

Review Article



Major clinical research advances in gynecologic cancer in 2016: 10-year special edition

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ABSTRACT

In 2016, 13 topics were selected as major research advances in gynecologic oncology. For ovarian cancer, study results supporting previous ones regarding surgical preventive strategies were reported. There were several targeted agents that showed comparable responses in phase III trials, including niraparib, cediranib, and nintedanib. On the contrary to our expectations, dose-dense weekly chemotherapy regimen failed to prove superior survival outcomes compared with conventional triweekly regimen. Single-agent non-platinum treatment to prolong platinum-free-interval in patients with recurrent, partially platinum-sensitive ovarian cancer did not improve and even worsened overall survival (OS). For cervical cancer, we reviewed robust evidences of larger-scaled population-based study and cost-effectiveness of nonavalent vaccine for expanding human papillomavirus (HPV) vaccine coverage. Standard of care treatment of locally advanced cervical cancer (LACC) was briefly reviewed. For uterine corpus cancer, new findings about appropriate surgical wait time from diagnosis to surgery were reported. Advantages of minimally invasive surgery over conventional laparotomy were reconfirmed. There were 5 new gene regions that increase the risk of developing endometrial cancer. Regarding radiation therapy, Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC)-3 quality of life (QOL) data were released and higher local control rate of image-guided adaptive brachytherapy was reported in LACC. In addition, 4 general oncology topics followed: chemotherapy at the end-of-life, immunotherapy with reengineering T-cells, actualization of precision medicine, and artificial intelligence (AI) to make personalized cancer therapy real. For breast cancer, adaptively randomized trials, extending aromatase inhibitor therapy, and ribociclib and palbociclib were introduced.

Keywords: Precision Medicine; Artificial Intelligence; Genital Neoplasms, Female; Ovarian Neoplasms; Breast Neoplasms

INTRODUCTION

This series of review of “major clinical research advances in gynecologic cancer” has been published since 2007 for the last 10 years. Of the 10-year topics addressed in this series of review (**Table 1**), we tried to choose, so called, ‘Top 10 practice changers’ that had a great impact on the current practice: 1) human papillomavirus (HPV) vaccines for the prevention

Major clinical research advances in gynecologic cancer
Table 1. Ten-year topics reviewed in major clinical research advances in gynecologic cancer in *Journal of Gynecologic Oncology*

Study year	Cervix	Uterine corpus	Ovary	Breast and others
2007 [1]	HPV vaccine; IMRT; MIS	Adjuvant RT in IR; adjuvant CCRT in high-risk; hormone therapy for FP	Ovarian cancer symptom index; screening; VEGF-targeted therapy	-
2008 [2]	HPV vaccine; role of imaging during therapy; fertility-sparing surgery	Adjuvant RT in IR cancer; extent of LND; robot surgery in EMCA; CTX in LMS	Adjuvant CTX; NAC in advanced disease; surgery for ROC; new biomarkers; screening and treatment in <i>BRCAM</i>	-
2009 [3]	HPV-based screening; HPV vaccine; CCRT with GP; pazopanib	Systematic LND	Treatment timing of ROC; DD-CTX; CTX in PS-ROC; targeted agents	-
2010 [4]	Detection and prevention of HPV	Laparoscopy in staging operation; PORTEC-2; extensive LND; CTX in carcinosarcoma	Bevacizumab; CTX in ROC; NAC; screening by dual tests; origin of high-grade serous ovarian cancer	-
2011 [5]	HPV vaccine; HPV-based screening; treatment of LACC	Sentinel LN mapping	TCGA report; bevacizumab; PARPi; RRSO; ROMA	Prevention and treatment strategies; CTX-induced early menopause
2012 [6]	HPV test; paclitaxel/carboplatin vs. paclitaxel/cisplatin in stage IVB disease; 3D image-based high-dose rate brachytherapy	Targeted agents (mTORi, bevacizumab); sandwiched RT for UPSC; preoperative prediction of LN metastasis; Tx of low risk group; survival outcomes of laparoscopy	Bevacizumab; PARPi; erlotinib; patupilone; AMG386; genomic mutations (<i>BRCA</i> , <i>DICER1</i> , <i>PIK3CA</i>)	Update of practice guidelines; new promising therapeutic strategies against HER2- or hormone receptor-positive advanced breast cancer
2013 [7]	GOG240; screening; laparoscopic PALND before CCRT in LACC	Metformin; reclassification according to genomic features of TCGA	DD-paclitaxel/carboplatin; IP CTX; NAC update; targeted agents (bevacizumab, cediranib, farletuzumab)	IMRT; tamoxifen for 10 years; 1-year adjuvant trastuzumab; approval of pertuzumab in NAC setting with a pathologic CR as surrogate endpoint
2014 [8]	GOG240; CIRCCa trial; HPV-TIL; Z-100; Cobas HPV test; HPV-based screening; self-collection	GOG249; ASTRO guidelines; uterine power morcellation	Olaparib; cediranib and olaparib; pazopanib maintenance; opportunistic BS	Adjuvant ovarian suppression; adjuvant exemestane with ovarian suppression in premenopausal women
2015 [9]	HPV vaccine; 2 dose, nonavalent, therapeutic vaccine	HRT and EMCA risk; trabectedin for LMS; Lynch syndrome; ESMO-ESGO-ESTRO guidelines for RT	Prevention and screening; NAC; personalized therapy; 5th OCCC; immunotherapy	Adjuvant Tx in vulvar cancer; targeted therapy; palbociclib; oncotype Dx; nodal RT; cavity shave margins
2016 (present study)	HPV vaccine; standard of care treatment for LACC	MIS; surgical wait time; genetic risk	Prevention; Tx of partially PS-ROC; DD weekly paclitaxel/carboplatin; NAC; JGOG3014; niraparib; cediranib; nintedanib	CTX at End-of-Life; immunotherapy; precision medicine; AI; adaptive trials (neratinib, veliparib-carboplatin); letrozole for 10 years; MammaPrint; ribociclib, palbociclib, and letrozole

AI, artificial intelligence; ASTRO, American Society for Radiation Oncology; BRCAM, BRCA mutation; BS, bilateral salpingectomy; CCRT, concurrent chemoradiation therapy; CIRCCa, cediranib in recurrent cervical cancer; CR, complete response; CTX, chemotherapy; DD, dose dense; EMCA, endometrial cancer; ESGO, European Society of Gynecologic Oncology; ESMO, European Society for Medical Oncology; ESTRO, European Society for Radiotherapy and Oncology; FP, fertility preservation; GOG, Gynecologic Oncology Group; GP, gemcitabine cisplatin; HPV, human papillomavirus; HRT, hormone replacement therapy; IMRT, intensity-modulated radiation therapy; IP, intraperitoneal; IR, intermediate risk; JGOG, Japanese Gynecologic Oncology Group; LACC, locally advanced cervical cancer; LMS, leiomyosarcoma; LND, lymph node dissection; MIS, minimally invasive surgery; mTORi, mechanistic target of rapamycin inhibitor; NAC, neoadjuvant chemotherapy; OCCC, ovarian cancer consensus conference; PALND, para-aortic lymph node dissection; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PORTEC, Post-Operative Radiation Therapy in Endometrial Cancer; PS, platinum sensitive; ROC, recurrent ovarian cancer; ROMA, risk of ovarian malignancy algorithm; RRSO, risk reducing salpingo-oophorectomy; RT, radiation therapy; TCGA, The Cancer Genome Atlas; TIL, tumor infiltrating lymphocyte; UPSC, uterine papillary serous cancer; VEGF, vascular endothelial growth factor.

Author Contributions

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

of cervical cancer; 2) HPV-based cervical cancer screening; 3) incorporation of bevacizumab into combination chemotherapy in recurrent, persistent, or metastatic cervical cancer; 4) omission of lymphadenectomy or use of sentinel lymph node (LN) mapping in low-risk endometrial cancer; 5) risk-reducing salpingo-oophorectomy (RRSO) in high-risk population and opportunistic salpingectomy in general population for the prevention of ovarian cancer; 6) poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor in platinum-sensitive recurrent ovarian cancer; 7) bevacizumab in epithelial ovarian cancer both at primary and recurrent settings irrespective of platinum sensitivity; 8) more frequent application of neoadjuvant chemotherapy (NAC) in advanced stage ovarian cancer; 9) pertuzumab in NAC setting with a pathologic complete response (CR) as a surrogate endpoint in breast cancer; and 10) palbociclib and oncotype Dx in breast cancer.

In 2016, there were several study results that confirmed the previous ones including 10-year topics with higher level of evidence, whereas others reported results contrary to our expectations. We began to incorporate cutting edge fields of oncology in this review, for

example, precision medicine and artificial intelligence (AI), even though, unfortunately, there was not much achievement in gynecologic oncology for now.

OVARIAN CANCER

1. Surgical prevention and risk factors of ovarian cancer

Until now, there is no effective preventive method for ovarian cancer adopted in general population. Interventions that reduce ovarian cancer risk are particularly important given the limited screening options and high mortality rates that have not changed significantly over the past several decades.

Since the incorporation of opportunistic salpingectomy into the preventive recommendations of ovarian cancer in average risk population by the Society of Gynecologic Oncology (SGO) [3,9], supporting evidence of a large, community-based health system was published in 2016. A retrospective cohort study of a total of 12,143 benign hysterectomy cases over the 3 years from 2011 to 2014 reported a significant rise in rate of concomitant salpingectomy from 2011–2012 (14.7%; 95% confidence interval [CI]=13.3%–16.1%) to 2013–2014 (44.6%; 95% CI=42.6%–46.5%) ($p<0.001$) [10]. Meanwhile, there was no clinical difference in operating time, length of stay, or blood loss between hysterectomy alone and hysterectomy with salpingectomy. A survey regarding the most important barrier to performing salpingectomy was answered by 249 out of 543 physicians (response rate 46%). Two most common responses were no barriers (54%) and difficulty in accessing the tube (36%). Although the real preventive effect was to be determined, the authors showed that it was feasible to incorporate opportunistic salpingectomy into gynecologic practice at a large scale without any other surgical repercussions.

Hartmann and Lindor [11] published an in-depth review on the role of risk-reducing surgery in hereditary breast and ovarian cancer syndrome in *The New England Journal of Medicine*. In this review, they addressed issues related to the care of women in families with hereditary breast and ovarian cancer syndrome who have not had cancer including optimal risk assessment for breast and ovarian cancers, the efficacy of risk-reducing surgery and side effects of these procedures. Among *BRCA1* and *BRCA2* mutation carriers, the average cumulative risk of ovarian cancer by 80 years of age was 45% and 12%, respectively. There are multiple factors that influence on the likelihood of the development of breast or ovarian cancer in *BRCA1* or *BRCA2* mutation carriers, for example, positive family history and age. The observed risk of breast or ovarian cancer is higher among carriers with a positive family history than among those without family history. An affected 30-year-old *BRCA2* carrier has a 12.2% cumulative risk of ovarian cancer developing by 80 years of age. By contrast, an unaffected 60-year-old *BRCA2* carrier has a 3.9% cumulative risk of ovarian cancer developing by that age. There were accumulating evidence showing that RRSO involved a significant ovarian cancer risk reduction by 80%–90% among *BRCA1* and *BRCA2* carriers [12–19], for whom, therefore, between the ages of 35 and 40 years who have completed their childbearing current guidelines recommend RRSO [20]. A multicenter prospective cohort study of 2,482 *BRCA1* and *BRCA2* carriers showed that RRSO group, compared with non-RRSO group, had lower all-cause mortality (hazard ratio [HR]=0.40; 95% CI=0.26–0.61) and ovarian cancer-specific mortality (HR=0.21; 95% CI=0.06–0.80). Despite the sparsity of long-term follow-up data regarding the side effects of premature menopause caused by RRSO in *BRCA1* and *BRCA2* carriers, approximately 80% and 95% of those who had undergone RRSO showed significantly reduced cancer-related worry and satisfaction with their decision to undergo surgery [21].

So far, concomitant hysterectomy with RRSO was not thought to be justified for cancer prevention but could just simplify tamoxifen therapy for reduction of the risk of breast cancer, because tamoxifen is associated with an increased risk of endometrial cancer [11]. A multicenter prospective cohort study, which was published in *JAMA Oncology*, demonstrated the risk for uterine cancer and distribution of specific histologic subtypes in *BRCA* mutation carriers after RRSO without hysterectomy [22]. During a median 5.1 years (interquartile [IQR]=3.0–8.4 years) follow-up of 1,083 women with *BRCA1* or *BRCA2* mutation who underwent RRSO without a prior or concomitant hysterectomy, 8 incident uterine cancers including 5 serous and/or serous-like endometrial carcinomas were observed 7.2 to 12.9 years after RRSO (*BRCA1*: 0.18 expected [observed to expected ratio 22.2; 95% CI=6.1–56.9; $p < 0.001$]). This study suggested that the *BRCA1* mutation was linked to an increased risk of uterine serous carcinoma. This risk should be considered when discussing hysterectomy at the time of RRSO in *BRCA1* mutation carriers although more studies are needed to determine how beneficial it would be for them.

Aside from the strongest risk factors for ovarian cancer such as age, family history, and germline mutations of *BRCA1* and *BRCA2*, there is a central hypothesis supported by many epidemiologic studies: chronic lifetime ovulation increases ovarian cancer risk. However, a 50-year prospective cohort study of 15,528 mothers in the Child Health and Development Studies cohort reported a contradictory findings [23]. Out of all those women, only 116 cases were identified over the next 50 years. Contrary to expectation, however, women with irregular periods at age 26 had double the risk of ovarian cancer by age 70 (95% CI=1.1–3.4) and triple the risk by age 77 (95% CI=1.5–6.7). This study may have a clinical value in discovering high-risk traits like irregular menstruation, which is commonly observed in polycystic ovarian syndrome, gives clinicians the opportunity of earlier detection and better survival for this ‘silent killer.’ Another notable study of risk factors for ovarian cancer in 2016 was about etiologic heterogeneity by histology. Wentzensen et al. [24] demonstrated women with higher parity had a reduced risk of all subtypes compared with nulliparity (p -value for heterogeneity < 0.001): the most and least risk reduction was seen in clear cell (relative risk [RR]=0.35; 95% CI=0.27–0.47) and serous carcinomas (RR=0.81; 95% CI=0.73–0.90), respectively. Age at menopause, endometriosis, and tubal ligation were only associated with endometrioid and clear cell histologies. A 5-year increase in postmenopausal hormone therapy use was associated with an increased risk of serous (RR=1.21; 95% CI=1.17–1.25) and endometrioid (RR=1.25; 95% CI=1.15–1.36) carcinomas, but not in mucinous (RR=1.09; 95% CI=0.94–1.26) and clear cell (RR=0.69; 95% CI=0.52–0.92) carcinomas. In line with this study findings, long-term use of estrogen-only therapy for 10 years or more was also reported as a histology-specific risk factor only for serous (51.4%, odds ratio [OR]=1.63; 95% CI=1.27–2.09) and endometrioid (48.6%, OR=2.00; 95% CI=1.17–3.41) ovarian cancer in a pooled analysis of a total of 2,126 women (906 ovarian cancer and 1,220 controls) [25]. The substantial heterogeneity of individual risk factor across ovarian cancer subtypes underscores the importance of establishing preventive procedures by cancer subtypes.

2. Update of chemotherapy in ovarian cancer contrary to expectations

Because a longer platinum-free interval (PFI) is associated with better survival outcomes, it was often thought that introducing a non-platinum agent and resultant prolongation of PFI might improve the sensitivity to following platinum. At the 2016 American Society of Clinical Oncology (ASCO) annual meeting, Pignata et al. [26] presented the results of the multicenter Italian trials in ovarian cancer (MITO)-8 study, a phase III open-label, multicenter randomized clinical trial evaluating the survival impact of single-agent non-platinum

treatment to prolong PFI in patients with recurrent, partially platinum-sensitive ovarian cancer recurring 6–12 months after previous platinum-based chemotherapy. Contrary to expectations, extending PFI with single-agent non-platinum chemotherapy did not improve and even worsened the overall survival (OS) in this group of patients. In this study, a total of 215 patients were randomized to receive a non-platinum based chemotherapy (pegylated liposomal doxorubicin [PLD], topotecan, or gemcitabine) (n=107) or a platinum-based chemotherapy (carboplatin/paclitaxel or carboplatin/gemcitabine) (n=108). A median PFI before randomization was 8 months. During a median follow-up of 38 months, median OS for non-platinum vs. platinum groups was 21.8 vs. 24.5 months (HR=1.38; 95% CI=0.99–1.94; p=0.060). Median progression-free survival (PFS) after second treatment was 12.8 vs. 16.4 months (HR=1.41; 95% CI=1.04–1.92; p=0.025). This study findings suggested that immediate re-treatment with platinum-based chemotherapy might remain the standard treatment strategy in recurrent, partially platinum-sensitive ovarian cancer.

Another big trial which showed results against expectations was weekly vs. every-3-week paclitaxel and carboplatin for advanced stage ovarian cancer (Gynecologic Oncology Group [GOG] 262) published in *The New England Journal of Medicine* [27]. A total of 692 patients were randomly assigned to receive either carboplatin area under the curve (AUC) 6 plus weekly paclitaxel 80 mg/m² or carboplatin AUC 6 plus 3-weekly paclitaxel 175 mg/m², with optional bevacizumab for both groups. By contrast to the previous Japanese study (Japanese Gynecologic Oncology Group [JGOG] 3016) which showed significant OS and PFS benefits in dose-dense weekly paclitaxel regimen (carboplatin AUC 6 plus weekly paclitaxel 80 mg/m²) compared with conventional triweekly regimen (carboplatin AUC 6 plus 3-weekly paclitaxel 180 mg/m²) [28], GOG262 study did not show a longer PFS in patients treated with weekly paclitaxel than 3-weekly paclitaxel (median PFS 14.7 vs. 14.0 months, HR=0.89; 95% CI=0.74–1.06; p=0.180). Among 112 (16%) who did not opt to receive bevacizumab, however, patients treated with weekly paclitaxel showed 3.9-month longer PFS than those treated with 3-weekly paclitaxel (median PFS 14.2 vs. 10.3 months, HR=0.62; 95% CI=0.40–0.95; p=0.030). In contrast, patients treated with bevacizumab had a median PFS of 14.9 months and 14.7 months with weekly and 3-weekly paclitaxel, respectively. Weekly regimen was associated with a higher rate of grade ≥3 anemia (36% vs. 16%) and grade ≥2 sensory neuropathy (26% vs. 18%) than 3-weekly regimen. GOG262 was a negative study that failed to prove the benefit of weekly paclitaxel over the conventional regimen. Because of non-randomization of bevacizumab use and possible adverse effect of bevacizumab on weekly paclitaxel, a solid conclusion in terms of bevacizumab use together with dose-dense weekly paclitaxel needs further investigation.

Compared with the results of previous 2 phase III randomized trials regarding NAC vs. primary cytoreductive surgery (PCS) in advanced stage ovarian cancer [29,30], both of which demonstrated non-inferiority of NAC, a recently published large-scaled retrospective cohort study of women with stage IIIC–IV epithelial ovarian cancer showed that PCS was associated with longer OS than NAC in otherwise healthy women with advanced stage ovarian cancer under the age of 70 [31]. Of 22,962, 19,836 (86.4%) and 3,126 (13.6%) underwent PCS and NAC, respectively. From each group, 2,935 patients were included in propensity score matching. Median OS was significantly longer in the PCS group than in the NAC group (37.3 vs. 32.1 months, HR=1.18; 95% CI=1.11–1.26; p<0.001). However, sensitivity analysis of performance status revealed that if 60% of women receiving NAC had a performance status of 1 to 2 compared with 50% in the PCS group, which would negate the significant association of PCS with improved survival. This finding suggests that the survival improvement in PCS

group could be explained by a higher prevalence of limited performance status in NAC group. A SGO/ASCO practice guideline for NAC in newly diagnosed, advanced ovarian cancer published in 2016 [32,33] recommended that women with a high perioperative risk or a low likelihood of residual disease <1 cm (ideally no visible disease) should receive NAC. However, PCS is still preferred if residual disease <1 cm (ideally no visible disease) with acceptable morbidity is most likely to be achievable.

Lastly, contrary to the expectations from the promising results of the previous randomized phase II study (JGOG3014) [34], which showed a tendency of PFS superiority of the irinotecan plus cisplatin group compared with paclitaxel plus carboplatin group in a subset analysis of ovarian clear cell carcinoma (CCC) patients without residual disease or with residual disease <2 cm, a randomized phase III trial of irinotecan plus cisplatin compared with paclitaxel plus carboplatin as first-line chemotherapy for CCC (JGOG3017) failed to show significant survival benefit between the groups [35]. In this study, a total of 667 ovarian CCC patients were randomized to receive irinotecan 60 mg/m² (day 1, 8, and 15) plus cisplatin 60 mg/m² (day 1) every 4 weeks or paclitaxel 175 mg/m² plus carboplatin AUC 6 every 3 weeks. With a median follow-up of 44.3 months, 2-year PFS rates were 73.0% and 77.6% in irinotecan plus cisplatin and paclitaxel plus carboplatin group, respectively (HR=1.17; 95% CI=0.87–1.58; p=0.850). The negative results of this trial suggest that there are limitations of existing anticancer agents to improve prognosis of ovarian CCC. The authors emphasized identification of driver mutations of CCC for personalizing treatment of CCC.

3. Update of targeted therapy in ovarian cancer

The current options for maintenance therapy in ovarian cancer include bevacizumab and olaparib, a PARP inhibitor. However, bevacizumab is capable of improving PFS by just a few months and olaparib is only approved in patients with a germline *BRCA* mutation (*gmBRCA*) which is about 10%–15% of ovarian cancer patients. Recently, niraparib, a highly selective PARP 1/2 inhibitor, was reported to show a significant PFS improvement in platinum-sensitive, recurrent ovarian cancer, regardless of the presence or absence of *gmBRCA*s or homologous recombination deficiency (HRD) in the *The New England Journal of Medicine* [36]. In the randomized, placebo-controlled, phase III trial performed by the European Network for Gynecological Oncological Trial (ENGOT) groups, a total of 553 patients (203 with *gmBRCA* and 350 without *gmBRCA*) were 2:1 randomly assigned to receive niraparib 300 mg or placebo. Median PFS of niraparib and placebo groups was 21.0 vs. 5.5 months in the patients with *gmBRCA* (HR=0.27; 95% CI=0.17–0.41; p<0.001) as compared with 9.3 vs. 3.9 months in the patients without *gmBRCA* (HR=0.45; 95% CI=0.34–0.61; p<0.001) and 12.9 vs. 3.8 months in the patients without *gmBRCA* but with HRD (HR=0.38; 95% CI=0.24–0.59; p<0.001). Despite more than 10% of patients had grade ≥3 adverse events following treatment with niraparib (33.8% had thrombocytopenia, 25.3% had anemia, and 19.6% had neutropenia), all of which were resolved with dose adjustment, this study witnessed such large PFS benefits in recurrent ovarian cancer patients. Of note, this could be a breakthrough for ovarian cancer patients who suffer from tumor recurrence because niraparib showed a significant survival improvement across a broad patient population representing 70% of all ovarian cancer patients.

The other remarkable targeted agents of which the results of phase III randomized trials were published in 2016 were cediranib, an oral antiangiogenic vascular endothelial growth factor receptor (VEGFR) 1–3 inhibitor, and nintedanib, an oral triple angiokinase inhibitor of VEGFR, platelet-derived growth factor receptor, and fibroblast growth factor receptor [37,38]. Preliminary results of the 2 trials were presented in 2013 at the European Cancer Conference

in Amsterdam (ICON6 for cediranib) and the 18th International Meeting of European Society of Gynecologic Oncology (ESGO) (Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group [AGO-OVAR] 12 for nintedanib), both of which were introduced in this series of review in 2014 [7]. To be brief, during a median follow-up of 19.5 months of 456 patients with platinum-sensitive recurrent ovarian cancer in ICON6, median PFS was 11.0 vs. 8.7 months in cediranib maintenance group (cediranib alongside chemotherapy followed by maintenance) and placebo group (placebo alongside chemotherapy followed by placebo maintenance), respectively (HR=0.56; 95% CI=0.44–0.72; $p<0.001$). Unfortunately however, due to the shortage of cediranib supply, the promising yet immature OS results at the first presentation in 2013 [7] were not confirmed yet. For nintedanib, median PFS benefit of the nintedanib addition to standard carboplatin and paclitaxel compared with placebo group was found in AGO-OVAR 12 study of 1,366 patients who underwent upfront surgery and standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (17.2 vs. 16.6 months, HR=0.84; 95% CI=0.72–0.98; $p=0.024$). A post-hoc analysis revealed that the significant difference of PFS between the nintedanib and placebo groups was found only in the non-high-risk subgroup, which was defined as the International Federation of Gynecology and Obstetrics (FIGO) stage III and postoperative residual tumor ≤ 1 cm, or FIGO stage II (median PFS 27.1 vs. 20.8 months, 95% CI=0.61–0.91). The most common adverse event was diarrhea (grade 3, 21% vs. 2%; grade 4, $<1\%$ vs. 0%). Drug-related adverse events leading to death occurred in 3 assigned nintedanib group (one due to non-drug-related sepsis associated with diarrhea and renal failure; one due to peritonitis; and one without diagnosis of cause), compared with one patient assigned placebo (cause unknown). The addition of nintedanib to first-line chemotherapy with carboplatin and paclitaxel appeared associated with greater gastrointestinal adverse events. Pending OS results, however, warrants further studies for the clinical value of nintedanib in advanced ovarian cancer patients with lower tumor burden after primary debulking surgery.

CERVICAL CANCER

1. Robust evidences for expanding HPV vaccine coverage

Following the previous studies supporting HPV vaccination for preventing HPV infection, cervical intraepithelial neoplasia (CIN) and cervical cancer [9], there were several reports published in 2016 which might spur parents, policy makers and medical professionals to think more about the importance of HPV vaccinations.

First, Benard et al. [39] determined the population-based CIN trends from 2007 to 2017 when adjusting for changes in cervical cancer screening practices and HPV vaccination implementation using the New Mexico HPV Registry, the statewide surveillance program in the US that includes complete cervical screening, diagnosis and treatment information since HPV vaccine was introduced in 2007. In this study, a total 13,520 CIN1, 4,296 CIN2, and 2,823 CIN3 were diagnosed among 15 to 29-year-old women during study period. In 2008, 48% of girls 13 to 17 years old had received at least one HPV vaccine dose and 17% received all 3 doses, which increased to 59% and 40% by 2014, respectively. After adjustment for changes in cervical screening across the period, significant reductions of CIN incidence were observed for all grades of CIN among female individuals 15 to 19 years-old (annual percentage change [APC] for CIN1=-9.0; 95% CI=-12.0, -5.8; $p<0.001$; APC for CIN2=-10.5; 95% CI=-18.8, -1.2; $p=0.030$; APC for CIN3=-41.3; 95% CI=-65.7, 0.3; $p=0.050$). For women 20 to 24 years old, reduction in the CIN2 incidence was also significant (APC=-6.3; 95% CI=-10.9,

-1.4; $p=0.020$). Incidence reductions greater than expected based on vaccination coverage suggest several factors likely contributed to the CIN rates: cross-protection, efficacy of less than 3 doses, and herd immunity. Population-level decreases in CIN among cohorts partially vaccinated for HPV suggests that the age at which we begin cervical screening might be raised soon, which would be one of the first step in integrating cervical cancer screening and HPV vaccination.

Second, 7-year follow-up data of Vaccine Immunogenicity and Efficacy (VIVIANE) study [40], a phase III, double-blind, randomized controlled trial of HPV 16/18 vaccine in women >25 years, were reported in *The Lancet Infectious Diseases* in 2016 [41]. In this study, a total of 5,747 women was in the vaccinated cohort ($n=2,877$ vaccine and $n=2,870$ control) and 4,407 were in the according-to-protocol cohort for efficacy ($n=2,209$ vaccine and $n=2,198$ control). At month 84, vaccine efficacy against 6-month persistent infection or CIN1+ associated with HPV 16/18 (primary endpoint of this study) was significant in all ages (90.5%, 96.2% CI=78.6–96.5). Vaccine efficacy against CIN1+ irrespective of HPV was also significant in the total vaccinated cohort (22.9%, 96.2% CI=4.8–37.7). Serious vaccination-related adverse events occurred in 0.2% and 0.3% of the vaccine and control group, respectively. This study findings have clinical implications that adult women >25 years might also choose to be vaccinated for the potential benefit from HPV vaccination because new HPV infections can occur throughout adult life.

Third, a new nonavalent vaccine was shown to have the potential to reduce the incidence of cervical cancer at a similar or lower cost than bi- and quadri-valent vaccines, despite the higher cost-per-dose of nonavalent vaccine [42]. In this study, a transmission model that incorporated factors affecting HPV transmission and cervical cancer incidence, such as, demographic dynamics, sexual behavior, and migratory patterns, was developed to quantify the economic and epidemiological impacts of switching to the nonavalent vaccine. The researchers found that a switch to nonavalent vaccine would drop incidence of cervical cancer by 73%, compared with 63% with older vaccines, and reduce mortality by 49% vs. 43%. Regarding the cost-effectiveness, both coverage expansion and switching to nonavalent vaccine were considered. For example, total 65,000 quality-adjusted life years (QALYs) yielded by complete switching to nonavalent vaccine at current coverages would be gained by vaccination of additional 11% of the population using bi- or quadri-valent vaccines. This expansion in bi- or quadri-valent vaccine coverage would cost 2.7 billion USD more than using nonavalent vaccine at current coverage to achieve the same benefit. Therefore, the authors addressed that switching to nonavalent vaccine and expansion of coverage could benefit both in health and in economic terms in the US.

ASCO released a statement on HPV vaccination for cancer prevention to provide the rationale behind, and a roadmap for, increasing HPV vaccination uptake as means of preventing HPV-related cancers including cervical cancer [43].

2. Standard of care treatment for locally advanced cervical cancer (LACC)

The current standard of care treatment for LACC includes pelvic external beam radiotherapy (EBRT) with concurrent cisplatin-containing chemotherapy and brachytherapy (category 1) [44]. Particularly, guidelines emphasize that brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery [44]. However, Robin et al. [45] found that only 44.3% of 15,194 patients with LACC in the National Cancer Database received standard of care treatment. Compared with no

boost at all (26.8%), an EBRT boost (23.8%) was advantageous (HR=0.72; $p<0.001$), but patients who received brachytherapy (49.5%) had superior OS (HR=0.55; $p<0.001$). This study showed that less than half of the patients receive standard of care even though it offers better survival outcomes in patients with LACC. Specifically, the likelihood of receiving no boost radiotherapy (RT) was increased for patients with lower incomes, Medicaid, or treatment at low-volume centers or non-comprehensive community cancer centers.

Weekly low-dose cisplatin in concurrent chemoradiation therapy (CCRT) is thought as a radio-sensitizer rather than cytotoxic agent. A prospective, single-arm, phase II study of CCRT with cisplatin and paclitaxel every 3 weeks for 4 cycles in LACC or locally recurrent cervical cancer (LRCC), the results of which were presented in the annual meeting of ASCO in Chicago [46]. In this study, 65 patients with LACC (FIGO stage IB2–IVB) or LRCC received cisplatin 75 mg/m² and paclitaxel 175 mg/m² every 3 weeks for 4 courses with concurrent RT (50 Gy, 25 courses), which started 2 weeks after chemotherapy cycle 1, and high-dose rate brachytherapy (6 Gy, 3 courses), which was performed during chemotherapy cycle 4. After median follow-up of 58 months (range, 2–184 months), there were 55 CRs (84.6%), 8 partial responses (12.3%), and 1 stable disease (1.5%). The 180-month PFS and OS rates were 66.6% and 67.3%, respectively. No deaths were reported after 4 years of treatment, although 2 patients succumbed during the follow-up due to secondary malignancies (uterine carcinosarcoma and pancreas adenocarcinoma). There was one grade-4 toxicity of leucopenia and grade-3 toxicities including proctitis (24.6%), leucopenia (15.4%), anemia (15.4%), diarrhea (13.9%), emesis (6.2%), cystitis (6.2%), and thrombocytopenia (1.5%). The authors concluded that CCRT with cisplatin and paclitaxel showed long-term durable responses with tolerable toxicity level.

UTERINE CORPUS CANCER

1. Update on surgery in uterine corpus cancer

The accumulating evidence is that suggested superiority of laparoscopic surgical approach compared with laparotomy for uterine cancer in terms of short-term safety and length of stay. A large trial of GOG Lamina-associated polypeptide 2 (LAP2) study by Walker et al. [47] reported comprehensive surgical staging for endometrial cancer could be performed laparoscopically with relatively small differences in recurrence rates (estimated difference at 3 years=1.14%; 90% lower bound=-1.278; 95% upper bound=3.996), although statistical non-inferiority boundaries of 15% recurrence rate with laparotomy was not reached. Wright et al. [32] conducted a population-based analysis to compare minimally invasive surgery to abdominal hysterectomy for uterine cancer using Surveillance, Epidemiology, and End Results (SEER)-Medicare database and published the results in the *Journal of Clinical Oncology*. Of 6,304 women aged 65 years or older with stage I–III uterine cancer who underwent a hysterectomy between 2006 and 2011, 65.7% and 34.3% underwent abdominal hysterectomy and minimally invasive hysterectomy, respectively. The minimally invasive procedure, of which 62.3% were robot-assisted hysterectomies, had a lower overall complication rate than the abdominal hysterectomies (22.7% vs. 39.7%, OR=0.46; 95% CI=0.41–0.51; $p<0.001$). Of note, the complication rate was higher after robot-assisted hysterectomy than laparoscopic hysterectomy (23.7% vs. 19.5%, OR=1.28; 95% CI=1.03–1.59; $p=0.030$). There was no association between the minimally invasive hysterectomy and overall mortality (HR=0.89; 95% CI=0.75–1.04) or cancer-specific mortality (HR=0.83; 95% CI=0.59–1.16). Thus, the study findings reassured that minimally invasive procedures did

not appear to compromise long-term survival but offer superior short-term outcomes in patients with endometrial cancer.

Another intriguing topic of surgical treatment for endometrial cancer was the timing for surgery. There were 2 relevant studies published in 2016. The earlier publication by Strohl et al. [48] reported negative impact of surgical delay on survival outcomes in *Gynecologic Oncology*. Using the National Cancer Database, a total of 40,184 women who underwent hysterectomy for the treatment of endometrial cancer from 2003 to 2011 and whose survival data were available was included in the analysis. Surgical wait time from diagnosis to surgery was longer than 6 weeks in 28% of patients, whose survival was worse than those treated within 6 weeks or diagnosis (HR=1.14; 95% CI=1.09–1.20; $p<0.001$). Age <40 years, black or Hispanic race, Medicaid or uninsured, or the lowest education quartile were associated with long surgical wait time >6 weeks. Diagnosis in 2010–2011 was also associated with long surgical wait time >6 weeks compared with diagnosis in 2003 (incidence rate ratio=1.32; 95% CI=1.24–1.40; $p<0.001$). On the other hand, there was another National Cancer Database study that reported the opposite, of which final version was actually released in March of 2017 [49]. Considering the limitations of the former study by Strohl et al. [48], no risk stratification according to grade and histology, separate analysis was performed in this study: low-risk (grade 1 or 2 endometrioid histology) and high-risk (nonendometrioid and grade 3 endometrioid histologies). Compared with patients who underwent surgery in the third or fourth week after diagnosis, 5-year crude survival of patients who had surgery in the first or second week after diagnosis was decreased by 14% for low-risk patients (87.4% [95% CI=86.5%–88.2%] vs. 73.0% [95% CI=70.6%–75.3%]) and by 20% for high-risk patients (66.9% [95% CI=65.3%–68.4%] vs. 46.5% [95% CI=43.5%–49.5%]). For both risk groups, 30-day postoperative mortality was significantly higher in patients undergoing surgery first or second week postdiagnosis than those undergoing surgery third or fourth week postdiagnosis (0.7% vs. 0.4%, $p<0.001$ for low-risk; 2.5% vs. 1.0%, $p<0.001$). Five-year survival worsened as diagnosis-to-surgery time delay ≥ 8 weeks in low-risk patients, but not in high-risk patients. These findings suggested that the target time-to-surgery after diagnosis be less than 8 weeks, especially for women with low-risk cancers. However, the type and extent of disease contributed more to survival outcomes than progress of disease during the surgical wait time. Therefore, referral to an experienced specialist in a high-volume cancer center should be prioritized over expedited surgery.

2. Identifying genetic risk of endometrial cancer

Five new gene regions that increase the risk of developing endometrial cancer were identified by a meta-analysis of 3 endometrial cancer genome-wide association study (GWAS) [50]: previous GWAS from 2 population studies (the UK Studies of Epidemiology and Risk factors in Cancer Heredity [SEARCH, $n=681$] and the Australian National Endometrial Cancer Study [ANECS, $n=606$]) and genotypes generated using Illumina Infinium 610K arrays, the National Study of Endometrial Cancer (NSECG), and the Collaborative Oncological Gene-environment Study (COGS) initiative. In this study, a total of 7,737 endometrial cancer cases and 37,144 controls without cancer of European ancestry were investigated. Five novel risk loci included likely regulatory regions on chromosomes 13q22.1, 6q22.31, 8q24.21, 15q15.1, and 14q32.33. Those 5 novel regions contained at least one endometrial cancer risk single nucleotide polymorphism (SNP) with $P_{\text{meta}} < 10^{-7}$ and most strongly associated SNP in each region was genotyped: rs11841589 (OR=1.15; 95% CI=1.11–1.21; $p=4.83 \times 10^{-11}$), rs13328298 (OR=1.13; 95% CI=1.09–1.18; $p=3.73 \times 10^{-10}$), rs4733613 (OR=0.84; 95% CI=0.80–0.89; $p=3.09 \times 10^{-9}$), rs937213 (OR=0.90; 95% CI=0.86–0.93; $p=1.77 \times 10^{-8}$), and rs2498796 (OR=0.89; 95% CI=0.85–0.93;

$p=3.55 \times 10^{-8}$), respectively. All the 5 SNPs were associated with endometrial cancer at genome-wide significance ($p < 5 \times 10^{-8}$). Specifically, functional studies of the 13q22.1 locus showed that rs9600103 is located in a region of active chromatin that interacts with promoter region of the Kruppel-like factor 5 (*KLF5*) (pairwise $r^2=0.98$ with rs11841589). *KLF5*, a transcription factor associated with cell cycle regulation, is thought to be active during the development of the uterus as well as tumorigenesis. Given in vitro suppression of gene expression by rs9600103-T endometrial cancer protective allele in allele-specific luciferase reporter assays using Ishikawa cells, regulation of *KLF5* expression could be implicated in tumorigenesis of endometrial cancer.

MAJOR TRENDS AND APPLICATION OF RT IN GYNECOLOGIC CANCER

1. Adjuvant RT in endometrial cancer

Endometrial cancer patients with high-risk features, such as, stage I grade 3 cancer with deep myometrial invasion or with substantial lymphovascular space invasion, stage II or III cancer, or cancer with non-endometrioid histology, have higher incidence of distant metastases and cancer-related death. In this regard, a randomized phase III Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC)-3 trial was performed to evaluate the efficacy and safety of adjuvant CCRT compared with that of RT alone in women with high-risk endometrial cancer. In *The Lancet Oncology*, de Boer et al. [51] reported the first results of PORTEC-3 trial focusing on 2-year toxicity and health-related quality of life (QOL) as secondary endpoints in those who received CCRT compared with RT alone. Overall, 686 women were randomly assigned (1:1) to receive RT alone or CCRT (2 cycles concurrent cisplatin 50 mg/m² and 4 adjuvant cycles of carboplatin AUC 5 and paclitaxel 175 mg/m²). During median follow-up of 42.3 months (IQR=25.8–55.1 months), toxicity and QOL data were available for 570 patients. Worse symptoms, which were quantified with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), for the CCRT group compared with RT alone at the completion of RT and at 6 months improved with time. At 12 and 24 months, global health or QOL, at least, was similar between groups. However, severe tingling or numbness, the well-known side-effects of carboplatin and paclitaxel, was still more frequently observed in CCRT group than RT alone group (25% vs. 6%, $p < 0.001$) at 24 months. Similarly, adverse events \geq grade 3, most of which (45%) being hematological, were found more frequently in CCRT group than RT alone group at the completion of RT and at 6 months (61% vs. 13%, $p < 0.001$). Most patients recovered quickly after the treatment and there was no significant difference of adverse events \geq grade 3 at 12 and 24 months. Only sensory neuropathy \geq grade 2 was deemed troublesome by 10% vs. <1% in CCRT and RT alone group ($p < 0.001$), respectively. PORTEC-3 trial showed that CCRT was feasible in patients with high-risk endometrial cancer with rapid recovery after treatment. However peripheral sensory neuropathy was not completely recovered in 25% of patients. Survival benefits for CCRT over RT alone, which are the primary endpoints, are to be determined yet should be weighed against the adverse events and QOL results of this report.

Regarding toxicity of RT in endometrial cancer patients, there was another interesting study that reported overuse of EBRT for stage I high-intermediate risk endometrial cancer despite the results of randomized trial. Previously, PORTEC-2 trial found that vaginal brachytherapy was as effective as EBRT in reducing local recurrences and was less toxic in patients with early

stage high-intermediate risk endometrial cancer [52]. Wright et al. [53] analyzed the patterns of use of EBRT for women with this group of patients using the National Cancer Database and the results were published in *American Journal of Obstetrics and Gynecology*. In this study of a total of 8,242 women who met inclusion criteria, 915 (11.1%), 2,614 (31.7%), and 4,713 (57.2%) received EBRT, brachytherapy, and no adjuvant RT, respectively. The use of EBRT was decreased from 18.1% in 2008 to 8.6% in 2012. However, patients who did not undergo lymphadenectomy were more than twice as likely to receive EBRT compared with those who had lymphadenectomy (RR=2.32; 95% CI=1.99–2.72). Women with stage IB/grade 2 tumors were also more likely to receive EBRT than those with stage IA/grade 3 tumors (RR=1.96; 95% CI=1.65–2.32). This study findings suggested that a concern about recurrence in the lack of information of the nodal status might drive both patient and physician to use EBRT when lymphadenectomy was not performed.

2. Development of image-guided RT

Last study was about image guided adaptive brachytherapy (IGABT) in LACC: a data analysis on 610 patients from a retrospective collection of data (retro-international study on magnetic resonance imaging (MRI)-guided brachytherapy in locally advanced cervical cancer [EMBRACE]). Fokdal et al. [54] showed in this study that the impact on local control and late morbidity of application of combined intracavitary/interstitial (IC/IS) brachytherapy in a large population of LACC. D90 of high-risk clinical target volume (CTV_{HR}) increased with systematic use of IC/IS (83±14 Gy vs. 92±13 Gy, p<0.010), without no difference in doses to organs at risk. Despite no significant difference in late morbidity rate between the IC/IS group (n=300) and IC group (n=310), the 3-year local control rate in patients with a CTV_{HR} volume ≥30 cm³ was 10% higher in the IC/IS group (p=0.020). This study suggested that significantly higher local control in large tumors could be obtained by combined IC/IS brachytherapy which improves the therapeutic ratio by enabling tumor specific dose escalation in LACC.

CHEMOTHERAPY AT THE END-OF-LIFE

Not only the disease status but also personal attitude toward life should be taken into account in end-of-life decision of further use of chemotherapy in palliative setting. Cancer care givers should, therefore, focus on shared decision-making and patient-physician communication which enables the patient to fully understand the potential benefit and harm of chemotherapy in the context of the specific needs of each individual patient. There were a few outstanding studies that addressed the palliative care in oncology, even though not specific for gynecologic cancer.

Rochigneux et al. [55] evaluated the factors associated with chemotherapy use at the end of life in a nationwide register-study of 279,846 patients who died from metastatic cancer, of whom 5.4% had cancer of female genital organs. The results were presented in the European Society of Medical Oncology (ESMO) 2016 Congress. A total of 19.5% of patients received chemotherapy during the last month before death. Female sex (OR=0.96; 95% CI=0.93–0.98), older age (OR=0.70; 95% CI=0.69–0.71), and higher number of chronic comorbidities (OR=0.83; 95% CI=0.82–0.84) were associated with less use of chemotherapy during the last month before death. Although patients with chemosensitive tumors, such as testis and ovary tumors, were more likely to receive chemotherapy during the last month before death (OR=1.21; 95% CI=1.18–1.25), however, there was no clear pattern between

the expected chemosensitivity of different cancers and the rates of chemotherapy use near death. Surprisingly high rates of end-of-life chemotherapy was found in patients with tumors which were not likely to respond chemotherapy, for example, metastatic pancreatic cancer and melanoma. Compared with university hospitals, for-profit clinics or hospital (OR=1.40; 95% CI=1.34-1.45) and comprehensive cancer centers (OR=1.43; 95% CI=1.36-1.50) were associated with more frequent use of end-of-life chemotherapy.

Good performance status of cancer patients is often used as one of criteria by which chemotherapy could be tolerably performed or not. Prigerson et al. [56] evaluated the effect of additional palliative chemotherapy on quality of life near death (QOD) according to performance status. Chemotherapy use in patients with ECOG score ≥ 2 at study entry was not associated with QOD improvement, contrary to our expectation (OR=1.06; 95% CI=0.51-2.21; $p=0.870$ for ECOG 2; OR=1.34; 95% CI=0.46-3.89; $p=0.590$ for ECOG 3). Even worse, among patients with good baseline performance status with ECOG 1, chemotherapy use was associated with worse QOD compared to who did not (OR=0.35; 95% CI=0.17-0.75; $p=0.010$). This study findings suggested that chemotherapy use near death could lead a lower QOD in patients with end-stage cancer, even with a good performance status.

Previous studies consistently showed that aggressive end-of-life care including chemotherapy was potentially futile [55,56]. In 2012, ASCO agreed to participate in 'Choosing Wisely' campaign, which was led by the American Board of Internal Medicine and aimed at minimizing unnecessary medical testing and interventions for a remote possibility of a benefit [57]. It was expected to reduce unnecessary costs, burdens or risks to patients and the healthcare system. At 2016 ASCO Annual Meeting, Chen et al. [58] presented the impact of ASCO's Choosing Wisely campaign on use of aggressive medical care for younger patients with cancer within the last month of life. From claims data of the HealthCare Integrated Research Database, a total of 28,731 patients with diagnosis of metastatic lung, colorectal, breast, pancreatic, and prostate cancers were included in this study analysis. Rates of overall aggressive care use including chemotherapy, RT, and invasive procedure between early 2012 before Choosing Wisely vs. 2014 were unchanged in patients with colorectal and breast cancers, and increased in lung, pancreatic and prostate cancers. Of aggressive cares, chemotherapy use ranged from 24% to 32% across cancers. This study showed that there was still a substantial overuse of aggressive end-of-life care among younger patients with end-stage cancers even after the health educational campaign in the US.

IMMUNOTHERAPY EDITING IMMUNE SYSTEM BY REENGINEERING T-CELLS

Chimeric antigen receptors (CARs, also known as chimeric immuno-receptors, chimeric t-cell receptors, and artificial t-cell receptors) are engineered receptors, typically, used to graft the specificity of a monoclonal antibody onto a T-cell with transfer of their coding sequence, allowing T-cells to recognize specific antigens found on tumors and eliminate them. Using the technique of adoptive cell transfer, CARs have shown impressive therapeutic effects in hematologic malignancies, especially in patients who suffered from chemoresistance [59]. Perales-Puchalt et al. [60] assessed the safety and effectiveness of T-cell redirected against follicle-stimulating hormone receptor (FSHR)-expressing ovarian cancer cells using CAR T-cell technology in immunocompetent tumor-bearing mice. The FSHR is thought to be selectively expressed in ovarian granulosa cells, while at low levels in

the ovarian endothelium and not in non-ovarian healthy tissues. They analyzed The Cancer Genome Atlas (TCGA) datasets from 404 high-grade serous ovarian cancers, and found that 56% of these tumors express FSHR mRNA. In other histologic subtypes, expression of FSHR was identified in 70% (16/23) of endometrioid type, 67% (6/9) of mucinous type and 33% (4/12) of clear cell type. Considering these findings, FSHR could be a new therapeutic target for subtypes which had poor prognosis, such as mucinous and clear cell. They generated a CAR using the full-length of the human FSHR (FSHCER), and identified the killing effects of that in cultured OVCAR-3 cell lines. In addition, they showed that T-cells expressing FSHCER-redirectioned CARs had significant therapeutic effects in immunocompetent mice with established FSHR⁺ ovarian tumors. There was no detectable toxicity or alternative targeting of any healthy tissue in this study. This study is expected to contribute for understanding the therapeutic mechanisms of T cell with adoptive transfer of target's coding sequence.

Axalimogene filolisbac (ADXS11-001) is a kind of cancer vaccine containing a live-attenuated *Listeria monocytogenes*. It was bioengineered to secrete a HPV16-E7 fusion protein. Immunotherapy with ADXS11-001 targets HPV-transformed cells with potential immunostimulatory and antitumor activities. Huh et al. [61] presented the promising results of a single-arm, phase II study of ADXS11-001 activity in persistent or recurrent metastatic cervical cancer in 2016 ASCO annual meeting GOG/NRG0265 study (NCT01266460). Of 26 treated, 18 patients received the maximum of 3 doses of ADXS11-001 1×10^9 CFU on day 1 and q28 days. Primary endpoints are the tolerability/safety of ADXS11-001 and 12-month OS rate. Although adverse effects grade ≥ 1 were detected in all patients, 91% were just grade 1–2, including nausea, vomiting, chills, fatigue, and fever most common. Twelve-month OS rate was 38.5% (24.5% in historical controls). In addition, median PFS was 3.1 months (95% CI=2.8–3.7 months) and median OS was 7.7 months (95% CI=3.9–12.4 months). This study findings suggested that ADXS11-001 is well tolerable and active in persistent or recurrent metastatic cervical cancer.

Pembrolizumab is an immune checkpoint inhibitor that blocks the inhibitory interaction between programmed cell death 1 (PD-1) and its ligands, PD-L1 on tumor. Ott et al. [62] demonstrated an acceptable safety and preliminary antitumor activity of pembrolizumab in patients with advanced endometrial cancer who progress on chemotherapy in 2016 ASCO annual meeting (NCT02054806). Pembrolizumab was given 10 mg/kg every 2 weeks for up to 24 months or until confirmed progression, intolerable toxicity, death, or consent withdrawal. Twenty-four patients were enrolled. During median follow up of 69.9 weeks (range, 5.4 to 84.4 weeks), overall response rate was 13.0% (progesterone receptor [PR], n=3; 95% CI=2.8–33.6). Treatment-related adverse events occurred in 13 (54.2%) patients. Of them, 3 patients (13.0%) had grade 3 toxicities: one had back pain and asthenia (both resolved), one had diarrhea (resolved), and one experienced asthenia, anemia, hyperglycemia, and hyponatremia (all unresolved). Three patients of PR and 3 patients of standard deviation (SD) were observed. Six-months PFS and OS rates were 19.0% and 68.8%, respectively.

Lastly, a genetic analysis of Howitt et al. [63] identified the rational candidates who may benefit from therapies targeting PD-1 in cervical or vulvar squamous cell carcinoma (SCC) based on the expression of PD-L1. They suggested that alteration of 9p24.1 gene copy number results in increased PD-L1 expression in cervical and vulvar SCC. Co-amplification or co-gain of *CD274*, which encodes PD-L1, and *PDCD1LG2*, which encodes PD-L2 at 9p24.1 were observed in 32/48 (67%) of cervical and 10/23 (43%) of vulvar SCC. These findings help to determine which patients are more likely to respond to immunotherapy targeting PD-1, and which patients with these tumors are rational candidates for clinical trials of PD-1 blockade.

ACTUALIZATION OF PRECISION MEDICINE: FROM BENCH TO BED

The basic concept of precision medicine is a highly selective therapy for each individual based on their specific genetic abnormalities. A number of clinical trials have been designed for seeking the targetable molecules through the work of TCGA Project or other integrated genomic studies. Olaparib, a PARP inhibitor, in germline *BRCA*-mutated recurrent ovarian cancer is the start of their clinical products in the field of gynecologic oncology as like trastuzumab in human epidermal growth factor receptor 2 (HER2)-expressing breast cancer and vemurafenib in *BRAF*-mutated melanoma. The current medicine obviously evolves to the algorithm-based from evidence-based of the past.

Nevertheless, we still have some issues to resolve in the actualization of precision medicine, Tannock et al. [64] discussed about that in *The New England Journal of Medicine*. They suggested 2 reasons why the outcomes of inhibiting targeted molecules in clinical studies were not as good as those expected in preclinical studies. First, most molecular targeted agents up to now inhibit only a part of signaling pathways. Second, signaling pathways for cell proliferation or survival in cancer cells are usually plastic and adaptable. Cancer cells have a potential to develop resistance to a single molecular targeted agent with the possible exception of immune checkpoint inhibitors. It might be a result from up-regulation of the inhibitory pathway, mutation of the target, or activation of alternative pathways. In addition, they said that the development of intratumoral heterogeneity causes major limits to the potential targeting of mutated pathways based on molecular analysis of single tumor sample.

In editorial of March issue of *Gynecologic Oncology*, Coleman and Matulonis emphasized that the effort to overcome current limitations of precision medicine should be continued [65]. Mitamura et al. [66] proposed 2 plausible explanations for the disappointing response rates to anti-angiogenesis therapy in the pivotal phase III trials, including GOG218, ICON7, Ovarian Cancer Evaluation of Bevacizumab and Safety (OCEANS), and Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer (AURELIA) trials [67-70], which should have been higher given the promising results of earlier phase II trials [71]. One is the absence of stratification of patients according to chance of benefit. In other words, a personalized strategy for anti-angiogenesis therapy with identifying proper candidates might be necessary. Considering the OS benefit of bevacizumab in subgroup analysis of suboptimally debulked stage III or stage IV in ICON7 trial in contrast to no benefit in suboptimally debulked stage III patients in GOG218, first-line bevacizumab seems to be more beneficial in stage IV disease. In addition, they indicated that researches about histotype-specific response to anti-angiogenesis therapy in ovarian cancer were lacking. A retrospective analysis by Grisham et al. [72] reported higher than expected response rate with bevacizumab in low-grade serous histology (55% vs. 5%, with bevacizumab vs. chemotherapy alone), suggesting that bevacizumab has significant efficacy in this subtype. The other explanation for the disappointing response rate to anti-angiogenesis therapy in phase III trials is the development of resistance mechanisms within tumor. Resistance and escape mechanisms involved in anti-angiogenesis therapy included: 1) alternatives to angiogenesis for neovascularization; 2) acute hypoxia; and 3) recruitment of bone marrow-derived cells. The understanding of tumor biology including resistance mechanisms provide the insights on the selection of other therapies for the patients who are not thought as good responders of anti-angiogenesis therapy.

Two studies about the prediction of therapeutic response based on the specific gene mutations were also introduced in the special issue of precision medicine in *Gynecologic Oncology*. First, Murakami et al. [73] created a scoring system for prediction of drug response by applying single-sample gene set enrichment analysis using the dataset of advanced ovarian cancer GSE15622 from the National Center for Biotechnology Information (NCBI)'s Gene Expression Omnibus (GEO) website and TCGA Data Portal. C-score and T-score were calculated respectively with respect to platinum and taxane response on the subset of differential genes. High C-scores exclusively represented carboplatin responders, and conversely low C-scores exclusively represented carboplatin non-responders. The TCGA dataset high C-score group had a median PFS of 18.1 months (n=332), and the low C-score group had a median PFS of 16.0 months (n=160; p=0.02). In high T-score groups, cases treated with a taxane-platinum regimen had significantly higher OS and/or PFS than those with a nontaxane-platinum regimen. Second, Frimer et al. [74] found 21 germline mutations in 11 genes in 7 consecutive patients with uterine serous carcinoma. Nine (42.8%) germline mutations were found in hereditary colon cancer genes, most commonly *MLH*. Seven (33.3%) germline mutations were found within genes which involved in the homologous recombination pathway, most commonly *RAD51D*. All 3 patients who are platinum-sensitive (42.7%) had homologous recombination germline mutations, such as *RAD50*, *NBN*, and *ATM*. However, they did not find significant differences between pathway-associated mutations and survival in their small cohort.

Precision medicine is now moving on the clinical practice from the clinical trials. The efforts for applying precision medicine and establishing tailored therapies to each individual patient with gynecologic cancers should be continued.

APPLYING AI TO MAKE PERSONALIZED CANCER THERAPY REAL

AI has been increasingly used in various fields including autonomous vehicles (such as drones and self-driving cars), search engines (such as Google search), and online assistants (such as Siri). Most of all, one of the most promising uses of AI is medical diagnosis. Despite the huge amount of research papers and textbooks available for accurate diagnosis, AI seems to have an infinite amount of potential to analyze. Therefore, there is a great expectation that personalized cancer therapy could be ideally realized through this attractive system (**Fig. 1**). There were a few notable reports of personalized cancer therapy applying AI in 2016.

Kyrgiou et al. [75] tried to develop a clinical decision support scoring system (DSSS) based on artificial neural networks (ANN), which was first introduced by McCulloch and Pitts in 1943, for personalized management of women with cervical abnormalities. They collected data of liquid-based cytology, HPV-related biomarkers (E6&E7 mRNA and p16INK4a) and colposcopic findings from 2,267 women with or without cervical abnormalities. Of them, the cytology and biomarker results were used to develop a clinical DSSS. Histology from colposcopy-directed punch biopsy or conization was considered as the gold standard. Compared to cytology with or without HPV test, ANN had a higher accuracy for diagnosis of high grade (CIN2+), low grade (CIN1) and normal histology. The sensitivity, specificity, positive predictive value and negative predictive value of ANN in predicting CIN2+ was 93.0%, 99.2%, 93.3%, and 99.2%, respectively. Authors expected that DSSS based on an ANN could improve the prediction of CIN2+ with the highest accuracy. Furthermore, clinical DSSS could optimize the personalized management in cervical screening.

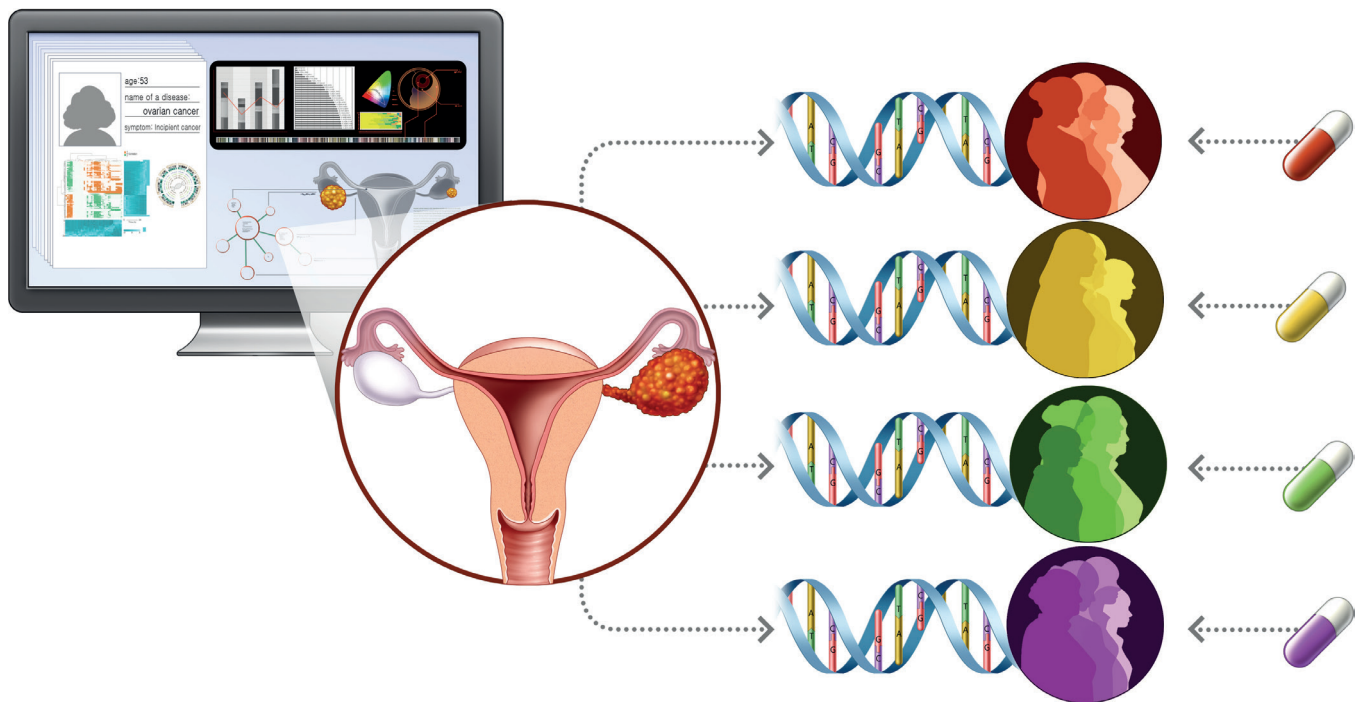


Fig. 1. Realization of personalized cancer therapy through artificial intelligence in gynecologic oncology.

Uzilov et al. [76] developed a personalized cancer therapy program in a clinical setting using an integrative genomic data of thyroid, colorectal and breast cancer. They collected the genomic data of 46 patients, and identified somatic mutations by whole exome sequencing or targeted panel sequencing. Based on these profiles of genetic and genomic alterations, therapeutic recommendations were made. Then, they were compared with commonly used cancer panels (Ion AmpliSeq Cancer Hotspot Panel v2 [CHPv2], OncoPrint Cancer Panel [OCP], and FoundationOne) regarding mean number of cancer-relevant somatic mutations, patients with drug recommendations and actionable alteration. In consequence, the integrative genomic approach detected more cancer-related somatic mutations (mean 17.3 cancer-relevant somatic mutations/patient, 13.3-, 6.9-, and 4.7-fold more than CHPv2, OCP, and FoundationOne, respectively) and actionable alterations (mean 4.9/patient, 7.5-, 2.0-, and 1.9-fold more than CHPv2, OCP, and FoundationOne, respectively) existing cancer panels. The findings altered the course of treatment in 4 cases, which suggested that a comprehensive, integrative genomic approach could significantly enhance genomics-based personalized cancer therapy strategies.

Similarly, Patel et al. [77] compared 4 existing commercial web tools (Drug-Gene Interaction Database [DGidb], My Cancer Genome [MCG], Personalized Cancer Therapy [PCT], and cBioPortal) for best identifying therapeutic recommendations for a given genetic mutations in cancers. They listed the affected genes and their frequencies including *TP53* (49.3%) and *PIK3CA* (40.0%) from 75 advanced breast cancer cases using targeted sequencing of 315 genes from 75 metastatic breast cancer biopsies. Food and Drug Administration (FDA)-approved drug recommendations by genetic mutation in each web tools were compared with those provided by FoundationOne. Only 3 (4.0%) cases had at least 1 gene with a same drug recommendation from all 5 sources, and 22 (29.3%) cases with an overlapping recommendation from 4 sources. This study findings suggested that further development

and standardization of various applicable web tools are needed and incorporation with AI will be required to improve the therapeutic interpretation.

BREAST CANCER

1. Adaptively randomized trials in clinical stage II or III breast cancer

Adaptive trials use a new approach to trial design; rather than creating a fixed framework of statistical assumptions that determines sample size and power, the trials react to results as they arrive. This approach potentially allows for faster and more flexible trial design [78]. The Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 trial (I-SPY 2 TRIAL) is a multicenter, adaptive phase II trial of neoadjuvant therapy for high-risk clinical stage II or III breast cancer. It evaluates multiple new agents added to standard chemotherapy to assess the effects on rates of pathological CR (i.e., absence of residual cancer in the breast or LNs at the time of surgery).

In the study of neratinib in early breast cancer, standard NAC plus neratinib, the tyrosine kinase inhibitor against HER2 was compared with control [79]. Among patients with HER2-positive, hormone receptor-negative cancer, the mean estimated rate of pathological CR was 56% (95% Bayesian probability interval [PI]=37%–73%) among 115 patients in the neratinib group, as compared with 33% among 78 controls (95% PI=11%–54%). The final predictive probability of success in phase III testing was 79%. This result means that neratinib added to standard therapy was highly likely to result in higher rates of pathological CR than standard chemotherapy with trastuzumab among patients with HER2-positive, hormone receptor-negative breast cancer. Confirmatory phase III study (under I-SPY 3 program) is planned.

Another I-SPY 2 TRIAL report in 2016 was veliparib, a PARP inhibitor, combined with carboplatin [80]. Patients with stage II or III breast cancer with a tumor 2.5 cm or larger in diameter; cancers are categorized into 8 biomarker subtypes on the basis of status with regard to HER2, hormone receptors, and a 70-gene assay. Veliparib-carboplatin plus standard therapy was considered for HER2-negative tumors and was therefore evaluated in 3 signatures. With regard to triple-negative breast cancer, veliparib-carboplatin had an 88% predicted probability of success in a phase III trial. The estimated rates of pathological CR in the triple-negative population were 51% (95% Bayesian PI=36%–66%) in the veliparib-carboplatin group versus 26% (95% PI=9%–43%) in the control group.

2. Extending aromatase-inhibitor adjuvant therapy to 10 years

As the risk of recurrence of hormone receptor-positive early breast cancer continues indefinitely, long-term (10 years or more) adjuvant endocrine therapies, including tamoxifen for 10 years, tamoxifen for up to 5 years followed by an aromatase inhibitor for 5 years, has been shown to reduce the risk of recurrence. In the MA.17R trial, even longer (up to 15 years after surgery) treatment with an aromatase inhibitor was assessed [81]. The MA.17R trial was a phase III, randomized, double-blind, placebo-controlled trial involving postmenopausal women (n=1,918) with primary breast cancer who had received 4.5 to 6 years of adjuvant therapy with an aromatase inhibitor. As most patients received with tamoxifen for 5 years before the aromatase inhibitor, these patients were randomized at the time-point of 10 years after surgery to receive 5 more years of letrozole or placebo. The 5-year disease-free survival (DFS) rate was 95% with letrozole and 91% with placebo (HR for disease recurrence or the occurrence of contralateral breast cancer, 0.66; p=0.010), meeting the primary endpoint.

However, the most cause of difference in DFS was reduction in contralateral breast cancers, and OS was not significantly different.

3. Seventy-gene signature as an aid to treatment decisions in early-stage breast cancer

Gene signatures, such as MammaPrint or OncotypeDX, have shown to improve prediction of clinical outcome in women with early-stage breast cancer. In the present study, the clinical utility of 70-gene signature test (MammaPrint) in addition to standard clinical-pathological criteria in selecting patients for adjuvant chemotherapy was assessed [39]. Women with early-stage breast cancer (n=6,693) were determined their genomic risk (using the 70-gene signature) and their clinical risk (using a modified version of Adjuvant! Online). Women at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did receive such therapy. In patients with discordant risk results, either the genomic risk or the clinical risk was used to determine the use of chemotherapy. A total of 1,550 patients (23.2%) were deemed to be at high clinical risk and low genomic risk. At 5 years, the rate of survival without distant metastasis in this group was 94.7% among those not receiving chemotherapy. This was 1.5 percentage points lower than that among those who received chemotherapy.

4. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness

The goal of screening mammography is to detect small malignant tumors before they grow large. Effective screening should therefore lead to the detection of a greater number of small tumors, followed by fewer large tumors over time. The authors used SEER data, 1975 through 2012, to calculate the tumor-size distribution and size-specific incidence of breast cancer among women 40 years of age or older [82]. The proportion of detected breast tumors that were small (invasive tumors measuring <2 cm or in situ carcinomas) increased from 36% to 68%. However, this trend was less the result of a substantial decrease in the incidence of large tumors. These suggest overdiagnosis with screening mammography. The authors conclude that the reduction in breast cancer mortality after the implementation of screening mammography was predominantly the result of improved systemic therapy.

5. Ribociclib as first-line therapy for hormone receptor-positive, advanced breast cancer

Ribociclib (LEE011) is a small-molecule inhibitor of cyclin-dependent kinase (CDK)4/6. Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) trial is randomized, placebo-controlled, phase III trial of the letrozole and ribociclib or placebo as initial therapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer (n=688) [83]. The duration of PFS was significantly longer in the ribociclib group than in the placebo group (HR=0.56; p=3.29×10⁻⁶ for superiority). Common grade 3 or 4 adverse events were neutropenia (59.3% in the ribociclib vs. 0.9% in the placebo group) and leukopenia (21.0% vs. 0.6%).

6. Palbociclib and letrozole in advanced breast cancer

Palbociclib is a small-molecule inhibitor of CDK4 and CDK6, which already acquired accelerated FDA approval. PALOMA-2 trial was a phase III trial that was designed to confirm the phase II results of palbociclib plus letrozole versus letrozole alone as first-line therapy in postmenopausal women with ER-positive, HER2-negative advanced breast cancer [84]. The median PFS was 24.8 months in the palbociclib-letrozole group, and 14.5 in the placebo-

letrozole group (HR=0.58; $p<0.001$). The most common grade 3 or 4 adverse events were neutropenia (66.4% vs. 1.4%), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%). These data confirm the role of palbociclib in combination with letrozole as first-line therapy.

CONCLUSION

In 2016, it seems hard to say there were many groundbreaking researches in gynecologic oncology. However, personalized cancer therapy supported by big data from AI and integrated genomic analysis has become the mainstream in this field of oncology. Unfortunately, gynecologic oncology appears at the very beginning stage of this state of the art. Further active research in this promising field of oncology is expected.

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