Major clinical research advances in gynecologic cancer 2007

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INTRODUCTION

In 2007, remarkable clinical research advances in prevention, diagnosis and treatment of gynecologic cancer were achieved. This report documents nine of the most significant advances in gynecologic cancer research. Three significant advances were chosen for each major gynecologic cancer: cervical cancer, endometrial cancer, and ovarian cancer. In cervical cancer, the clinical trials on human papillomavirus (HPV) vaccines, the use of intensity-modulated radiotherapy (IMRT), and advances in minimally-invasive surgery technique were reviewed. In endometrial cancer, the role of adjuvant external beam radiation therapy (EBRT) in early stage intermediate-risk endometrial carcinoma (ESIREC), the comparison of chemoradiation with radiation as an adjuvant therapy in early stage high-risk endometrial carcinoma (ESHREC), and the efficacy of hormone therapy in women who want to preserve fertility were documented. In ovarian cancer, the ovarian cancer symptom index (OCSI) which were anticipated to be useful for early diagnosis, preliminary but promising results of trials on ovarian cancer screening, and target therapy using vascular endothelial growth factor (VEGF) related molecules were reviewed.

MAJOR CLINICAL RESEARCH ADVANCES

1. HPV vaccines

In several trials, HPV vaccines were demonstrated to be effective in preventing cervical intraepithelial neoplasia (CIN). In a trial on 12,167 women aged from 15 to 26, the quadrivalent vaccine (Gardasil®) effectively prevented over 90% of CIN 2 or more advanced lesions in per-protocol or modified intention-to-treat analysis.1 Similarly, in a trial on 18,644...
women aged from 15 to 25, the bivalent vaccine (Cervarix®) prevented about 90% of HPV 16, 18 associated CIN 2 or more advanced lesions in modified intention-to-treat analysis. However, in intention-to-treat analysis, the quadrivalent vaccine showed much lower efficacy. Putting these results together, in a group who were not infected with HPV, HPV vaccines were highly effective in preventing CIN even if the vaccines were not given on schedule. However, in a group whose HPV infection status was unknown, the efficacy of HPV vaccines was considerably compromised. This low efficacy of HPV vaccines in the group of unknown HPV status was thought to be due to the ineffectiveness of HPV vaccines in women who were already infected with HPV 16 or 18. The ineffectiveness of HPV vaccines in women with preexisting infection was reconfirmed in a study demonstrating that HPV vaccination does not accelerate the clearance of the virus in women with preexisting infection. In addition; warts, vulva and vaginal intraepithelial neoplasia were also effectively prevented by the quadrivalent vaccine. In a trial on 5,455 women, the quadrivalent vaccine showed 100% efficacy in per-protocol analysis and 34% efficacy in intention-to-treat analysis.

Since HPV vaccines were known to be more effective in women who were not infected with HPV, studies on efficacy and safety of HPV vaccines in younger women were performed. In a trial on 773 women aged from 10 to 25, the antibody titer after HPV vaccination were compared between younger group aged from 10 to 14 and older group aged from 15 to 25. The antibody titer of younger group was two-times higher than that of older group, but the incidence and severity of adverse events were similar between two groups.

In a study, the strong immune response after a boost vaccination was observed in 114 women who were vaccinated with quadrivalent vaccine five years ago. This strong immune response suggested that the efficacy of HPV vaccines could be long lasting.

2. IMRT in cervical cancer

Because IMRT can produce highly conformal dose distributions unachievable using conventional approaches, IMRT has been used in head and neck and prostate cancers. Although there is little doubt that IMRT will gain increasingly widespread clinical applications, studies on the use of IMRT in cervical cancer were sparse. Although there is no prospective trial on the use of IMRT in cervical cancer, a retrospective study comparing IMRT with conventional radiotherapy as a postoperative adjuvant therapy was recently reported. In the study, local recurrence rate and acute or chronic toxicities of 33 patients who received IMRT were compared with those of 35 patients who received conventional radiotherapy. Local recurrence rates were similar between the IMRT and the conventional radiotherapy groups. However, significantly less acute and chronic toxicities were observed in the IMRT group. Therefore, we thought that IMRT will gradually replace the conventional radiotherapy in cervical cancer.

3. Minimally-invasive surgery

Since Wertheim reported his series on the use of abdominal hysterectomy in 1912, after combined with a complete pelvic lymph node dissection by Meigs in the 1940s, the radical abdominal hysterectomy have been the standard of care in the treatment of cervical cancer. Since the late 1980s, advances in laparoscopic technology have enabled diverse minimally-invasive techniques in the surgery of cervical cancer: radical vaginal hysterectomy, laparoscopy-assisted radical hysterectomy, total laparoscopic radical hysterectomy. Compared to radical abdominal hysterectomy, minimally-invasive surgery produced lower blood loss, short hospital stay, and quicker return of bowel function without compromising radicality represented by specimen size, number of lymph node, and recurrence rate. In 2007, in addition to laparoscopic surgery, the robot-assisted radical hysterectomy was reported. Robot surgery was known to have advantages over laparoscopic surgery in respect of improved dexterity, three-dimensional viewing, greater degrees of freedom allowed by the robotic instruments, surgical precision with tremor filtration, and the comfortable, fatigue-reducing console of the robotic system. Kim et al reported less morbidity of robot surgery after performing robot radical hysterectomy and pelvic lymph-
Boggess compared the result of 13 robot-assisted radical hysterectomies with that of 48 historic radical abdominal hysterectomies. The robot-assisted radical hysterectomy produced higher yield of lymph nodes, similar operative time, less blood loss and analgesics use. Although there is no study comparing the laparoscopic radical hysterectomy with the robot radical hysterectomy and the robot surgery has many drawback such as complexity, high cost and the absence of tactile sense, the robot surgery was anticipated to gain more clinical applications through rapidly developing robotic technology.

4. The role of adjuvant EBRT in ESIREC

In early endometrial cancer with risk factors, the indication and method of adjuvant therapy remains to be unclear. Historically, the postoperative adjuvant radiotherapy have been performed in such patients. However, the four clinical trials on adjuvant radiotherapy in early endometrial cancer failed to demonstrate the survival benefit of radiotherapy. In 2007 annual meeting of ASCO, the result of the largest clinical trial on the effect of adjuvant radiotherapy in early endometrial cancer was presented. In the trial (ASTEC/NCIC-CTG-EN.5) which the British and Canadian groups participated in, 905 patients with ESIREC underwent surgery and were randomized into two groups who received the adjuvant EBRT or not. All patients underwent hysterectomy and bilateral adnexectomy but only 29% of women underwent lymphadenectomy. Brachytherapy was allowed only in conditions as follows: performed by center policy, stated before randomization, used in both groups. About half of patients received the brachtherpay. During follow-up period, ninety disease-related deaths were observed. Overall survival, disease-specific survival, and recurrence-free survival were similar between two groups. However, local recurrence confined to vagina or pelvis was fewer in the EBRT group than in the control group (3% vs 7%). Acute toxicity and grade 3 or 4 chronic toxicity of EBRT group were two times more than those of control group. In conclusion, the adjuvant EBRT did not increase the survival in women with ESIREC but slightly reduced the local recurrence rate which could be cured with the salvage treatment.

5. The role of adjuvant chemoradiation in ESHREC

Since the role of EBRT in early endometrial cancer was known to be limited, the results of trials testing other modalities than radiotherapy as an adjuvant therapy in ESHREC were reported. In RTOG 9708, the efficacy of adjuvant chemoradiation was shown in patients with ESHREC. Forty-six patients who had grade 2 or 3 endometrial adenocarcinoma with either >50% myometrial invasion, cervical stromal invasion, or pelvic-confined extraterine disease underwent surgery without lymph node evaluation, pelvic radiotherapy with brachytherapy, and chemotherapy. At four years, local and distant recurrence rates were 5% and 19% respectively and no recurrence occurred in patients with early endometrial cancer (1C, 2A, 2B). These low recurrence rates suggested that the adjuvant chemoradiation is highly effective in ESHREC.

In 2007 annual meeting of ASCO, the result of clinical trial (NSGO-EC-9501/EORTC 55991) comparing the chemoradiation with the radiotherapy as an adjuvant therapy in ESHREC was presented. Three-hundred eighty-two patients with ESHREC underwent surgery and received the adjuvant chemoradiation or radiotherapy. Most of patients had early endometrial cancer but patients with stage 3A or 3C were included in the trial. In addition, considerable number of endometrial cancer with serous or clear cell types was also included. Overall survival and progression-free survival were higher in the chemoradiation group than in the radiotherapy group. Furthermore, the actual survival advantage of chemoradiation over radiotherapy could be more pronounced considering that, due to toxicities, the drop-out rate of chemoradiation group was higher than that of radiotherapy group and the survival analysis was performed via intention-to-treat method. Distant recurrences were more common than local recurrences in both groups. Compared to radiotherapy, the chemoradiation reduced local and distant recurrences. However, the trial was criticized for unclear description of lymphadenectomy, lack of standard treatment protocol in chemotherapy and radiation.
Although the participants in the ASTEC/NCIC-CTG-EN.5 trial and the NSGO-EC-9501/EORTC 55991 trials were roughly considered as intermediate-risk group and high-risk group respectively, there was a significant overlap of eligible population in both trials. Therefore, it is still hard to induce a general conclusion about the role and best method of adjuvant therapy in early endometrial cancer.

6. Hormone therapy in women who want to preserve fertility

For young women with endometrial cancer who want to preserve fertility, it could be hard to apply the standard treatment, hysterectomy. In such a case, hormone therapy could be an option if the tumor is well-differentiated and do not invade myometrium. However, there are no prospective study on the efficacy of hormone therapy in endometrial cancer. Ushijima et al reported the result of the multi-center clinical trial which investigated the effect of progestin treatment in 28 patients with endometrial cancer and 17 patients with atypical complex hyperplasia. Participants took medroxyprogesterone 600mg and aspirin 81mg every day for 26 weeks. At 8th, 16th, and 26th weeks, endometrial biopsy was performed. Complete response was observed in 55% of patients with endometrial cancer and in 82% of patients with atypical endometrial hyperplasia. No mortality and irreversible toxicity were observed but weight gain and liver dysfunction were observed in some patients. At three year follow-up, twelve pregnancies and seven normal deliveries were observed. However, fourteen recurrences were found in 30 patients (47%) between 7 and 36 months.

7. Ovarian cancer symptom index (OCSI)

Although the ovarian cancer has been known to be asymptomatic, there were reports that the ovarian cancer has early symptoms, even if they are non-specific. If we can diagnose the early ovarian cancer by symptoms, we could expect the better prognosis. Therefore, in July 2007, the Gynecologic Cancer Foundation (GCF), the Society of Gynecologic Oncologists (SGO), the American Cancer Society (ACS) released the consensus statement recommending a medical checkup if a woman had more than one of four symptoms which are common in ovarian cancer. The consensus statement is based on the case-control study which was performed by Goff et al in 2006. Goff et al investigated the symptoms of 149 women with ovarian cancer and 488 women in control group. In the study, the participants were divided into the exploratory and the confirmatory groups. In the exploratory group, the symptoms of women with ovarian cancer were compared with those of control group. As a result, the ovarian cancer symptom index (OCSI) using four symptom category was made. Four symptom categories were as follows: pelvic/abdominal pain, increased abdominal size/bloating, difficulty eating/feeling full, urinary frequency/urgency. Positive result was defined as the presence of more than one symptom categories which occurred within 12 months and more frequent than twelve days per month. As a result of applying the OCSI to the confirmatory group, the OCSI showed the sensitivity of 86.7% and the specificity of 86.7% in women younger than 50 and the sensitivity of 66.7% and the specificity of 90% in women at or older than 50.

8. Ovarian cancer screening

Ovarian cancer screening on general population is well-known to be ineffective. However, preliminary but notable results of studies using CA-125 and/or ultrasonography for ovarian cancer screening were reported in 2007. The preliminary result of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) was presented in the 2007 annual meeting of SGO. In about 39,000 women, annual serum CA-125 level measurement and transvaginal ultrasonography were performed for four years. Sixty-two (63%) of 98 women with newly diagnosed ovarian cancer were detected via screening tests. Ninety percent of women detected via CA-125 elevation had advanced stage ovarian cancer and 77% of women detected via transvaginal ultrasonography had stage 1 or 2 ovarian cancer. Women with abnormal ultrasonography underwent more surgeries than the women with CA-125 elevation. Positive predictive values of each test were very low. The effect of the screening tests on the mortality rate will be analyzed in the final report.
In 2007 annual meeting of ASCO, Skates et al reported the promising result of the new screening strategy for ovarian cancer. Serial CA-125 level measurement was performed on 2,343 women who were asymptomatic and at high-risk for ovarian cancer. Ovarian cancer risk of an individual woman was calculated by analyzing serial CA-125 values via Risk of Ovarian Cancer Algorithm (ROCA). According to the calculated ovarian cancer risk, a woman was arranged for another CA-125 level measurement, transvaginal ultrasonography, or referral to a specialist. The positive predictive value and specificity of ROCA method were 14% and 83%, respectively. There is an ongoing trial investigating the efficacy of ROCA method in general population.

9. Target therapy using VEGF related molecules

In 2007, there were many advances in target therapy of ovarian cancer. Especially, the molecules related with VEGF were tested in many trials of ovarian cancer treatment. Results of trials using bevacizumab, the monoclonal antibody against VEGF, were presented at the 2007 annual meeting of ASCO. Micha et al treated 20 patients with advanced ovarian cancer with bevacizumab 15 mg/kg every three week in addition to paclitaxel and carboplatin. Complete and partial response were observed in 30% and 50% of patients, respectively. Gastrointestinal perforation was not observed but grade 3 hypertension occurred in two patients. There are ongoing trials (GOG-218, ICON-7) comparing the efficacies of paclitaxel and carboplatin with or without bevacizumab in patients with advanced ovarian cancer.

Trials evaluating the efficacy of bevacizumab in recurrent ovarian cancer also showed the promising results. In a trial, bevacizumab 15 mg/kg was given to 44 patients with recurrent, platinum-resistant ovarian cancer and partial response was observed in seven women (15.9%). In another trial on recurrent ovarian cancer, 21% of patients responded to bevacizumab. In both trials, various adverse events of bevacizumab such as hypertension, proteinuria, gastrointestinal perforation occurred. Gastrointestinal perforation was more common in heavily pretreated patients. A study reported that the combination of metronomic chemotherapy and bevacizumab is active in recurrent ovarian cancer. Seventy patients with recurrent ovarian cancer were given oral cyclophosphamide 50 mg every day and bevacizumab 10 mg/kg every two weeks. Partial response was observed in 24% of patients, but four episodes of gastrointestinal perforation or fistula, two episodes each of brain ischemia and pulmonary hypertension, and three treatment-related deaths occurred. The result of phase 2 trial on VEGF trap which binds to and antagonizes VEGF was reported. VEGF 2mg or 4mg was given to 162 patients with recurrent, platinum-resistant ovarian cancer and partial response was observed in 11% of patients. Treatment-related adverse events were similar with those of bevacizumab.

CONCLUSION

Like other specialties, the clinical research advances in gynecologic oncology could be grouped into two categories: the growth of evidence-based medicine represented by clinical trial and the introduction of new technology such as IMRT, robot surgery, and target therapy. In 2008, we expect that more evidence will accumulate and more innovative technology will be adopted into the practice of gynecologic oncology.

REFERENCES


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초록

2007년 부인암 임상 분야의 주요 진전

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2007년에 부인암의 예방, 진단 및 치료 분야에서 여러 가지 중요한 임상 연구 결과가 발표되었다. 이 중에 자궁경부암, 자궁내막암, 난소암의 세 암종에서 각각 3가지씩의 중요한 진전 사항을 선정하여 소개하고자 한다. 자궁경부암 분야에서는 인유두종바이러스 백신에 대한 임상시험 결과, 최근 점차 사용이 확대되고 있는 세기조절방사선요법 및 복강경에 이어 로봇 수술의 도입에 이르고 있는 최소침습수술이 주목된다. 자궁내막암에서는 초기 중등도위험군 자궁내막암에서 외부방사선요법의 역할, 초기 고위험군 자궁내막암에서 보존화학방사선요법과 보조방사선요법의 비교 및 임신력 보존을 원하는 여성들 대상으로 한 호르몬 요법의 임상시험 결과가 있다. 난소암에서는 조기 진단에 도움이 될 것으로 기대되는 난소암 선별검사 및 혈관내피성장인자 관련 표적치료가 중요한 연구결과이다.

중심단어: 부인과, 비뇨생식기계 종양, 생의학 연구

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