC 6 every three weeks is thought to be the current standard regimen for ovarian cancer.

Because many patients eventually recurred in spite of aggressive cytoreduction and adjuvant chemotherapy, several modifications of adjuvant therapy such as intraperitoneal chemotherapy, consolidation chemotherapy, and addition of biologic agents have been attempted to improve survival. In the ASCO annual meeting, the result of a phase 3 trial comparing dose dense weekly administration of paclitaxel plus carboplatin with current standard tri-weekly regimen was presented. Six-hundred thirty-seven patients with stage 2-4 epithelial ovarian, fallopian tube or primary peritoneal cancer were randomized into two arms. Patients in the experimental arm received paclitaxel 80 mg/m^2 on day 1, 8, and 15 plus carboplatin AUC 6 on day 1 every three weeks. Patients in the control arm received paclitaxel 180 mg/m^2 on day 1 plus carboplatin AUC 6 on day 1 every three weeks. After a median follow-up of 29 months, the median duration of PFS of the experimental arm (28 months) was longer than that of the control arm (17 months). Similarly, the OS rate at 2 years of the experimental arm (84%) was higher than that of the control arm (78%). Toxicities were similar in both arms although grade 3 and 4 anemia was reported more frequently in the experimental arm.[31]

Different from previous modifications such as intraperitoneal or consolidation chemotherapy, weekly paclitaxel regimen is easy to administer and showed comparable toxicities with standard regimens. Incorporation of weekly paclitaxel regimen into current practice should be encouraged.

There was also an advance in the treatment of early ovarian cancer. The benefit of adjuvant therapy is known to be unclear in moderate-risk ovarian cancer because the prognosis of these patients is excellent regardless of adjuvant therapy. Therefore, in stage 1 ovarian cancer, adjuvant chemotherapy was usually limited to high-risk patients defined as 1C with any grade, any stage with grade 3, 1B with grade 2.[32,33] At the IGCS biennial meeting, a study demonstrating the survival benefit of platinum-based adjuvant chemotherapy in moderate-risk patients was presented. Authors re-analyzed the long-term follow-up results of EORTC-ACTION trial. In the EORCT-ACTION trial, 448 patients with 1A-B with grade 2-3 or 1C-2A with any grade ovarian cancer were postoperatively randomized into adjuvant platinum-based chemotherapy vs. observation. The primary analysis showed a significantly better disease-free survival (DFS) in the treatment group.[34] As a subset analysis, authors investigated the 5- and 10-year DFS and OS of moderate-risk patients who were defined as 1B-C with grade 1 or 1A with grade 2. In accordance with the result of primary analysis, platinum-based chemotherapy significantly improved DFS and OS in moderate-risk patients.[35]

Because it is the subset analysis, the long-term follow-up result of EORTC-ACTION trial should be interpreted cautiously. Decision on whether moderate-risk patients receive adjuvant platinum-based chemotherapy should be individualized.

9. Neoadjuvant chemotherapy in advanced ovarian cancer

Primary surgical cytoreduction followed by adjuvant chemotherapy is the standard care for patients with stage 3 or 4 ovarian cancer. However, aggressive cytoreduction is not feasible for some patients who have massive ascites or poor performance status. Therefore, there have been continuing interests

in neoadjuvant chemotherapy followed by cytoreduction for selected patients.

Several uncontrolled studies reported that neoadjuvant chemotherapy followed by cytoreduction is feasible, and some studies suggested that outcomes of neoadjuvant chemotherapy plus cytoreduction are comparable to those of initial cytoreduction.[36,37] In contrast, some studies suggested that survival of patients who received neoadjuvant chemotherapy plus cytoreduction might be inferior to that of initial cytoreduction. For example, a meta-analysis of 22 studies regarding neoadjuvant chemotherapy showed that a higher number of neoadjuvant chemotherapy cycles was correlated negatively with survival.[38] Because definitive evidence favoring neoadjuvant chemotherapy plus cytoreduction are lacking, aggressive initial cytoreduction was the standard of care for patients with advanced ovarian cancer. Neoadjuvant chemotherapy tended to be used in elderly or medically frail patients.

The result of a phase 3 clinical trial directly addressing this issue was presented at the IGCS biennial meeting. Seven-hundred eighteen patients with stage 3C-4 ovarian, fallopian tube and peritoneal cancer were randomized into primary cytoreduction vs. neoadjuvant chemotherapy plus cytoreduction. The primary cytoreduction group received initial cytoreductive surgery followed by 6 cycles of adjuvant chemotherapy. The neoadjuvant group underwent three cycles of chemotherapy followed by debulking surgery and adjuvant three cycles of chemotherapy. Optimal debulking (largest residual tumor $\leq$ 1 cm) was achieved more in the neoadjuvant group than in the primary cytoreduction group. After median follow-up of 4.8 years, PFS and OS were similar between two groups. However, patients in the primary cytoreduction group suffered more complications. Authors concluded that neoadjuvant chemotherapy followed by cytoreduction can be considered as the preferred treatment for patients with advanced ovarian cancer because neoadjuvant chemotherapy showed lower morbidity and similar survival with initial cytoreduction.[39]

Although it is uncertain whether the neoadjuvant chemotherapy followed by cytoreduction could be accepted as the standard treatment for advanced ovarian cancer, more popular use of neoadjuvant chemotherapy for patients with advanced ovarian cancer is strongly anticipated.

10. Surgery for recurrent ovarian cancer

The benefit of initial cytoreduction in the treatment of ovarian cancer is well-established. However, the benefit of secondary cytoreduction in patients with recurrent ovarian cancer is unclear because of the lack of randomized trials addressing this issue. Based on uncontrolled series, subsets of patients for whom secondary cytoreduction may be beneficial were identified. For example, excision of all gross residual disease, longer remission period after initial treatment, localized recurrences were associated with improved survival after secondary cytoreduction.[40,41] However, it is difficult to preoperatively predict whether it will be possible to excise all gross residual disease. The DESKTOP OVAR trial was conducted to find preoperative predictors of complete resection in secondary cytoreduction. Via retrospective analysis of 267 patients with recurrent ovarian cancer who underwent secondary cytoreduction, good performance status, complete resection at initial surgery, and absence of ascites $>$500 ml were identified as predictors of successful secondary cytoreduction. A complete resection was possible in 79 percent of patients if all of these factors were present (AGO score positive).[42]

At the IGCS biennial meeting, the result of prospective validation of AGO score system was presented. In that trial (AGO-DESKTOP 2), 412 patients with first relapse of platinum-sensitive recurrent ovarian cancer were screened. Of 193 patients who were eligible for surgery (AGO score positive), 127 patients underwent surgery and complete resection was achieved in 76% of patients.[43] These findings suggested the usefulness of AGO score system. According to authors, a randomized trial based on AGO score system is already planned.

11. New biomarkers for ovarian cancer

Accurate triage method is essential in the management of pelvic mass. Accurate triage enables us to identify women who should undergo surgery for pelvic mass and to choose the appropriate surgical method. However, in reality, many women undergo surgery for an ovarian neoplasm but only a small percentage of these women will be diagnosed as an epithelial ovarian cancer (EOC).

The risk of malignancy index (RMI) is the most utilized algorithm for predicting malignancy in women with a pelvic mass. The RMI score is calculated by the combination of serum CA 125 level, pelvic sonography and menopausal status.[44] A study reported that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of RMI algorithm in detecting EOC and borderline tumors was 87.4%, 56.8%, 86.6%, and 58.1%, respectively.[45] However, operator variability in interpreting the sonographic features of pelvic mass contribute to inconsistencies of RMI score seen from center to center.[46]

Human epididymis protein 4 (HE4) is made up of two whey acidic protein domains and a four disulfide core and has been shown to be over-expressed in EOC. HE4 is not elevated in many benign conditions where CA 125 is elevated.[47] In a pilot study examining the cancer-predictive value of 11 markers, the dual marker combination of CA 125 and HE4 had the highest predictive value.[48] Based on the result of the pilot study, researchers designed an algorithm based on menopausal status, serum CA 125 and HE4 levels. Recently, the prospective validation result of the algorithm was published. Preoperative serum levels of CA 125 and HE4 were measured in 531 patients who were scheduled to undergo surgery for a pelvic mass. Using the predefined algorithm, patients were categorized into low- and high-risk groups for EOC. In post-

menopausal women, the algorithm classified 112 of 150 benign tumors as low-risk group giving a specificity of 75% and assorted 108 of 117 borderline tumors or cancers as high-risk group giving a sensitivity of 92%. In premenopausal women, the algorithm judged 151 of 202 benign tumors as low-risk group providing a specificity of 75% and classified 26 of 34 borderline tumors or cancers as high-risk group providing a sensitivity of 77%. Overall, 94% of EOC was correctly classified as high-risk group.[46]

At the ASCO annual meeting, another study on the value of HE4 was presented. Authors evaluated the value of HE4 in monitoring patients with EOC. In 80 patients with EOC, serial changes of serum CA 125 and HE4 levels were compared to the clinical status determined by computed tomography (CT). Analysis showed that changes of HE4 values were not inferior to that of CA 125 values in accordance with clinical status. In addition, HE4 was correlated with clinical status in 24% of patients in whom CA 125 was not correlated with clinical status.[49]

Considering these promising results, further study on the value of HE4 in other area, such as in the screening of ovarian cancer, should be encouraged.

12. Screening and treatment of ovarian cancer in women with BRCA mutations

Prevention and early detection of ovarian cancer have continued to be an area of progress. Because no single test or combination of tests has been proven to be useful in screening for ovarian cancer in the general population, researchers studied the effectiveness of screening strategy in selected high-risk women such as women with BRCA mutations.

Results of screening 120 women with BRCA mutations over a 4.7 year period were presented at the ASCO annual meeting. Eligibility criteria was as follows: older than 30, deleterious BRCA mutations, intact ovaries, participating in one of three prospective follow-up studies for at least one year following receipt of genetic test results. Result of transvaginal sonography (TVU) and CA 125 were obtained from structured questionnaires completed annually by participants. During a median 3.2 years of follow-up, 36 women reported at least one abnormality on either TVU or CA 125 which required short interval follow-up. Seven women had persistent abnormalities which lead to surgery. Of these, four women were diagnosed as having cancers after a mean of 4.7 years of screening. In addition, of 54 women who elected to undergo prophylactic salpingo-oophorectomy after screening for at least a year, one occult cancer was found after 5.6 years of screening. Specifically, there were three stage 1 ovarian cancers, one stage 3 ovarian cancer and one at least stage 2 tubal cancer. The authors concluded that screening with TVU and CA 125 was effective for some women with BRCA mutations, but not as effective as prophylactic surgery in preventing advanced ovarian or tubal cancers.[50]

For women with BRCA mutations who have already developed ovarian cancer, encouraging results of phase 1 trial using new biologic agents were presented at the ASCO annual meeting. AZD2281, a member of a class of drugs called PARP inhibitor was tested in a phase 1 trial including patients with wide range of drug-resistant cancers. AZD2281 blocks the pathway used by BRCA mutated cells to repair DNA damage. Of 44 patients with BRCA-mutated ovarian cancer, 32 patients were evaluable for response. Of 32 patients, 14 patients achieved partial response and eight patients showed stable disease. In addition, seven of 14 patients with response maintained responses for over 24 weeks.[51]

Advances in the early detection and treatment of ovarian cancer in subsets of women such as women with BRCA mutations may ultimately lead to similar progress for the women in the general population.

13. Sentinel lymph node in vulvar cancer

In vulvar cancer, morbidity from groin dissection is significant. For example, wound infection or breakdown is reported in 20% to 40% of patients. In addition, lymphedema of the legs with increased risk for erysipelas was observed in 30% to 70% of patients.[52,53] Therefore, the value of minimally invasive techniques such as sentinel lymph node (SLN) dissection has been evaluated. Several studies reported that SLN dissection is feasible and accurate in vulvar cancer.[54] However, the total number of patients in each study was small and most studies were single-institution studies. In addition, most studies just focused on the accuracy of SLN dissection using the result of full lymph node dissection as a standard reference. There have been no large studies evaluating the long-term safety of SLN dissection in vulvar cancer.

Recently, the result of multicenter prospective study on the safety of SLN dissection was published. For 403 patients with a tumor smaller than 4 cm and clinically negative groin lymph nodes, SLN dissection using radioactive tracer and blue dye was performed. Patients with positive SLN underwent an inguinofemoral lymphadenectomy and patients with negative SLN received no additional treatment. In 259 patients with unifocal tumor and negative SLN, six groin recurrences were diagnosed (2.3%) and 3-year survival rate was 97%. Patients who received only SLN dissection suffered less short- and long-term morbidities than patients who underwent full dissection. Authors concluded that SLN dissection is safe and should be part of the standard treatment in patients with early-stage vulvar cancer.[55]

In 2008, the largest study validating the accuracy of SLN dissection was published. In Germany, 127 patients with T1-T3 vulvar cancers and clinically negative groin lymph nodes received SLN dissection and subsequent inguinofemeral lymphadenectomy. Of 39 patients with positive groin lymph nodes, SLN was positive in 36 patients (sensitivity 92%). All three patients with false negative SLN had midline tumors. Authors concluded that tumors located in or close to the midline seem to be less suitable for SLN dissection.[54]

SLN dissection is feasible and accurate in early, non-midline vulvar cancers. However, considering that vulvar cancer is a rare tumor and the quality of SLN procedure is quite important to reduce the false negativity, we believe that the SLN procedure is better to be performed in centralized oncology centers.

14. Primary chemotherapy in low-risk GTT

For low-risk gestational trophoblastic tumor (GTT), various regimens have been used and were known to be similarly effective.[56] However, there were only few clinical trials prospectively comparing the efficacy of regimens. Only four randomized controlled trials were identified and included in the Cochrane review which was presented at the IGCS biennial meeting.

According to the review, five different regimens were identified in literatures and comparisons between regimens were performed. In result, pulsed dactinomycin was superior to weekly methotrexate without a significant increase in toxicity. Eight-day methotrexate-folinic acid did not show significant advantage over 5-day methotrexate both in reducing toxicity or primary cure rate. The combination of methotrexate-dactinomycin resulted in significantly increased toxicity without improving primary cure rate.[57]

Superiority of pulsed dactinomycin was confirmed by a randomized phase 3 trial performed by GOG. Two-hundred forty patients with low-risk GTT were randomized into weekly methotrexate 30 mg/m^2 vs. biweekly dactinomycin 1.25 mg/m^2. Significantly more complete response was observed in dactinomycin group and toxicities were tolerable in both groups.[58]

Although a trial comparing biweekly dactinomycin with 8-day methotrexate-folinic acid is lacking, biweekly dactinomycin is thought to be more convenient than 8-day methotrexate-folinic acid. Therefore, biweekly dactinomycin should be considered for standard regimen of low-risk GTT.

CONCLUSION

In 2008, there were many important advances regarding gynecologic cancer. Especially, many studies were performed for ovarian cancer which is the most lethal gynecologic cancer. Therefore, we assigned five of 14 topics into ovarian cancer. To improve the outcome of this obstinate disease, not only the optimization of management but the effective screening method should be developed. Researches on identification of novel biomarkers such as HE4 and high-risk populations such as women with BRCA mutation should be encouraged.

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