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Review Article

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Major clinical research advances in gynecologic cancer in 2017

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ABSTRACT

In 2017, 10 topics were selected as major clinical research advances in gynecologic oncology. For cervical cancer, efficacy and safety analysis results of a 9-valent human papillomavirus (HPV) vaccine and long-term impact of reduced dose of quadrivalent vaccine were updated. Brief introduction of KEYNOTE trials of pembrolizumab, a monoclonal antibody that blocks the interaction between programmed death (PD)-1 and its ligands, PD-L1 and PD-L2, followed. Tailored surveillance programs for gynecologic cancer related with Lynch syndrome and update on sentinel lymph node mapping were reviewed for uterine corpus cancer. For ovarian cancer, 5 topics were selected including poly(ADP-ribose) polymerases inhibitors and immunotherapy. The other potential practice changers covered in this review were lymphadenectomy in advanced disease, secondary cytoreductive surgery in recurrent disease, weekly dose-dense regimen for first-line chemotherapy, incorporation of bevacizumab maintenance in platinum-sensitive recurrent disease, and effect of platinum-free interval prolongation. Conflicting opinions of academic societies on periodic pelvic examination were introduced in conjunction with relevant literature review. For the field of radiation oncology, results of 2 big trials, The Postoperative Radiation Therapy in Endometrial Carcinoma-3 and Gynecologic Oncology Group-258, for endometrial cancer and recent advance in high-dose-rate brachytherapy for cervical cancer were reported. Topics for breast cancer covered adjuvant capecitabine after preoperative chemotherapy, adjuvant pertuzumab and trastuzumab in early human epidermal growth factor receptor 2-positive disease, olaparib for metastatic cancer in patients with a germline *BRCA* mutation, 20-year risks of recurrence after stopping endocrine therapy at 5 years, and contemporary hormonal contraception and the risk of breast cancer.

Keywords: Poly(ADP-ribose) Polymerase Inhibitors; Molecular Targeted Therapy; Immunotherapy; Ovarian Neoplasms; Breast Neoplasms

INTRODUCTION

This series of review, "major clinical research advances in gynecologic cancer," is now in its 11th edition. We have tried to outline the major progress that has been achieved in clinical gynecologic cancer research and care each year. Every author reviewed scientific literature

Author Contributions

Conceptualization: S.D.H., L.K.H., M.M.R., K.M.K., K.J.W.; Project administration: S.D.H., K.J.W.; Supervision: M.M.R., K.J.W.; Writing - original draft: S.D.H., K.M., L.K.H., K.M.K.; Writing - review & editing: S.D.H., K.M., M.M.R., K.M.K., L.K.H., K.J.W.

Table 1. Ten topics of major clinical research advances in gynecologic cancer in 2017

Site of cancer	Topic	Reference
Uterine cervix	1. Update on HPV vaccination	[4]
	2. Pembrolizumab in advanced cervical cancer	[11,12]
Uterine corpus	3. Tailored surveillance programs for gynecologic cancer related with LS	[15,16]
	4. SLN mapping	[22-24]
Ovary	5. Update on PARP inhibitors	[28,29]
	6. Prediction of the response to immunotherapy	[30,34]
	7. Update on conventional treatment methods: LION, DESKTOP III, ICON8, MITO-8, GOG-213	[36-38,40,41]
	8. Screening of gynecologic cancer: periodic pelvic exam	[44-47]
	9. Update on RT	[48,49,51]
Breast	10. Adjuvant capecitabine after preoperative chemotherapy; adjuvant pertuzumab and trastuzumab in early HER2-positive disease; olaparib for metastatic cancer in patients with a germline *BRCA* mutation; 20-year risks of recurrence after stopping endocrine therapy at 5 years; contemporary hormonal contraception and the risk of breast cancer	[52-57]

DESKTOP, The Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent ovarian cancer; GOG, Gynecologic Oncology Group; HPV, human papillomavirus; ICON; International Collaborative Ovarian Neoplasm; LION, Lymphadenectomy in Ovarian Neoplasms; LS, Lynch syndrome; MITO, Multicenter Italian Trials in Ovarian Cancer; PARP, poly(ADP-ribose) polymerases; RT, radiation therapy; SLN, sentinel lymph node.

that was published in peer-reviewed journals or presented at major conferences in 2017 and selected outstanding advances through the consensus meeting. "2017" was a year when we took a major step forward in the field of targeted therapy in gynecologic oncology.

In particular, poly(ADP-ribose) polymerase (PARP) inhibitor has taken center stage based on several promising research results of survival improvement without significant increase of adverse effects (AEs). For the first time in this review series, we have an invited section about "update on PARP inhibitor in 2017," which was written by Professor Mansoor Raza Mirza and his colleague, Dr. Maj Kamille Kjeldsen.

Herein, we summarized 10 topics of major clinical research advances in gynecologic cancer in 2017 (**Table 1**).

CERVICAL CANCER

1. Update on human papillomavirus (HPV) vaccination

HPV vaccines, including the bivalent HPV 16 and 18 L1 virus-like particle vaccine and the quadrivalent HPV 6, 11, 16, and 18 L1 virus-like particle (qHPV) vaccine, are effective at preventing up to 70% of cervical and other HPV-related cancers [1]. In addition to HPV subtypes 6, 11, 16, and 18, a 9-valent HPV (9vHPV) vaccine (Gardasil 9®; Merck & Co., Inc., Kenilworth, NJ, USA) would also protect against HPV subtypes 31, 33, 45, 52, and 58, and could prevent around 90% of cervical cancers [2,3]. In *Lancet*, Huh et al. [4] showed that prophylactic administration of the 9vHPV vaccine is highly efficacious in preventing HPV infection, cervical cytological abnormalities and high-grade cervical intraepithelial neoplasia (CIN) histology. The final efficacy of the 9vHPV vaccine was observed for up to 6 years after first administration, and HPV type-specific antibody responses were checked over 5 years. A total of 14,215 women aged 16–26 years old were randomly assigned (1:1) by central randomization and received 3-dose over 6 months of 9vHPV or qHPV vaccine. The incidence of high-grade cervical, vulvar and vaginal disease related to HPV 31, 33, 45, 52, and 58 was 0.5 cases per 10,000 person-years in the 9vHPV and 19.0 cases per 10,000 person-years in

the qHPV groups. The efficacy of the 9vHPV vaccine compared with the qHPV vaccine for the primary outcome of high-grade cervical, vulvar, and vaginal disease related to HPV 31, 33, 45, 52, and 58 was 97.4% (95% confidence interval [CI]=85.0–99.9). Antibody titers against HPV 6, 11, 16, and 18 in the 9vHPV vaccine group remained non-inferior to those in qHPV vaccine recipients, showing that protection against the original 4 HPV types remained high over entire study. No clinically significant differences in serious adverse events were noted between the study groups, and no vaccine-related deaths were observed.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination at age 11 or 12 years, and it can be given starting at age 9 years. In 2016, the ACIP recommended reducing the number of HPV vaccine shots from 3 to 2 for girls and boys between the ages of 9 and 14. Based on the available immunogenicity evidence, a 2-dose schedule (0, 6–12 months) will have similar efficacy to a 3-dose schedule (0, 1–2, 6 months), if the HPV vaccination schedule is started before the 15th birthday [5,6]. There is a promising report adds to growing evidence that 2-doses of HPV vaccine is enough. In 2017 Society of Gynecologic Oncology (SGO) annual meeting, Zeybek and Rodriguez [7] presented the results of a study that used insurance data from 11,335 women who received at least one dose of HPV vaccine. Of them, 1,975 received a single dose, 2,089 received 2-doses, and 7,271 women received 3- or more doses. Women who received only a single dose had higher incidence of high-grade cytology, high-grade CIN histology, adenocarcinoma in situ (AIS) and invasive cancer. At 5 years after first dose, 2.3% of single-dose women had high-grade CIN histology, compared with 1.5% of those who received 2-doses, and 1.8% for 3-doses. Also at 5 years, 4.3% of single-dose women were considered to be in a “high-risk group” (any of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion [ASC-H], high-grade cytology, high-grade CIN histology, AIS, or invasive cancer), compared with 3% of 2-dose women and 3.9% of 3-dose women. The difference between a single dose and 2-doses was statistically significant for the high-risk grouping and high-grade CIN histology (p=0.04 and p=0.09, respectively). However, comparing 2- and 3-doses did not reach significance for either the high-risk group or high-grade CIN histology (p=0.17 and p=0.79, respectively).

2. Pembrolizumab in advanced cervical cancer

Pembrolizumab (Keytruda®; Merck & Co., Inc.) is a highly selective humanized monoclonal antibody that blocks the interaction between programmed death (PD)-1 and its ligands, PD-L1 and PD-L2, and allows the immune system to destroy cancer cells. Since US Food and Drug Administration (FDA) approved pembrolizumab in advanced melanoma in 2014, the FDA approved it for non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, microsatellite instability-high cancer, and gastric cancer till now [8]. The recent identification of a higher PD-L1 expression in HPV-inducing cervical cancers suggests that PD-1 also may be an attractive therapeutic target for patients with advanced cervical cancer [9,10].

Frenel et al. [11] yielded a result that pembrolizumab treatment is active in patients with PD-L1-positive advanced cervical cancer from the phase Ib KEYNOTE-028 (NCT02054806) trial. To assess the safety and efficacy of pembrolizumab in PD-L1-positive advanced cervical cancer, a total of 24 patients were enrolled in this cohort; 18 (75%) were PD-L1-positive in the tumor only and 6 (25%) were positive in the tumor and stroma. All enrolled patients were treated with pembrolizumab 10 mg/kg every 2 weeks for up to 24 months. Overall response rate (ORR; the proportion of patients achieving either a confirmed complete response

[CR] or partial response [PR]) was 17% (4/24; 95% CI=5%–37%) on the basis of RECIST v1.1, with no CR and 4 PR achieving patients. Three patients had stable disease (13%; 95% CI=3%–32%) and 16 patients had progressive disease (67%; 95% CI=45%–84%) as best overall response. Median time to response in the 4 patients who had PR was 1.9 (range, 1.7–8.2) months, and median duration of response was 5.4 (range, 4.1–7.5) months. Median progression-free survival (PFS) was 2 (95% CI=2–3) months, and median overall survival (OS) was 11 (95% CI=4–15) months in all study population. Grade 3 treatment-related AEs were observed in 5 patients and included neutropenia, rash, colitis, Guillain-Barré syndrome, and proteinuria. No grade 4 AEs and deaths related treatment were observed.

After KEYNOTE-028, phase II KEYNOTE-158 study (NCT02628067) is ongoing to investigate the antitumor activity of pembrolizumab in a larger multi-cohort of patients with advanced cervical cancer who were previously treated. In American Society of Clinical Oncology (ASCO) 2017 Annual Meeting, Schellens et al. [12] presented the promising preliminary results from KEYNOTE-158 including data of the first 47 patients who had been followed up for at least 18 weeks. Patients who received at least 1 prior treatment for cervical cancer were enrolled without first checking their tumor PD-L1 or other tumor biomarker expression. Patients were treated with pembrolizumab 200 mg every 3 weeks for 2 years or until progression. ORR was 17% (95% CI=8%–31%), and it was not associated tumor PD-L1 expression evaluated retrospectively by immunohistochemistry. Further, among the 15 patients who had at least 27 weeks of follow-up, ORR was estimated as 27% (95% CI=8%–55%). Research team concluded that pembrolizumab is also effective in patients with previously treated advanced cervical cancer and expected increased ORR with longer follow-up.

CORPUS CANCER

1. Tailored surveillance programs for gynecologic cancer related with Lynch syndrome (LS)

LS, or hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant genetic condition caused by germ-line mutations in the mismatch repair (MMR; *MSH2*, *MLH1*, *MSH6*, *PMS2*, or *EPCAM*) genes [13]. Because the mutations in these onco-protective genes eventually lead to neoplastic changes and tumorigenesis, its carriers are at high-risk of colorectal cancer, as well as other cancers including endometrial cancer (second most common), ovary, stomach, and small intestine. The international collaborative group on HNPCC defined the Amsterdam I and II criteria that are widely used to identify candidates for genetic testing which can make a diagnosis of LS [14].

Families meeting Amsterdam criteria should be counseled on colorectal and endometrial cancer risk, and those with certain genetic mutations could be offered tailored cancer surveillance programs, according to the results of 2 studies published in *JAMA Oncology*. Samadder et al. [15] calculated the standardized morbidity ratios (SMRs) of LS-related cancers in 202 families who met Amsterdam I and II criteria for LS. In this population-based study, 202 families with 443 (2.6%) of the cases were members of the families that fulfilled the Amsterdam criteria, among the 17,087 patients affected by colorectal cancer. First degree relatives of the Amsterdam criteria II pedigrees showed increased risks for colorectal (SMR=10.10; 95% CI=9.43–10.81), endometrial (SMR=5.89; 95% CI=5.09–6.78), stomach (SMR=2.90; 95% CI=2.02–4.03), and small intestine (SMR=7.72; 95% CI=5.17–11.08) cancer. Furthermore, second-degree relatives also had excess risk for colorectal (SMR=4.31; 95%

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CI=3.98–4.65) and endometrial (SMR=2.70; 95% CI=2.30–3.14) cancers. Similar elevated cancer risks were found for relatives of families meeting Amsterdam I criteria.

The second study is a retrospective cohort study of 1,063 individuals (495 men, 568 women) with LS germline mutations. Ryan et al. [16] suggested that certain mutated gene and mutation type could be associated with age at onset of LS-related cancers. The most commonly identified mutation was *MSH2* in study population, and endometrial cancers were diagnosed in 30% (83/279). The median onset age of endometrial cancer was 47 (32–72), 49 (17–71), and 53 (42–66) years for women with *MSH2*, *MLH1*, and *MSH6* mutations, respectively. In addition, women with truncating mutations (usually product incomplete and non-functional protein) on *MLH1* presented with endometrial cancer at 6.6 years later ages than those with non-truncating mutations, although it did not apply to *MSH2* and *MSH6* mutation carriers. Based on the results, authors recommended that gynecological surveillance should be focused from age 30 years for those with *MSH2* mutations, from age 35 years for those with non-truncating *MLH1* mutations, and from age 40 years for those with *MSH6* and truncating *MLH1* mutations with a rate threshold of 0.5% cancers per screen.

2. Sentinel lymph node (SLN) mapping acceptable in endometrial cancer

Since the late 1970s, SLN mapping has been developed for several solid malignancies to identify lymph node metastases with less surgical morbidity resulted from complete lymphadenectomy [17]. SLN mapping is already established as one of the standard staging procedures in breast cancer and melanoma [18-20]. Comparably, because of the complexity and bilaterality in 2 major routes of uterine lymphatic drainage, adapting its use in endometrial cancer is unsatisfactory until now. However, at last, it was revealed that SLN mapping have a high diagnostic accuracy in detecting nodal metastases and can safety replace complete lymphadenectomy in endometrial cancer staging.

Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) trial was designed for primary objective to estimate the sensitivity and negative predictive value of SLN mapping using robotic assisted fluorescence imaging the trace indocyanine green (ICG) in detecting nodal metastases in patients with endometrial cancer. In *Lancet Oncology*, Rossi et al. [21] reported the results of this FIRES trial with a sensitivity to detect nodal metastases of 97.2% (95% CI=85.0–100), and a negative predictive value of 99.6% (95% CI=97.9–100). Eligible patients of this trial were confirmed endometrial cancer by endometrial sampling and clinically suspected stage I disease with no physical examination findings or radiologic evidences for extrauterine disease, irrespective of histologic type or grade. A total of 340 women underwent SLN mapping with complete pelvic lymphadenectomy, and 196 (57.6%) of them also underwent para-aortic lymphadenectomy. In 293 (86.2%) patients who had successful mapping of at least one mapped SLN, nodal metastases were identified in the SLN in 35 (97.2%) of 36 patients who had positive nodes. Although FIRES trial did not present the oncological outcomes with the SLN mapping, surgeons should be relieved that SLN mapping can accurately stage endometrial cancer with overcoming the morbidity of complete lymphadenectomy.

A systematic review and meta-analysis of 55 studies including 4,915 women investigating the utility of SLN mapping for endometrial cancer staging was reported by Smith et al. [22] in *American Journal of Obstetrics & Gynecology*. Authors emerged that SLN mapping successfully identified nodal metastases in endometrial cancer with the pooled sensitivity which was relatively high at 96% (95% CI=92–98). In this study, the pooled overall SLN detection

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rates were relatively high at 81% (95% CI=77–84) with 51% (95% CI=45–54) bilateral nodal detection. Authors showed that histologic type, grade, average patient body mass index ≥30 kg/m^2 and surgical approach did not affect the detection rates. However, the use of cervical injection with combination blue dye and radiotracer or ICG dye alone increased the overall SLN detection rate than uterine injection (56% vs. 33%; p=0.003).

Although the accumulated evidences from SLN mapping studies in endometrial cancer seems to be promising, there are still many controversies. Among them, further consensus for the appropriate patient selection and optimal treatment algorithm to differentially manage high- and low-grade patients are importantly required by the SGO's Clinical Practice Committee and SLN Working Group [23]. Based on the current literature, SGO recommended the SLN mapping can appropriately stage endometrial cancer of low-risk histology as grade 1–2 endometrioid type, especially clinically uterine-confined disease. High-risk histology such as carcinosarcoma, serous papillary and clear cell carcinoma can be staged by SLN mapping with similar oncologic outcomes compared to low-risk histology in retrospective studies [24,25]. However, in these cases, intraoperative sampling for suspicious lesions is mightily important. In addition, they suggested that complete para-aortic lymphadenectomy should be additionally performed in consideration with individualized patient characteristics and tumor-based risk factors (depth of myometrial invasion, histologic type, and pelvic node status) at surgeon's discretion.

OVARIAN CANCER

1. Update on PARP inhibitors in 2017

PARP inhibitors are changing the course of disease in ovarian cancer patients. A phase II randomized trial as maintenance therapy for platinum-sensitive relapse [26] and a phase III trial in the same population [27] has demonstrated significant clinical benefit resulting in approval of olaparib and niraparib both by FDA and by European Medicines Agency (EMA). In 2017 results of 2 more phase III trials (ENGOT-Ov21/SOLO2 & ARIEL3) were reported confirming significant clinical benefit to these patients.

In ARIEL3, at total of 564 patients (196 *BRCA* mutant, 158 *BRCA* wild-type with high loss of heterozygosity [LOH] and 110 *BRCA* wild-type with low or intermediate LOH) with platinum-sensitive relapse who were responding to platinum-based therapy were 2:1 randomly assigned to receive maintenance therapy with oral rucaparib 600 mg twice daily or placebo [28]. Median PFS in the *BRCA* mutant group (130 [35%] in the rucaparib group vs. 66 [35%] in the placebo group) was 16.6 months (95% CI=13.4–22.9) in the rucaparib group vs. 5.4 months (3.4–6.7) in the placebo group (hazard ratio [HR]=0.23; 95% CI=0.16–0.34; p<0.001). In patients with high LOH carcinoma, i.e., both *BRCA* mutant and *BRCA* wild type with high LOH (236 [63%] in the rucaparib group vs. 118 [62%] in the placebo group), median PFS was 13.6 months (10.9–16.2) vs. 5.4 months (5.1–5.6; 0.32 [0.24–0.42]; p<0.001). Analysed data on the intention-to-treat population (n=564) demonstrated PFS 10.8 months (8.3–11.4) in the rucaparib group vs. 5.4 months in the placebo group (5.3–5.5; 0.36 [0.30–0.45]; p<0.001). Treatment-emergent adverse events of grade 3 or greater were reported in 209 (56%) patients in the rucaparib group and 28 (15%) in the placebo group, the most common of which were anaemia or decreased haemoglobin concentration and increase in alanine aminotransferase or aspartate aminotransferase concentration. Elevations in liver enzymes were generally transient, self-limiting, and not associated with other signs of liver toxicity. Results on secondary end-points including OS are pending.

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ENGOT-Ov21/SOLO2 study was a phase 3 confirmatory study to demonstrate efficacy of this drug as maintenance therapy in *BRCA* mutant population with platinum-sensitive relapse in patients who were in response to platinum-based therapy. Two hundred ninety-five patients with *BRCA1/2* mutation were enrolled and randomly assigned 2:1 to receive maintenance olaparib (196 patients) administrated as tablets (300 mg in 2 150 mg tablets, twice daily) and placebo (99 patients) [29]. Investigator-assessed median PFS was significantly longer in the olaparib group than in the placebo group (19.1 months [95% CI=16.3–25.7] with olaparib vs. 5.5 months [5.2–5.8] with placebo, HR=0.30; 95% CI=0.22–0.41; p<0.001). As for rucaparib, the most common grade 3 or worse adverse event was anaemia.

These 2 trials have confirmed findings from earlier reported randomized trials that PARP inhibitors provide a substantial clinical benefit to *BRCA* mutant patients. ARIEL3 trial also confirmed the findings of ENGOT-Ov16/NOVA trial that clinical benefit of PARP inhibitors is present in whole population of platinum-sensitive relapsed ovarian cancer patients who are responding to platinum-based therapy regardless of *BRCA* status and regardless of LOH/homologous recombination deficiency (HRD) status. Maintenance therapy with a PARP inhibitor in the recurrent setting provides the longest period without disease symptoms compared to no maintenance with manageable treatment related toxicities. We are changing course of disease of ovarian cancer patients.

Clinical research is now exploring the following major issues: 1) to find clinically predictive markers of response; 2) reasons for resistance to PARP inhibitor therapy; 3) if PARP inhibitors will be as beneficial in frontline therapy as in relapse setting; and 4) can we enhance efficacy of PARP inhibitors in combination with anti-angiogenic drugs and in combination with immunotherapy.

2. Prediction of the response to immunotherapy

There is a growing evidence of immune checkpoint inhibitors as treatment for patients with ovarian cancer. However, immune checkpoint inhibitors have demonstrated clinical response only in a small subpopulation of patients with ovarian cancer. Identification of predictive biomarkers is urgently needed to provide early indication of efficacy and warn of the development of AEs. Three major predictors for survival were identified so far, which include tumor infiltrating lymphocytes (TILs), PD-L1 expression and mutational burden [30,31]. Based on the study of melanoma, tumors have been classified into 4 groups based on the presence of TILs and PD-L1 expression: type I, adaptive immune resistance ($TIL^+/PD\text{-}L1^+$); type II, immunological ignorance ($TIL^-/PD\text{-}L1^-$); type III, intrinsic induction ($TIL^-/PD\text{-}L1^+$); type IV, tolerance ($TIL^+/PD\text{-}L1^-$) [32]. Webb et al. [33] suggested that immune responses to ovarian cancer could be different among histologic subtypes with high-grade serous ovarian cancers (HGSOCs) most likely associated with a favorable TIL response. They also showed that type I patterns were more common in HGSOCs.

In 2017, Ovarian Tumor Tissue Analysis Consortium published a large-scale multicenter observational, prospective survival cohort study in more than 5,500 ovarian cancer patients in *JAMA Oncology* to evaluate histotype-specific survival associations with $CD8^+$ TILs in epithelial ovarian cancer [34]. Following immunohistochemical analysis, $CD8^+$ TILs only within the epithelial components of tumor islets, but not those in the stroma or abutting tumor cells, were counted. Based on the estimated number of $CD8^+$ TILs/high powered field (HPF), patients were grouped into 4 from negative (none) to low (1–2) to moderate (3–19) and to high (≥20). They showed that HGSOCs were most infiltrative and $CD8^+$ TILs in HGSOCs were significantly

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associated with longer OS (median OS, 2.8, 3.0, 3.8, and 5.1 years for patients with negative, low, moderate, and high levels of $CD8^+$ TILs, respectively; p for trend=4.2×10^{-16}). This nearly log-linear relationship was observed regardless of extent of residual disease, receipt of standard treatment, and germline *BRCA1* mutation. Among the other 4 major histotypes of ovarian cancer including endometrioid, mucinous, clear cell, and low-grade serous cancers, the significant associations between CD8+ TILs and OS were present in women with endometrioid and mucinous cancers (p for trends=0.008 and 0.040, respectively).

This is the largest study on intraepithelial $CD8^+$ TILs in ovarian cancer to date, which showed a robust dose-response relationship between $CD8^+$ TILs and OS in patients with HGSOC. It is essential to predict the response to immunotherapy. For the clinical standpoint, this study suggests that certain immunotherapy should be indicated in the HGSOC patients with high immune infiltration of $CD8^+$ TILs.

3. Update on conventional treatment methods

We herein summarized outstanding practice-changeable updates, first 2 of which were on surgery and the other 3 were about medical treatment including targeted therapy.

Current surgical treatment guidelines of advanced ovarian cancer include bilateral pelvic and para-aortic lymph node dissection [35]. Results of a large randomized trial, the Lymphadenectomy in Ovarian Neoplasms (LION) study, which did not support the current guidelines, were presented at ASCO 2017 Annual Meeting [36]. The conclusion of LION study was that patients with advanced ovarian cancer with clinically negative lymph node who undergo a complete resection need not also undergo systematic lymphadenectomy because it has no effect on PFS or OS. A total of 647 patients were randomly assigned to lymphadenectomy (n=323) or no-lymphadenectomy group (n=324). Between the 2 groups, similar proportions of each group went on to receive platinum and taxane based chemotherapy following surgery. OS and PFS of the 2 groups were not different (median OS, 66 vs. 69 months; HR=1.06; 95% CI=0.83–1.34; p=0.650 and median PFS, 26 months for both, HR=1.11; 95% CI=0.92–1.34; p=0.300). Operation time was longer in lymphadenectomy group (340 vs. 288 minutes; p<0.001), and resultantly blood loss (650 vs. 500 mL; p<0.001) and transfusion rate (63.7% vs. 56.0%; p=0.005) were higher in lymphadenectomy group than those in no-lymphadenectomy group. In line with that, serious post-operative complications, including reoperation for complications, infections, and mortality within 60 days of surgery, also occurred more frequently in lymphadenectomy group than those in no-lymphadenectomy group. Therefore, the investigators indicated that lymphadenectomy can be safely omitted because it did not improve survival outcomes even if 56% of the patients had occult nodal disease.

Another update in 2017 is the role of secondary cytoreductive surgery in recurrent ovarian cancer. A phase III randomized trial of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) The Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent ovarian cancer (DESKTOP) III/ENGOTOv20 was conducted to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer. The interim analysis was presented at the ASCO 2017 Annual Meeting and 2017 European Society of Gynaecological Oncology (ESGO) Congress in Vienna, Austria [37]. A total of 407 patients with ovarian cancer first relapsed after more than 6 months platinum-free interval (PFI) and positive AGO-score, which was defined as performance status 0, ascites ≤500 mL, and complete resection at initial surgery, were randomized to second line chemotherapy alone vs. cytoreductive surgery followed by chemotherapy. PFS was longer in surgery arm than no-surgery arm

(median PFS, 19.6 vs. 14 months; HR=0.66; 95% CI=0.52–0.83; p<0.001). The median time to start of the first subsequent therapy (TFST) was 21 vs. 13.9 months, respectively (HR=0.61; 95% CI=0.48–0.747; p<0.001). OS data were expected in 2019. Complete resection rate was 72.5%. Sixty-day mortality rates were 0% and 0.5% in the surgery and no-surgery arm, respectively. There was no significant difference of grade 3 or higher acute adverse events between the 2 groups. Even though we have to wait for the OS data, the investigators were so excited to offer secondary surgery in platinum-sensitive recurrent ovarian cancer in combination with chemotherapy as a viable option.

International Collaborative Ovarian Neoplasm (ICON)-8 trial reaffirmed standard 3-week dosing schedule for paclitaxel rather than boosting up to a weekly dose-dense regimen, which was presented at the European Society for Medical Oncology (ESMO) 2017 Congress in Madrid, Spain [38]. A total of 1,566 women with stage IC grade 3 to IV epithelial ovarian cancer were randomized 1:1:1 to arm1 (standard, triweekly paclitaxel 175 mg/m^2 plus carboplatin area under the curve [AUC] 5–6), arm2 (weekly paclitaxel 80 mg/m^2 plus triweekly carboplatin AUC 5–6), or arm3 (weekly paclitaxel 80 mg/m^2 plus carboplatin AUC 2). Among them, 48% underwent primary debulking surgery and 50% had interval debulking surgery after neoadjuvant chemotherapy. Grade 3 or higher toxicity was observed in 42%, 63%, and 53% in each groups. At the time point of when 64% patients experienced disease progression as of February 2017, restricted mean PFS was 24.4, 24.9, and 25.3 months in arm1, 2, and 3, respectively. Therefore, ICON-8 indicated that weekly dose-dense paclitaxel as part of the first-line treatment of ovarian cancer did not extend PFS in this population, although well-tolerated. Obviously, these results of ICON-8 were contrasting to those of Japanese Gynecologic Oncology Group (JGOG)-3016. Because both studies were robust and appropriately powered, investigators thought that the different results seen were possibly due to the pharmacogenomics differences between Caucasian and Japanese ethnic groups. Triweekly carboplatin-paclitaxel was recommended to remain unmodified as a standard first-line regimen in ovarian cancer at least in the Caucasian women.

Next update on medical treatment of ovarian cancer is trying non-platinum chemotherapy to prolong the PFI. The extension of PFI by introducing non-platinum agents was hypothesized as a strategy to increase the platinum sensitivity, thus improving the outcome of partially sensitive disease [39]. The Multicenter Italian Trials in Ovarian Cancer (MITO)-8 conducted a prospective randomized phase III trial to verify this hypothesis, so called, the efficacy of PFI prolongation in advanced ovarian cancer [40]. A total of 215 patients with ovarian cancer who experienced disease progression 6 to 12 months after their last platinum-based chemotherapy were 1:1 randomized to the standard arm (n=108, platinum-based chemotherapy followed by non-platinum based chemotherapy at subsequent relapse) or the experimental arm (n=107, non-platinum based chemotherapy followed by platinum-based chemotherapy at subsequent relapse). There was no OS difference between the 2 arms (median OS, 21.8 vs. 24.5 months; HR=1.38; 95% CI=0.99–1.964; p=0.06). PFS was even significantly shorter in the experimental arm than standard arm (median PFS, 12.8 vs. 16.4 months; HR=1.41; 95% CI=1.04–1.92; p=0.025). Although MITO-8 closed before the planned number of events, the study group concluded that platinum-based chemotherapy should not be delayed in this population of partially sensitive recurrent ovarian cancer because there was nothing to be gained by using a non-platinum first.

The last item in this section in terms of remarkable updates in ovarian cancer treatments was the effect of adding bevacizumab to standard platinum-based chemotherapy in women with

platinum-sensitive recurrent ovarian cancer. A phase III randomized trial (NRG Oncology/Gynecologic Oncology Group [GOG]-213) reported a clinically significant OS improvement in *Lancet Oncology* [41]. A total of 674 women with recurrent platinum-sensitive ovarian cancer were randomly assigned to standard chemotherapy (n=337, 6 cycles of triweekly paclitaxel 175 mg/m^2 and carboplatin AUC 5) or the same chemotherapy regimen plus bevacizumab 15 mg/kg every 3 weeks and continued as maintenance q 3 weeks until disease progression or unacceptable toxicity (n=377). Researchers performed sensitivity analysis of OS and found that bevacizumab added to paclitaxel and carboplatin might favorably affect OS in this population (median OS, 42.2 vs. 37.3 months; adjusted HR=0.823; 95% CI=0.680–0.996; p=0.045). PFS was significantly longer in the bevacizumab group vs. chemotherapy alone group (median PFS, 13.8 vs. 1.4 months; HR=0.63; 95% CI=0.53–0.74; p<0.001). Furthermore, bevacizumab was associated with greater objective response rate compared with chemotherapy alone (78% vs. 59%) and higher CR rate (32% vs. 18%). Despite 9 (3%) treatment-related deaths in the bevacizumab group compared with 2 (1%) in the chemotherapy alone group, any new safety signals nor toxicity that significantly increased treatment discontinuation was not observed. Thus, the addition of bevacizumab to standard chemotherapy and followed by maintenance therapy until progression might be an important therapeutic strategy which resulted in clinically meaningful OS improvement of median 5 months in the patients with platinum-sensitive recurrent ovarian cancer.

SCREENING OF GYNECOLOGIC CANCER: PERIODIC PELVIC EXAMINATION

The pelvic examination can be an important screening and diagnostic tool of gynecologic malignancy. In particular, there is a universal consensus as well as robust evidence on the periodic Pap test, which is often done in conjunction with a pelvic examination, is highly effective in screening for cervical cancer. However, there was a conflicting medical advice regarding periodic pelvic examination in asymptomatic women: pros of the American College of Obstetricians and Gynecologists (ACOG) for yearly pelvic exam [42] and cons of the American College of Physicians (ACP) against it [43].

In 2017, the US Preventive Services Task Force (USPSTF) released a statement about the use of pelvic exams in primary care, "the current evidence is insufficient to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic, non-pregnant adult women" [44] after a systematic review of available clinical evidence [45]. In this review, there was no trials examined the effectiveness of the pelvic examination in reducing all-cause mortality and reducing cancer. In the 4 studies which reported accuracy for the screening pelvic examination for ovarian cancer, low positive predictive values and false positive rates with a lack of precision in accuracy estimates were consistently found because of low prevalence of ovarian cancer. Thus, they concluded that there was no direct evidence supporting overall benefits and harms of the pelvic examination as a 1-time or periodic screening test.

Following the statement of the USPSTF, SGO released a position statement concerning that the statement of the USPSTF would be easily misinterpreted as a recommendation against pelvic examinations with the result being a deficiency in care provided to women [46]. The SGO recommended that providers continue to offer pelvic exams to every patient presenting for a well-woman examination even if there is no clinical data showing a clear reduction in

morbidity or mortality at a population level, because offering a pelvic exam to every woman could serve as an opportunity for patient to discuss the benefits and risks, and to make an informed decision whether to undergo a pelvic exam. In terms of the informed decision, Sawaya et al. [47] reported the effect of professional societies' conflicting recommendations about pelvic examinations on women's desire for a routine examination. A total of 190 women were randomly assigned to review the summary of one of the 2 medical groups' recommendations: ACOG and ACP, followed by an interview. Women in the ACP group were less likely to indicate they would opt for an examination compared with those in the ACOG group (39% vs. 82%). The vast majority of women in the study (94%) said that potential benefits and harms should routinely be discussed with patients prior to the examination. The authors concluded that there is a pressing need for improving patient counselling concerning yearly pelvic examination.

UPDATE ON RADIATION THERAPY (RT)

Results of the 2 big trials of RT in endometrial cancer were presented at the ASCO 2017 Annual Meeting in Chicago, USA: The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC)-3 [48] and GOG-258 [49].

After quality of life data which were released in 2016 [50], final results of the PORTEC-3 trial of adjuvant chemotherapy and RT vs. RT alone for women with high-risk endometrial cancer were presented this year [48]. A total of 660 women who met the inclusion criteria were randomly assigned to RT (n=330, 48.6 Gy in 1.8 Gy fractions) or adjuvant chemotherapy during and after radiotherapy (CTRT) (n=330, 2 cycles of cisplatin 50 mg/m^2 in week 1 and 4 of RT, followed by 4 cycles of triweekly carboplatin AUC 5 and paclitaxel 175 mg/m^2). Primary endpoints were OS and failure-free survival (FFS). CTRT failed to show significant 5-year FFS (75.5% vs. 68.9%; HR=0.77; 95% CI=0.58–1.03; p=0.078) or OS (81.8% vs. 76.7%; HR=0.79; 95% CI=0.57–1.12; p=0.183) benefits compared with RT alone. Of note, however, there was a significant FFS improvement with CTRT compared with RT alone in stage III patients by 11% at 5 years (5-year FFS, 69.3% vs. 58.0%; HR=0.66; 95% CI=0.45–0.97; p=0.032). Five-year OS in stage III patients was 79% vs. 70% (HR=0.69), indicating only the difference in FFS reached statistical significance. In PORTEC-3, study population included women with high-risk endometrial cancer which were International Federation of Gynecology and Obstetrics (FIGO) stage I grade 3 with deep myometrial invasion and/or lymphovascular space invasion; stage II or III; or serous/clear cell histology. Based on the study results, CTRT cannot be recommended as standard adjuvant treatment for patients with stage I and II high-risk endometrial cancer. Even for those with stage III patients, longer follow-up of OS data may be needed to evaluate the impact of CTRT. Of questions raised about PORTEC-3 was that stage I and II early stage cancer should be studied separately from stage III advanced stage cancer.

GOG-258 was a randomized phase III trial of cisplatin and tumor volume-directed RT followed by carboplatin and paclitaxel for 4 cycles (C-RT) vs. carboplatin and paclitaxel for 6 cycles (CTX) in patients with optimally debulked, advanced stage III–IVA endometrial cancer (<2 cm residual disease) [49]. A total of 813 were randomized to C-RT arm (n=407) or CTX arm (n=406), and finally the trial interventions were given to 333 in C-RT arm and 347 in CTX arm. During median follow-up of 47 months, C-RT regimen did not improve recurrence-free survival (RFS) compared to CTX alone (HR=0.9; 95% CI=0.74–1.10) even

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though C-RT reduced the incidence of vaginal (3% vs. 7%; HR=0.36; 95% CI=0.16–0.82) and pelvic/paraaortic (10% vs. 21%; HR=0.43; 95% CI=0.28–0.66) recurrence. Distant metastasis, however, were more common with C-RT vs. CTX alone (27% vs. 21%; HR=1.36; 95% CI=1.00–1.86). OS data were not yet mature for final analysis. The key message from GOG-258 was RT has a strong effect on preventing loco-regional recurrence, especially on both paraaortic and pelvic areas.

The last update in the field of RT is about high-dose-rate (HDR) brachytherapy in cervical cancer. Results of a prospective, multicenter study of the efficacy of HDR brachytherapy with different doses were presented at the American Society for Radiation Oncology (ASTRO) Annual Meeting [51]. A total of 601 patients with stage IIB or IIIB cervical cancer received 46 Gy of curative-intent pelvic external beam RT in 23 fractions, and then, they were randomly assigned to HDR brachytherapy with or without chemotherapy in one of 4 arms: arm1, 4 fractions of 7 Gy; arm2, 2 fractions of 9 Gy; arm3, 4 fractions of 7 Gy plus 40 mg/m^2 cisplatin weeks 1 through 5; arm4, 2 fractions of 9 Gy plus 40 mg/m^2 cisplatin weeks 1 through 5. Even if researchers failed to show significant different 5-year OS among the arms, however, significantly more patients achieved 5-year tumor control in arms1 (88%; 95% CI=81–92) and 3 (89%; 95% CI=82–94), both of which were the arms assigned fractions of 7 Gy radiation, than arms2 (78%; 95% CI=71–84) and 4 (75%; 95% CI=67–82; p<0.001). A subgroup analysis of combined the 2-fraction arms (arm1 and 3) and the 4-fraction arms (arm2 and 4) showed that the locoregional control benefit with the 4-fraction schedule became even more evident (88% vs. 77%; p<0.001). The results indicated that there was an 11% reduction in local failure with the 4-fraction schedule without difference in the grade 3 or greater toxicity.

BREAST CANCER

1. Adjuvant capecitabine for breast cancer after preoperative chemotherapy

Neoadjuvant chemotherapy is a common approach for patients with operable or inoperable breast cancers, and achieving pathologic complete response (pCR) is associated with good prognosis after definitive surgery. But the rate of pCR ranges from 13% to 22% among patients with human epidermal growth factor receptor 2 (HER2)-negative primary breast cancer. No adjuvant chemotherapy has been established for patients who have residual invasive breast cancer after the receipt of neoadjuvant chemotherapy.

CREATE-X trial enrolled and randomly assigned 910 patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy to receive standard postsurgical treatment (mainly endocrine treatment and radiotherapy) either with capecitabine or without (control) [52]. Disease-free survival, which was the primary endpoint, was longer in the capecitabine group than in the control group (74.1% vs. 67.6% at 5 years; HR=0.70; p=0.01). OS was longer in the capecitabine group than in the control group (89.2% vs. 83.6% at 5 years; HR=0.59; p=0.01). The difference was more dramatic in patients with triple-negative breast cancer in both disease-free survival (69.8% vs. 56.1%; HR=0.58) and OS (78.8% vs. 70.3%; HR=0.52).

This is the first study to demonstrate the role of adjuvant chemotherapy for patients without pCR after neoadjuvant chemotherapy, and could be applied mainly for triple-negative breast cancer with large residual breast cancer burden.

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2. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer

Pertuzumab is a humanized monoclonal antibody that has mechanisms of action complementary to those of trastuzumab, binding to the dimerization domain and inhibiting HER2 heterodimerization with other HER family receptors. Pertuzumab added to trastuzumab and docetaxel has already shown efficacy in HER2-positive metastatic breast cancer, and also as a part of neoadjuvant regimens. In the APHINITY trial, the role of pertuzumab when added to adjuvant trastuzumab and chemotherapy was investigated.

It was a large study, involving 549 centers across 43 countries, randomizing 4,805 patients into chemotherapy and trastuzumab plus either pertuzumab (2,400 patients) or placebo (2,405 patients) [53]. About two-thirds (63%) of the patients had node-positive disease and 36% had hormone-receptor-negative disease. Disease recurrence occurred in 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group (HR=0.81; p=0.045). The estimates of the 3-year rates of invasive-disease-free survival were 94.1% in the pertuzumab group and 93.2% in the placebo group. In patients with node-positive disease, the 3-year rate of invasive-disease-free survival was 92.0% vs. 90.2% (HR=0.77; p=0.02). Heart failure, cardiac death, and cardiac dysfunction were infrequent in both treatment groups. But diarrhea was more frequent with pertuzumab (9.8% vs. 3.7%) during chemotherapy.

This is a large study demonstrating the benefit of pertuzumab in the adjuvant setting, but the small magnitude of benefit in the overall population should be considered to take into consideration, before applying in daily clinical practice.

3. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation

Olaparib is a PARP inhibitor already approved for the treatment of ovarian cancer, and it has promising antitumor activity in patients with metastatic breast cancer and a germline *BRCA* mutation. In the OLYMPIAD trial, olaparib was compared with standard therapy in patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer [54].

Patients who had received no more than 2 previous chemotherapy regimens for metastatic disease was enrolled and were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles). Of the 302 patients, 205 were assigned to receive olaparib and 97 were assigned to receive standard therapy. Median PFS (7.0 vs. 4.2 months; HR=0.58; p<0.001) and the response rate (59.9% vs. 28.8%) were significantly better in the olaparib group. The rate of grade 3 or higher adverse events was lower in the olaparib group (36.6% vs. 50.5%).

This is the first to show the role of PARP inhibitors in a phase 3 trial. Also, talazoparib, another PARP inhibitor, demonstrated efficacy in similar patient group with metastatic breast cancer in a phase III trial (Litton J, Rugo HS, Ettl J, Hurvitz S, Gonçalves A, Lee KH, et al. A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA* mutation. Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX. Philadelphia, PA: American Association for Cancer Research, Abstract GS6-07) [55].

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4. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years

Some patients with breast cancer experience late recurrence even 10 or more years after surgery, and extending the administration of endocrine therapy beyond 5 years, which was the standard duration, offers further protection but has additional side effects. This meta-analysis combined individual patient data from 88 trials in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) database of randomized trials, and investigated the absolute risk of subsequent distant recurrence if therapy stops at 5 years [56].

Breast cancer recurrences occurred at a steady rate throughout the study period from 5 to 20 years. Among the patients with stage T1 disease, the risk of distant recurrence was 13% with no nodal involvement (T1N0), 20% with one to 3 nodes involved (T1N1–3), and 34% with 4 to 9 nodes involved (T1N4–9); among those with stage T2 disease, the risks were 19% with T2N0, 26% with T2N1–3, and 41% with T2N4–9. Given the TN status, the factors of tumor grade and Ki-67 status were of only moderate independent predictive value for distant recurrence, but the progesterone receptor and HER2 was not predictive. The absolute risk of distant recurrence among patients with T1N0 breast cancer was 10% for low-grade disease, 13% for moderate-grade disease, and 17% for high-grade disease.

After 5 years of adjuvant endocrine therapy, breast cancer recurrences continued to occur steadily and the risk of distant recurrence is not negligible even with tumors with low stage. Extending endocrine therapy beyond 5 years could be guided with this information in a very large population.

5. Contemporary hormonal contraception and the risk of breast cancer

Hormonal contraception is frequently used, but little is known about its impact on the risk of breast cancer. Nationwide registries of Denmark were used for information about the use of hormonal contraception, breast cancer diagnoses, and potential confounders [57].

Among 1.8 million women who were followed on average for 10.9 years (a total of 19.6 million person-years), 11,517 cases of breast cancer occurred. The relative risk of breast cancer among all current and recent users of hormonal contraception was 1.20. After discontinuation of hormonal contraception, the risk of breast cancer was still higher among the women who had used hormonal contraceptives for 5 years or more than among women who had not used hormonal contraceptives. Women who currently or recently used the progestin-only intrauterine system also had a higher risk of breast cancer with relative risk of 1.21. The overall absolute increase in breast cancers diagnosed among current and recent users of any hormonal contraceptive was 13 per 100,000 person-years, or approximately 1 extra breast cancer for every 7,690 women using hormonal contraception for 1 year.

The risk of breast cancer was higher among women who currently or recently used contemporary hormonal contraceptives but absolute increases in risk were small.

CONCLUSION

We, gynecologic oncology, stand at the beginning stage of the era of molecular targeted therapy. Thousands of candidate molecules are on the waiting list for real practice changers

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which are capable of improving survival outcomes of gynecologic cancer patients. Further progress of pioneer researches is expected.

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