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Review Article

Major clinical research advances in gynecologic cancer in 2015

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ABSTRACT

In 2015, fourteen topics were selected as major research advances in gynecologic oncology. For ovarian cancer, high-level evidence for annual screening with multimodal strategy which could reduce ovarian cancer deaths was reported. The best preventive strategies with current status of evidence level were also summarized. Final report of chemotherapy or upfront surgery (CHORUS) trial of neoadjuvant chemotherapy in advanced stage ovarian cancer and individualized therapy based on gene characteristics followed. There was no sign of abating in great interest in immunotherapy as well as targeted therapies in various gynecologic cancers. The fifth Ovarian Cancer Consensus Conference which was held in November 7–9 in Tokyo was briefly introduced. For cervical cancer, update of human papillomavirus vaccines regarding two-dose regimen, 9-valent vaccine, and therapeutic vaccine was reviewed. For corpus cancer, the safety concern of power morcellation in presumed fibroids was explored again with regard to age and prevalence of corpus malignancy. Hormone therapy and endometrial cancer risk, trabectedin as an option for leiomyosarcoma, endometrial cancer and Lynch syndrome, and the radiation therapy guidelines were also discussed. In addition, adjuvant therapy in vulvar cancer and the updated of targeted therapy in gynecologic cancer were addressed. For breast cancer, palbociclib in hormone-receptor-positive advanced disease, oncotype DX recurrence score in low-risk patients, regional nodal irradiation to internal mammary, supraclavicular, and axillary lymph nodes, and cavity shave margins were summarized as the last topics covered in this review.

Keywords: Precision Medicine; Genital Neoplasms, Female; Ovarian Epithelial Cancer; Breast Neoplasms

INTRODUCTION

Outstanding researches in 2015 are largely categorized into three. First part is the follow-up results of the previous landmark randomized controlled trials in gynecologic cancer, such as, ICON7 for bevacizumab and chemotherapy or upfront surgery (CHORUS) trial for neoadjuvant chemotherapy in advanced ovarian cancer. Second part is great progress of targeted and immunotherapies, particularly in ovarian cancer. Attempt to genetically characterize chemoresistance and individual tumor behavior was also interesting. Third part is the updates of practice guidelines and professional recommendations based on the results of large-scaled clinical trials and/or meta-analyses. It is noteworthy that more and

Table 1. Fourteen topics of major clinical research advances in gynecologic cancer in 2015

Site of cancer	Topic	Reference
Ovary	1. Prevention and screening of ovarian cancer	[2,4,5,12]
	2. Update of neoadjuvant chemotherapy in ovarian cancer: right therapy to right person	[15]
	3. Personalized therapy for the best possible chance of survival in ovarian cancer	[21,22,23,24]
	4. Fifth Ovarian Cancer Consensus Conference in Tokyo	
	5. Immunotherapy update: anti-PD-1/PD-L1 antibody in ovarian cancer	[25,26]
Uterine cervix	6. HPV vaccine update: two dose, 9-valent, therapeutic vaccine	[28,36,42]
Uterine corpus	7. Old age as a reason for abandoning power morcellation in presumed fibroids	[43,44,45]
	8. Hormone therapies and endometrial cancer risk	[48,49]
	9. Trabectedin: another FDA-approved option for leiomyosarcoma	[56]
	10. Endometrial cancer and Lynch syndrome	[58,59]
	11. Radiation therapy in endometrial cancer: ESMO-ESGO-ESTRO consensus conference guidelines	[63,64,65]
Others	12. Vulvar cancer adjuvant therapy	[71]
	13. Targeted therapy update in gynecologic cancer	
	1) Update of anti-angiogenic drugs in ovarian cancer	[74,75,76]
	2) Other promising targeting agents in ovarian cancer	[81,82,84,85]
	3) Update of targeted therapy in cervical and endometrial cancer	[88,90,91]
Female breast	14. Breast cancer	
	1) Palbociclib in hormone-receptor-positive advanced breast cancer	[93]
	2) Oncotype DX Recurrence Score in low-risk breast cancer	[97]
	3) Regional nodal irradiation to internal mammary, supraclavicular, and axillary lymph nodes in breast cancer	[98,99]
	4) Cavity shave margins in breast cancer	[100]

ESGO, European Society of Gynecologic Oncology; ESMO, European Society of Medical Oncology; ESTRO, European Society for Radiotherapy and Oncology; FDA, the Food and Drug Administration; HPV, human papillomavirus; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1.

more researchers seemed to start and keep their interest in personalized therapy rather than 'one size fits all.' **Table 1** summarizes fourteen topics of major clinical research advances in gynecologic cancer in 2015.

PREVENTION AND SCREENING OF OVARIAN CANCER

Ovarian cancer usually has no specific symptoms in its early stages and therefore most cases are diagnosed at advanced stage with extensive peritoneal seeding. Consequent poor prognosis of as low as around 40% of 5-year overall survival (OS) has pushed many researchers to develop effective screening modality which can lead to significant reduction of ovarian cancer mortality, however, in vain. The only previous screening study that thus far reported mortality data, the ovarian component of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial, failed to prove the reduction of ovarian cancer deaths [1].

The study of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) published in *Lancet* firstly reported that in postmenopausal women from the general population, annual screening with multimodal strategy is safe and could reduce ovarian cancer deaths [2]. From 2001 to 2005, a total of 202,638 women aged 50–74 who had an average risk of ovarian cancer from 13 centers in National Health Service Trusts in England, Wales, and Northern Ireland were randomly allocated to join one of the three groups in a 1:1:2 ratio: annual multimodal screening (MMS) with serum cancer antigen 125 (CA125) interpreted with used of the risk of ovarian cancer algorithm (ROCA), annual transvaginal ultrasound screening (USS), or no screening. Women in MMS group with abnormal ROCA would undergo other tests with risk-based interval, possibly leading to surgery. Women in USS group had just ultrasound exams every year, with more test, if needed, to follow up on suspicious results. Median follow-up

was 11.1 years (interquartile range [IQR], 10.0–12.0). Ovarian cancer was diagnosed in 1,282 (0.60%) women with similar incidence rate in the three groups, however, mortality due to ovarian cancer was 148 (0.29%), 154 (0.30%), and 347 (0.34%) in the MMS, USS, and no screening groups, respectively. Despite insignificant mortality reduction over years 0–14 of 15% (95% confidence interval [CI], −3 to 30; p=0.100) with MMS and 11% (95% CI, −7 to 27; p=0.210) with USS, a prespecified analysis of ovarian cancer death of MMS vs. no screening with exclusion of prevalent cases showed significant decrease of death rates (p=0.021), with an overall average mortality reduction of 20% (95% CI, −2 to 40) and a reduction of 8% (95% CI, −27 to 43) in years 0–7 and 28% (95% CI, −3 to 49) in years 7–14 in favor of MMS, suggesting the long-term effect of an MMS screening program.

This trial results suggested that 641 women had to be screened annually for 14 years to save one life. False-positive rate, that resulted in unnecessary surgery for which ovaries had benign pathology or were normal, was 2.3 times higher in the MMS group than in the no screening group. The rate of major complications from those operations was 3.1%, which was similar to that of benign surgery report (2.9%) from NHS gynecological oncology centers. Although previous report from the UKCTOCS psychosocial study did not show that screening tests increased general anxiety [3], failure to prove the mortality reduction in the primary analysis and increase of unnecessary operations in this trial warrants further follow-up studies for firm conclusions on the efficacy and cost-effectiveness of ovarian cancer screening.

Considering this unclear situation for the efficacy and cost-effectiveness of ovarian cancer screening, the only available way likely to affect mortality is prevention. Society of Gynecologic Oncology (SGO) published five recommendations for the prevention of ovarian cancer in Cancer [4]. First, oral contraceptives reduce the risk of ovarian cancer and are considered safe for *BRCA1* and *BRCA2* mutations carriers. In a recent meta-analysis [5], oral contraceptive users with an average risk of ovarian cancer were shown to have a 40%–50% lifetime risk reduction. Although a recently published systematic review concluded that there is a small increased risk of breast cancer in oral pill users (odds ratio [OR], 1.08; 95% CI, 1.00 to 1.17), women with *BRCA1* or *BRCA2* mutations should consider taking oral pills to reduce their ovarian cancer risk not only because a significant reduction in the risk of ovarian cancer for *BRCA1* and *BRCA2* mutation carriers (summary relative risk [SRR], 0.50; 95% CI, 0.33 to 0.75), but also because there was no significant association between modern oral contraceptive use and breast cancer risk in these women (SRR, 1.13; 95% CI, 0.88 to 1.45) [6]. Second, tubal ligation is associated with a reduction in ovarian cancer in both the general population (34%) [7] and high-risk women (57% in *BRCA1* mutations carriers) [8]. Third, risk-reducing salpingo-oophorectomy (RRSO), the most proven method so far for the prevention of ovarian cancer in women with *BRCA1* or *BRCA2* mutation, was shown to have a 70%–85% reduction in ovarian cancer [9]. Because the cumulative incidence of ovarian cancer in *BRCA1* mutation carrier is low under the age of 40 years but reaches more than 10% by the age of 50 years, all guidelines recommend RRSO be performed between 35 and 40 years [10]. However, inevitable early menopause and consequently increasing cardiovascular mortality after RRSO at this early ages as well as surgical complication, even if the incidence rate is not high, make RRSO be indicated only for women at high-risk for breast and ovarian cancer. Fourth, genetic counseling and testing are imperative for women with an inherited increased risk for ovarian cancer to assess their risk [11]. Lastly, by contrast of high-risk women, for average risk women, opportunistic salpingectomy at the time of elective pelvic surgeries including hysterectomy and as an alternative to other sterilization could theoretically reduce the incidence of type 2 ovarian cancer. Because most relevant studies showed that there

was no additional detrimental effect of opportunistic salpingectomy after childbearing was complete, despite currently the absence of confirmative data demonstrating a reduction in ovarian cancer risk, opportunistic salpingectomy was included in the potential prevention strategies in the general population.

Another 2015 study to consider for the effective prevention of ovarian cancer is a meta-analysis of menopausal hormone use and ovarian cancer risk by Collaborative Group on Epidemiological Studies of Ovarian Cancer [12]. Current guidelines regarding postmenopausal hormone therapy need to be updated in terms of the risk of ovarian cancer because some are based on small retrospective studies potentially biased by selective participation or recall and others do not even mention ovarian cancer. During the prospective follow-up of 12,110 postmenopausal women from 52 epidemiological studies, current or recent use was associated with elevated the risk of ovarian cancer (relative risk [RR], 1.37; 95% CI, 1.29 to 1.46; p<0.001) and the risk was increased even with <5 years of use (RR, 1.43; 95% CI, 1.31 to 1.56; p<0.001) [12]. Definite increase of ovarian cancer risk was observed only in serous (RR, 1.53; 95% CI, 1.40 to 1.66; p<0.001) and endometrioid types (RR, 1.42; 95% CI, 1.20 to 1.67; p<0.001). Notably, elevated risk of these two common histologic types remains high even about 10 years after stopping long-term hormone therapy (RR, 1.215; 95% CI, 1.07 to 1.46; p=0.005). In conclusion, the authors summarized that 5-year hormone user might have one extra ovarian cancer per 1,000 users.

UPDATE OF NEOADJUVANT CHEMOTHERAPY IN OVARIAN CANCER: RIGHT THERAPY TO RIGHT PERSON

Following the first phase III trial of the European Organization for Research and Treatment of Cancer (EORTC) by Vergote et al. [13], full paper of the CHORUS trial, of which the abstract had been presented at the 2013 American Society of Clinical Oncology (ASCO) annual meeting in Chicago [14], was finally published in *Lancet* [15]. CHORUS was the second phase III, non-inferiority, randomized controlled trial of primary chemotherapy vs. primary surgery for newly diagnosed advanced ovarian cancer. In this study, a total of 550 patients with stage III or IV ovarian cancer were randomized to primary surgery group (n=276) and primary chemotherapy group (n=274). The median follow-up of total 99 evaluable survivors was 4.4 years (IQR, 3.5–4.1). Survival outcomes were not different, although in favor of primary chemotherapy group, between the two groups (median OS 25.8 vs. 23.7 months; hazard ratio [HR], 0.89; 95% CI, 0.73 to 1.08; median progression-free survival (PFS) 12.0 months vs. 10.7 months; HR, 0.91; 95% CI, 0.76 to 1.09). However, grade 3 or 4 postoperative adverse events were more frequently observed in primary surgery group than in primary chemotherapy group (24% vs. 14%; p=0.007). Shorter median survival (22–24 months) of CHORUS trial than other similar trials [13,16] might be due to higher average age (median age, 65 years) and poorer performance status of study population. The authors concluded that primary chemotherapy was non-inferior to primary surgery in terms of survival benefit and could be an acceptable standard of care for women with advanced ovarian cancer given the lower postoperative morbidity and mortality in primary chemotherapy group. Notwithstanding, relatively short operation time (median 120 minutes for both groups) and lower-than-expected optimal debulking rate (41% in primary surgery group and 73% in primary chemotherapy group; p<0.001) raised serious critics on the issue of quality control for the best surgical effort.

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Despite those critics, timely confirmation of the non-inferiority of neoadjuvant chemotherapy (NAC) and interval cytoreduction in advanced ovarian cancer by CHORUS trial have made more gynecologic oncologists prescribe NAC rather than implement primary surgery for the patients with advanced stage ovarian cancer [17,18]. Nevertheless, there was no R0 prediction models that is generally accepted yet. Nick et al. [19] introduced, so called, Anderson algorithm for personalized surgical therapy in *Nature Review Clinical Oncology*. The authors reported the significant increase of R0 resection rates from 44% (pre-implementation) in 2013 to 84% (post-implementation) for patients who were eligible for primary surgery ($p<0.01$). There was also a trend towards improved R0 resection rate in patients undergoing NAC (65% pre-implementation vs. 100% post-implementation; $p=0.15$). Among key features of the algorithm, diagnostic laparoscopy is offered to all surgically fit patients and two surgeons independently score the resectability of disease according to the validated predictive model [20]. Patients with scores <8 are offered primary cytoreduction, while those with scores ≥8 are offered NAC first. Improvement of R0 resection rate through this rational and personalized surgical approach is anticipated to be translated into survival improvement.

PERSONALIZED THERAPY FOR THE BEST POSSIBLE CHANCE OF SURVIVAL IN OVARIAN CANCER

Currently, all the patients with ovarian cancer, even though they do not seem to be a single disease but a group of pretty much heterogeneous populations, were treated with the same standard method, typically a maximal cytoreductive surgery followed by platinum-based combination chemotherapy. Developing a suitable targeted therapy that effectively halts the progression of the disease in a personalized manner based on one's genetic makeup is essential. In this regard, there were several outstanding researches conducted on personalized precision medicine for the treatment of ovarian cancer in 2015.

There were interesting studies that tried to find out genomic characterization of chemoresistant ovarian cancer. First, Australian Ovarian Cancer Study Group reported the first genetic map of how high-grade serous ovarian cancer (HGSC) evolves in response to chemotherapy by performing whole-genome sequencing of tumor and germline DNA samples from 92 patients at different stages of the disease: primary refractory, resistant, sensitive, and matched acquired resistant disease [21]. Although the researchers did not detect recurrent point mutations that were actionable in recurrence samples, they found that at least four common molecular events were associated with acquired resistance: multiple independent reversions of germline *BRCA1* or *BRCA2* mutations, loss of *BRCA1* promoter methylation, an alteration in molecular subtype, and recurrent promoter fusion associated with overexpression of the drug efflux pump MDR1 in about 8% of HGSC relapse samples. Gene breakage, which commonly inactivated tumor suppressor genes such as *RB1, NF1, RAD51B*, and *PTEN*, was also shown to contribute to acquired chemoresistance. On the other hand, *CCNE1* amplification was common in primary resistant and refractory disease. These findings could be of some help avoiding drugs that are likely to be ineffective in the first place. However, the heterogeneity of tumor and selective pressure of chemotherapy implicate that diverse approaches are essential in order to overcome chemoresistance in HGSC. Another outstanding study of chemoresistance in HGSC identified a disintegrin and metalloproteinase with thrombospondin motifs (*ADAMTS*) mutations as a possible predictor of chemosensitivity in ovarian cancer without *BRCA1* or *BRCA2* mutations [22]. Using the whole-exome sequencing data for the 210 cases in a discovery cohort from the

Cancer Genome Atlas (TCGA), the association of gene mutation with response status was quantified. *ADAMTS* mutations, an overall mutation rate of approximately 10.4%, were shown to be significantly associated with a higher chemosensitivity (100% for *ADAMTS*-mutated vs. 64% for *ADAMTS* wild-type cases; p<0.001). Moreover, *ADAMTS* mutations were associated with longer OS (HR, 0.54; 95% CI, 0.42 to 0.89; p=0.010) and PFS (HR, 0.42; 95% CI, 0.38 to 0.70; p<0.001). The associations remained the same with OS (HR, 0.53; 95% CI 0.32 to 0.87; p=0.010) and PFS (HR, 0.40; 95% CI, 0.25 to 0.62; p<0.001) even after adjustment by *BRCA1* or *BRCA2* mutation, surgical stage, residual tumor, and patient age. These findings suggested that there were still more events other than *ADAMTS* or *BRCA1/2* mutations that predicted better chemotherapy response because those mutations accounted for only 30% (10% and 20%, respectively) out of 70% of the clinical chemosensitivity rates. The last study that evaluated the genetic association with chemotherapy response was a genome-wide association study (GWAS) for mucinous ovarian carcinoma (MOC), of which the genetic susceptibility based on GWAS has never been reported before in part because of its rarity around 3% (Nature genetics [26]). With a total of 1,644 cases and 21,693 controls from Ovarian Cancer Association Consortium (OCAC)-Collaborative Oncology Gene-environment Study (COGS), three new risk associations were identified at: 2q13, 2q31.1, and 19q13.2. Of the three, 2q13 and 19q13.2 were MOC-specific, whereas 2q31.1 was involved with both MOC and HGSC. Because of the lack of available data of primary MOC, colorectal cancer (CRC) was used for primary MOC in the expression quantitative trait locus (eQTL) analysis on the basis of the moleculo-histologically common pathways of development between MOCs and CRCs. Thus, eQTL analyses of primary HGSC and CRC revealed that *PAX8* at 2q13 and *HOXD9* at 2q31.1 were candidate MOC susceptibility genes and functional study also supported these findings that overexpression of *HOXD9* in MOC cells enhanced neoplastic phenotypes of MOC. This study finding appears noteworthy because MOCs which is highly resistant to chemotherapy might be effectively prevented by identifying genetically susceptible women.

Dr. Bitler et al. [23] identified the relationship between *ARID1A* and EZH2 as the first potential effective target for the treatment of ovarian clear cell carcinoma, of which more than 50% *ARID1A* is mutated and loses genomic instability, and typically shows low response rate to platinum-based chemotherapy, in particular, in its late stages. *ARID1A*, a component of the switch/sucrose nonfermentable (SWI/SNF) chromatin-remodeling complex, changes the structure of nucleosomes to modulate transcription and normally prevents tumorigenesis. EZH2, the catalytic subunit of polycomb repressive complex 2 that inhibits gene from being expressed into tumor-fighting proteins by generating the lysine 27 trimethylation mark on histone H3, is often overexpressed in clear cell carcinoma. Authors showed that inhibition of the EZH2 methyltransferase caused regression of *ARID1A* mutated clear cell carcinoma in a synthetic lethal manner by inhibiting phosphatidylinositol 3-kinase (PI3K)/AKT signaling. These findings were published in *Nature Medicine* for the promise of highly specific small molecule EZH2 inhibitors as a new paradigm for pharmacologically targeting *ARID1A* mutation in ovarian clear cell carcinoma.

Another personalized approach for helping extend OS of the patients with ovarian cancer might be adjuvant hormone therapy (AHT) after surgery [24]. To elucidate the uncertainty over the oncologic safety of hormone replacement therapy (HRT) in recently castrated women due to ovarian cancer, a total of 150 patients who had been diagnosed with epithelial ovarian cancer <9 months prior to enrollment were 1:1 randomly assigned into AHT or control group. At a median follow-up of 19.1 years in patients who remained alive, 71% of AHT group have died compared with 91% in control group. The authors reported that there

were significant improvement of OS (HR, 0.63; 95% CI, 0.44 to 0.90; p=0.011) and relapse-free survival (RFS) (HR, 0.67; 95% CI, 0.47 to 0.97; p=0.032) in the AHT group, and the significance was still there even after adjustment for known prognostic factors (HR, 0.45; 95% CI, 0.30 to 0.69; p<0.001 for OS; and HR, 0.53; 95% CI, 0.34 to 0.81; p=0.004 for RFS). One of the interesting findings of this study was the effect of AHT on OS seemed to start as early as 4 to 5 years after randomization and persist for 20 years. Based on the finding that there was no difference of adverse event such as transient ischemic attack, cerebrovascular accident, myocardial infarction, fracture, or second primary cancer between the two groups (12% vs. 16%; p=0.64) and no cardiovascular or neurologic death in the AHT group, those women who suffer from severe menopausal symptoms after surgical treatment for ovarian cancer could be safely prescribed HRT without compromising their survival. However, the small sample size and the large CIs around the HRs observed in this study warrant a larger trial which confirms these results in this patient population.

FIFTH OVARIAN CANCER CONSENSUS CONFERENCE IN TOKYO

The fifth Ovarian Cancer Consensus Conference was held in Jikei University School of Medicine, Tokyo, Japan from sixth to ninth of November, 2015. Japanese Gynecologic Oncology Group (JGOG) hosted this conference with support of Japanese Society of Obstetrics and Gynecology (JSOG), Japanese Society of Gynecologic Oncology (JSGO), and Japanese Society of Medical Oncology (JSMO). Approximately one hundred participants attended to the conference and discussed the four topics: individualized therapy and patient factors (group A: chaired by P. Harter and M. Bookman), first line intervention (group B: chaired by J. Ledermann and JW. Kim), rare tumors (future approaches) (group C: chaired by M. Quinn and K. Fujiwara), and recurrent disease (group D: chaired by E. Pujade-Lauraine and D. Aoki). Group A discussed the most important factors including targetable markers to be evaluated prior to therapy for stratification and/or treatment selection with regard to front-line and recurrent settings. In addition, special patient subpopulations were also discussed for any specific considerations. Three topics of group B were 'What defines the clinical subgroups that should be used for comparator trials?', 'What different control arms could be considered for trials of first-line therapy?', and 'What should the endpoints be for first line trials?: OS vs. PFS and PFS2 for maintenance trials'. Three categories of rare tumors discussed by group C were rare epithelial tumor including low-grade serous, mucinous, and clear cell carcinoma, germ cell, and sex cord stromal tumors. For those, the standard treatment regimens and investigational treatments that need to be assessed were considered. The last group D also talked about three topics. First, MR. Mirza presented the subgroups for clinical trials in recurrent ovarian cancer in terms of multiple treatment lines, refractory, resistant, platinum-sensitive, asymptomatic CA125 elevation, prior use of antiangiogenic therapy, *BRCA* mutation, etc. Second topic which was presented by A. Oza was the control arms for clinical trials in recurrent ovarian cancer according to the main subgroups. The last topic of group D was the endpoints for clinical trials in recurrent ovarian cancer and presented by I. Vergote. The possible candidates included PFS, response evaluation criteria in solid tumors (RECIST)/CA125, OS, patient-reported outcomes (PROs) and symptom benefit and health-related quality of life, cost-effectiveness, etc., according to the main subgroups. The conference was closed after final presentation and voting on statements for all the items discussed.

IMMUNOTHERAPY UPDATE: ANTI-PD-1/PD-L1 ANTIBODY IN OVARIAN CANCER

Nowadays, achievement of proper host immunity from immunotherapy is one of the hottest topics in the cutting edge cancer research as well as oncology practice. Programmed cell death-1 (PD-1) is one of the immune checkpoint receptors which suppresses anti-cancer immune reactions by binding with PD-1 ligand (PD-L1). In 2015, Hamanishi et al. [25] reported the results of a phase II clinical trial of nivolumab, an anti-PD-1 antibody, in platinum-resistant ovarian cancer (UMIN000005714). Nivolumab was intravenously administrated to 20 eligible patients, low-dose (1 mg/kg; n=10) and high-dose cohorts (3 mg/kg; n=10), every 2 weeks until 1 year or progression disease state. Overall adverse events were observed in 19/20 (95%), and grade 3 or 4 adverse events were observed in 8/20 (40%). The most common adverse events were thyroid dysfunction including hypothyroidism (n=8), thyroiditis (n=2), and etc. The best overall response rate (i.e., complete response [CR] and partial response [PR]) across the two cohorts was confirmed in 15% (95% CI, 3.2%–37.9%): 1 patient with PR in the low-dose cohort and 2 patients with CR in high-dose cohort. The median PFS of the two cohorts was 3.5 months (95% CI, 1.7 to 3.8 months), and the median OS was 20.0 months (95% CI, 7.0 months to not reached). In this study, high-dose nivolumab was more favorable than low-dose in terms of better clinical efficacy without increased drug-related toxicity. In immunohistochemistry (IHC) staining, high expression of PD-L1 was confirmed in 16/20 (80%). However, the expression on IHC staining of PD-L1 and objective response for nivolumab were not statistically correlated. Notably, one of the patients with CR had histology of clear cell carcinoma. This result suggests that the immunotherapy with anti-PD-L1 antibody might lead survival benefit in clear cell carcinoma of ovary which had relative poor response to conventional chemotherapy.

Another study of immunotherapy in ovarian cancer was an ongoing phase IB trial (NCT01772004) of anti-PD-L1 antibody, avelumab. In 2015 ASCO annual meeting, Disis et al. [26] demonstrated the safety and efficacy of avelumab treatment in 75 patients with previously treated, recurrent or refractory ovarian cancer. Avelumab was administrated 10 mg/kg every 2 weeks in patients with ECOG performance state 0–1. At January 2015, the median duration of treatment was 10 weeks (range, 2–54 weeks), and 27 patients remained on treatment. In patients with followed-up duration >2 months, 4/23 (17.4%) patients experienced PR, and 11/23 (47.8%) had stable disease (SD). The median PFS was 11.9 weeks (95% CI, 5.9 weeks to not reached). Observed adverse events were fatigue, nausea, and diarrhea, however, all of them were manageable. Further analysis and study are warranted.

HPV VACCINE UPDATE: TWO DOSE, 9-VALENT, THERAPEUTIC VACCINE

Because of the uncertain clinical significance of cross-protection against non-vaccine HPV types [27], HPV vaccine which includes additional oncogenic types other than 16 and 18 has been developed in order to increase overall prevention of cervical cancer to more than 70%. In February, 2015, the results of a randomized, double-blind, phase 2b–3 study of the efficacy and immunogenicity of the nine-valent human papillomavirus (9vHPV) vaccine were published in the *New England Journal of Medicine* [28]. A total of 14,215 women between the ages of 16 and 26 were randomly assigned to receive a quadrivalent HPV (qHPV) vaccine control, which covers four HPV types (6, 11, 16, and 18), or investigational 9vHPV vaccine, which

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covers five additional oncogenic types (31, 33, 45, 52, and 58) in three doses over six months. Approximately 48% of the participants were already infected with some strains of HPV at the beginning of the study according to polymerase chain reaction (PCR) assays and serologic testing (48.3% vs. 47.9% of 9vHPV and qHPV vaccine group, respectively). Serum for antibody titers, genital swabs for HPV DNA testing, and liquid-based cytology were regularly collected over 4.5 years. The overall incidence rate of high-grade lesions was the same for both groups (14.0 per 1,000 person-years). In the subgroup analysis, however, whereas the incidence rate in the HPV-naïve women was 42.5% lower for 9vHPV group than that for qHPV group (2.4 vs. 4.2; 95% CI, 7.9 to 65.9), the rates in the HPV-infected women were similar in the two groups (23.1 vs. 22.1; 95% CI, −23.3 to 10.8). In that subgroup of HPV-naïve women, 9vHPV vaccine was 100% effective in preventing high-grade lesions related to the nine targeted HPV types (95% CI, 70.4 to 100), but the efficacy for the lesions not related to the vaccine HPV types was just 19.7% (95% CI, −34.5 to 52.5). Geometric mean titers of serum antibody to 9vHPV vaccine for HPV types 6, 11, 16, and 18 were not inferior to those to qHPV vaccine. Adverse events related to the injection site such as pain, swelling, and erythema were more common in 9vHPV vaccine group than qHPV vaccine group (90.7% vs. 84.9%) although most of these events were mild to moderate. Severe adverse events were more common in 9vHPV vaccine group. Although the durability of protection should be reevaluated in long-term follow-up study, this study clearly showed the importance of early 9vHPV vaccination before exposure to HPV. Based on these data, the American College of Obstetrics and Gynecologists (ACOG) published committee opinion on 9vHPV vaccination that the Advisory Committee on Immunization Practices recommended 9vHPV vaccination for girls and boys aged 11–12 years [29].

Previously a post-hoc analysis of the Costa Rica Vaccine trial in women who did not complete the three-dose regimen showed excellent efficacy of fewer than three doses against incident HPV 16/18 infections that persisted for at least 6 months [30]: one dose (100%, 95% CI, 79%–100%) and two doses (81%, 95% CI, 53%–94%) throughout 4 years after vaccination. Another outstanding study of efficacy of HPV vaccine in 2015 confirmed this dose-stratified vaccine efficacy findings using pooled dataset of the Costa Rica Vaccine and Papilloma Trial against Cancer in Young Adults (PATRICIA) trials which included 22,327 women who received three doses, 1,185 two doses, and 543 one dose [31-36]. The primary endpoint of this study was one-time detection of first incident HPV 16/18 infections accumulated during the 4 years of follow-up [36]. The investigators demonstrated similar efficacy regardless of the number of doses: three doses (77.0%, 95% CI, 74.7%–79.1%), two doses (76.0%, 95% CI, 62.0%–85.3%), and one dose (85.7%, 95% CI, 70.7%–93.7%). Of note, they observed, so called, cross protection against incident HPV 31/33/845 infections, only for those who received two doses six months apart (82.6%, 95% CI, 42.3%–96.1%), but not for those who received one dose (36.6%, 95% CI, −5.4%–62.2%) or two doses just one month apart (75.3%, 95% CI, 54.2%–87.5%). Because of the non-randomized nature and the small population numbers in the one-dose group of this study, one-dose policy does not seem to be applicable to a national immunization program until the more solid evidence of long-term efficacy of one-dose vaccination comes out.

Notwithstanding, currently available prophylactic vaccines have no therapeutic effects. CIN2/3 lesion can evolve from persistent HPV infections. However, some of CIN2/3 lesion undergoes spontaneous regression, presumably by an immune-mediated mechanism [37]. The current standard of care for CIN2/3 is surgical excision, for example, a loop electrosurgical excision procedure which could lead to reproductive morbidity [38]. There have been huge efforts to develop a non-surgical immune treatment for CIN2/3, but so

far the results are mixed [39-41]. *Lancet* published for the first time the promising results of a randomized, double-blind, placebo-controlled phase IIB study for the safety, efficacy and immunogenicity of VGX-3100, a therapeutic vaccine targeting HPV 16 and 18 E6 and E7 proteins for CIN2/3 [42]. A total of 167 patients aged 18–55 years with pathologically confirmed HPV-16 or -18 positive CIN2/3 were randomly assigned 3:1 to three-time (0, 4, and 12 weeks) intramuscular injections of VGX-3100 (n=125) or placebo (n=42). Pathologic regression to CIN1 or normal pathology 36 weeks after the first dose, the primary efficacy endpoint of this study, was observed in 53 (49.5%) of 107 VGX-3100 recipients and 11 (30.6%) of 36 placebo recipients (% point difference 19.0; 95% CI, 1.4 to 36.6; p=0.034) in the per-protocol analysis. A modified intention-to-treat analysis with 126 patients (114 VGX-3100 and 40 placebo) also revealed similar efficacy results (% point difference 18.2; 95% CI, 1.3 to 34.4; p=0.034). Most patients experienced injection site reactions. The authors expected their study results could change the treatment outline for cervical premalignant lesions.

OLD AGE AS A REASON FOR ABANDONING POWER MORCELLATION IN PRESUMED FIBROIDS

The Food and Drug Administration (FDA) of the US officially warned against the use of laparoscopic power morcellation for the removal of the uterus or uterine fibroids in April, 2014 based on the estimation of the prevalence, 1/458 women having surgery for presumed fibroids. In response to this decision, 48 gynecologists sent an open letter to the FDA for modification of current restrictive guidance in December, 2015. In this letter, they indicated an error of the prevalence of sarcoma overestimated by the FDA and corrected it from 1/458 (0.218%) to 1/1,550 (0.064%) through searching medical databases [43]. Two relevant studies of Wright et al. [44,45] addressed this issue further. First one was a large-scaled retrospective study of 41,777 women undergoing myomectomy, which confirmed similar prevalence of 0.09% (95% CI, 0.02%–0.27%) for women who underwent power morcellation [44]. Total of 3,220 (7.7%) patients underwent power morcellation, and year of surgery was significantly associated with that in multivariate analysis (2006 vs. 2012, prevalence ratio [PR], 2.12; 95% CI, 0.72 to 0.88). Black women (PR, 0.80; 95% CI, 0.72 to 0.88), uninsured patients (PR, 0.74; 95% CI, 0.57 to 0.95), and women with medical comorbidities (PR, 0.87; 95% CI, 0.77 to 0.98) were less likely to undergo power morcellation. In multivariate analysis for factors associated with uterine cancer, age was the strongest risk factor (<40 year vs. ≥60 years; PR, 54.33; 95% CI, 23.50 to 125.48). However, there was no statistically significant association with use of power morcellation (PR, 0.66; 95% CI, 0.20 to 2.18). Second study was a cohort simulation modeling study to determine risks and benefits of the use of electric power morcellation for hysterectomy for presumed benign diseases [45]. The researchers evaluated the efficacy of each the procedures from societal perspective stratified by age. Across all scenarios modeled, laparoscopic hysterectomy without morcellation was revealed the least costly and most beneficial approach method of three (abdominal, laparoscopic, or laparoscopic with power morcellation). Compared with other modalities, laparoscopic hysterectomy with morcellation was associated with increased cancer dissemination and cancer-associated deaths, especially in women age 60 years and older. However, laparoscopic hysterectomy with power morcellation was associated with fewer perioperative complications and fewer readmissions. In women age younger than 40 years, laparoscopic hysterectomy with morcellation may be more favorable than other in the circumstances by the scenario analysis in this study. Excess cases of disseminated cancer with power morcellation compared with abdominal surgery increased with age from 3.75/10,000 women (age 40–49),

to 12.97/10,000 (age 50–59), and to 47.54/10,000 (age ≥60). Compared with abdominal hysterectomy, these data equated to 0.3 (age 40–49), 5.07 (age 50–59) and 18.14 (age ≥60) excess deaths per 10,000 women. Results of a sensitivity analysis showed a 25% increase in cancer prevalence in each age group produced comparable mortality data. However, if a 25% reduction in cancer prevalence occurred, power morcellation would be the preferred treatment modality among women aged 40 to 49 years based on 0.05 fewer deaths per 10,000 women. Of note, the prevalence of uterine cancer was 0.19% (1/528) (95% CI, 0.15%–0.23%) in women who underwent myomectomy without power morcellation and 0.09% (1/1,073) (95% CI, 0.02%–0.27%) in those who had power morcellation. Although the prevalence of uterine cancer was not different between the two groups, this study enrolled the patients receiving only myomectomy, not included those with hysterectomy, generally performed in younger women had low-risk of uterine cancer. Therefore, this data should be cautiously applied in women with old age. Nevertheless, the authors concluded that as the incidence of cancer increases with age, power morcellation appeared to be associated more harm than benefit in women ≥50 years, while the benefits of morcellation compared with abdominal hysterectomy seemed to outweigh the risks in women <40 years.

Power morcellation for the removal of uterus or uterine fibroid is still a controversial issue. Women who are considering minimally invasive procedures with power morcellation should understand the potential risk of decreased survival leiomyosarcoma be present. They deserve more related data to better understand the real risk so that they could give informed consent before undergoing a procedure. We cannot neglect the clinical benefits of minimal invasive surgery, however, it seems to be necessary that power morcellation be cautiously performed in elderly women who had high-risk of uterine cancer with consideration of the potential risk of cancer dissemination.

HORMONE THERAPIES AND ENDOMETRIAL CANCER RISK

After the Women's Health Initiative Randomized Trial, it had been concluded that estrogen plus progestin increased breast cancer incidence [46,47]. In 2015, there were two studies suggesting that estrogen plus progestin significantly decreased endometrial cancer incidence. The first study was based on large cohort randomly assigned, in this trial (NCT000000611), Chlebowski et al. [48] reported that continuous estrogen plus progestin decreases endometrial cancer incidence of postmenopausal women. Eligible women were divided to estrogen plus progestin group (conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day; n=8,506) and placebo group (identical-appearing, n=8,102). Patients with endometrial cancer were fewer in the estrogen plus progestin group (66 patients, 0.06% per year) than the placebo group (95 patients, 0.10% per year, HR, 0.65; 95% CI, 0.48 to 0.89; p=0.007) for the entire follow-up period. During the drug intervention, fewer endometrial cancers were diagnosed in the estrogen plus progestin group, but the difference was not statistically significant (25 vs. 30 patients; HR, 0.77; 95% CI, 0.45 to 1.31; p=0.33). After the drug intervention, there was a significant difference of the endometrial cancer incidence between the two groups (41 patients, 0.08% per year vs. 65 patients, 0.13% per year; HR, 0.59; 95% CI, 0.40 to 0.88; p=0.008). The authors summarized the results that continuous combined estrogen plus progestin use reduced endometrial cancer incidence by 35% in postmenopausal women, and the effects were seen all histologic type.

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Collaborative Group on Epidemiological Studies of Ovarian Cancer also investigated the association between use of oral contraceptives and the subsequent risk of endometrial cancer, from 143,019 individual participant data of 36 epidemiological studies [49]. In this report, patients had ever used oral contraceptives were fewer in endometrial cancer group (35%; n=27,276) than control group (39%; n=115,743), with a median duration of use of 3.0 years (IQR 1–7) and 4.4 years (2–9), respectively (RR, 0.69; 95% CI, 0.67 to 0.72). Longer use of oral contraceptives was associated with the lower risk of endometrial cancer, and each 5 years of use had an RR of 0.76 (95% CI, 0.73 to 0.78; p<0.001). Ever-users had fewer carcinomas than women had never used oral contraceptives (RR, 0.69; 95% CI, 0.66 to 0.71), and the results was similar in type I and type II carcinomas. However, ever-use of oral contraceptives was not significantly associated with the risk of uterine sarcoma (RR, 0.83; 95% CI, 0.67 to 1.04). Over cumulative follow-up, the incidence of endometrial cancer was estimated to 1.7, 1.3, and 1.0 per 100 users in women who had used oral contraceptives for 5, 10, and 15 years, respectively. Like the studies mentioned earlier, longer use of oral contraceptives also results in a substantial proportional reduction in the incidence of endometrial cancer in this study. However, the point to make is that the type of oral contraceptives was confirmed to combined estrogen plus progestin in only 13 studies, and it was assumed to combined oral contraceptives in 23 studies. They suggested that this reduction in risk persists more than 30 years after use has ceased, therefore, public health effect of oral contraceptive use on endometrial cancer is most apparent many years after use has stopped.

TRABECTEDIN: ANOTHER FDA-APPROVED OPTION FOR LEIOMYOSARCOMA

Leiomyosarcoma is one of the most common subtypes of soft tissue sarcomas, which comprises approximately 1% of solid tumors. They are known to be resistant to standard chemotherapy and other targeted therapies, and an estimated median survival is 12 to 15 months for advanced or metastatic cases [50-52]. Therefore, practice guidelines primarily recommend them join clinical trials for the best hope of treatment. Trabectedin, originally isolated from a sea squirt, was one of the investigational drugs that have shown promising results in clinical trials of cancers including soft tissue sarcoma [53-55]. Based on the results of a phase III randomized clinical trial of trabectedin vs. dacarbazine in patients with unresectable, locally advanced or metastatic liposarcoma or leiomyosarcoma after prior therapy with an anthracycline and at least one additional systemic regimen (NCT01343277) [56], trabectedin finally got an approval of the US FDA in 2015 for the treatment of these two subtypes of soft tissue sarcoma. In this trial, a total of 518 patients who met the inclusion criteria were 2:1 randomized to receive trabectedin (n=345) at a starting dose of 1.5 mg/m^2 as a 24-hour intravenous infusion or dacarbazine (n=173) at a starting dose of 1 g/m^2 as a 20 to 120 minutes intravenous infusion. The primary endpoint was OS. Secondary endpoints were PFS, time to progression, objective response rate, and duration of response. Clinical benefit rate defined as the sum of CRs plus PRs plus SDs for at least 18 weeks and duration of stable disease were assessed to address those patients who experienced prolonged diseases control. Despite better PFS of trabectedin group than dacarbazine group in the final analysis of PFS (median PFS 4.2 vs. 1.5 months; HR, 0.55; p<0.001), interim analysis of OS showed only 13% reduction in risk of death in the trabectedin group compared with dacarbazine group (median OS 12.4 vs. 12.9 months; HR, 0.87; p=0.370). Clinical benefit rate was significantly higher in trabectedin group than that of dacarbazine group (34% vs. 19%, HR, 2.3; 95% CI, 1.45 to 3.70; p<0.001). Myelosuppression and transient elevation of transaminases were the

most common grade 3 to 4 adverse effects in trabectedin group. The approval of trabectedin for patients with these incurable malignancies might provide greater opportunity to improve the disease control.

ENDOMETRIAL CANCER AND LYNCH SYNDROME

Endometrial cancer is the most common gynecologic cancer in developed countries. Approximately 2%–5% of endometrial cancer is known to be associated with a hereditary cancer, mainly Lynch syndrome [57]. Lynch syndrome is an autosomal dominant disorder caused by a germline mutation in one of the DNA mismatch repair (MMR) genes: *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*. Endometrial cancer is the second most common malignancy in Lynch syndrome with cumulative risk by age 70 years between 15% and 30% [58]. For women with Lynch syndrome, nonetheless, neither is there clear evidence to support effective screening for endometrial cancer nor recommendations for reducing endometrial cancer risk. At this point, Dashti et al. [58] reported the associations of endometrial cancer risk with hormonal factors in women with Lynch syndrome were similar to those in the general population, providing directions in counseling women with a MMR gene mutation with regard to hormonal influences on endometrial cancer risk. This retrospective cohort study included 1,128 women with a MMR gene mutation from the Colon Cancer Family Registry across the United States, Australia, Canada, and New Zealand between 1997 and 2012. Primary outcome was self-reported diagnosis of endometrial cancer and primary exposures were self-reported endogenous and exogenous hormonal factors, for example, age at menarche, first and last live birth, and menopause, number of live births, hormonal contraceptive, and postmenopausal hormone use. One hundred thirty-three women had a diagnosis of endometrial cancer (incidence rate per 100 person-years 0.29; 95% CI, 0.24 to 0.34). Later age at menarche ≥13 years (vs. <13 years; HR per year 0.85; 95% CI, 0.73 to 0.99; p=0.04), multi-parity ≥1 live births (vs. nulliparous; HR, 0.21; 95% CI, 0.10 to 0.42; p<0.001), and ever use of hormonal contraceptives ≥1 years (vs. <1-year use; HR, 0.39; 95% CI, 0.23 to 0.64; p<0.001) were associated with a lower risk of endometrial cancer. However, no significant association was found between endometrial cancer and age at first and last live birth, age at menopause, and postmenopausal hormone use.

On the other hand, identifying patients with Lynch syndrome in endometrial cancer patients could benefit not only those with diagnosis of cancer but also their at-risk relatives [59]. Although IHC and microsatellite instability (MSI) analyses are screening tests typically performed on colon and endometrial cancer tissue to identify patients at risk for Lynch syndrome [60], the best screening method for Lynch syndrome in endometrial cancer is yet to be determined. False-negative rate was reported 5%–10% each with IHC and MSI testing. Therefore, Goodfellow et al. [59] evaluated if tumor IHC, MSI, and *MLH1* methylation analysis, test alone or combination of tests, best predicted Lynch syndrome using a large cohort of patients with endometrioid endometrial cancer from an NRG Oncology and Gynecologic Oncology Group (GOG) trial 210. A total of 1,002 tumors were analyzed for MSI, *MLH1* methylation, and MMR protein expression, and then classified as normal MMR, defective MMR associated with *MLH1* methylation (i.e., a sporadic epigenetic MMR defect), or probable MMR mutation (i.e., defective MMR but no methylation). Family history data were available for 938 patients. Of those, the combined data showed that 578 (61.6%), 253 (27.0%), and 107 (11.4%) were classified as normal MMR, sporadic epigenetic MMR defect, and probable MMR mutation, respectively. Among 6,615 relatives of 938 probands, 347 had

Lynch-associated cancers (LACs), including colon (n=142), endometrial (n=70), ovarian, stomach, hepatobiliary system, small bowel, renal pelvis or ureter, glioblastoma or brain, pancreas, and female reproductive tract. According to number and age of onset of LACs in first-degree relatives, familial risk of each proband was assigned to one of four: low, baseline, moderate and high. Overall 10.6% of probands had elevated (moderate 7.1% and high 3.4%) familial risk. On the other hand, germline mutation test results for forty-seven DNA samples from probands whose tumor MMR status was probable MMR mutation demonstrated nineteen (40.4%) germline mutations. Risk prediction through $PREMM_{1,2,6}$ showed that among the 34 with risk less than 10%, eight had mutations. Thus, the low sensitivity of $PREMM_{1,2,6}$ prediction model around 58% suggested that cancer family risk did not reliably predict germline mutation. Another interesting finding of this study was that some Lynch mutations were found in patients with endometrial cancer diagnosed at age >60 years. Despite younger age at diagnosis of endometrial cancer of mutations carriers than non-carriers (54.3 years vs. 62.3 years; $p<0.01$), there were five carriers (0.94%) diagnosed at age >60 years, which represents 24% of Lynch cases presenting with endometrial cancer. Overall, an estimated rate of LS from GOG210 was 3.89% considering the frequency of each class of predicted defect, somewhat lower than expected probably because of the small proportion of germline mutation testing and initial exclusion of prior CRC from GOG210. Nevertheless, the authors concluded that these results from a large cohort of endometrioid endometrial cancer seemed to be enough to indicate that all women with endometrioid endometrial cancer including women diagnosed at age >60 years should undergo Lynch screening that included IHC, *MLH1* methylation, and MSI tumor typing.

RADIATION THERAPY IN ENDOMETRIAL CANCER: ESMO-ESGO-ESTRO CONSENSUS CONFERENCE GUIDELINES

Following the American Society for Radiation Oncology (ASTRO) guidelines on endometrial cancer which was briefly reviewed in this series of 2014 [61] and thereafter endorsed by ASCO [62], European guidelines including adjuvant treatment in endometrial cancer were released from the first joint European Society for Medical Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) consensus conference on endometrial cancer, which was held in December 2014 in Milan, Italy [63-65]. Whereas the ASTRO guidelines suggested appropriate indications for treatments, the ESMO-ESGO-ESTRO guidelines consisted of recommended treatments according to risk groups: low, intermediate, high-intermediate, high, advanced, and metastatic. For low-risk endometrial cancer (stage I endometrioid, grade 1–2, <50% myometrial invasion, lymphovascular space invasion [LVSI] negative), no adjuvant treatment is recommended with level of evidence (LOE) I; strength of recommendation (SOR) A. For intermediate-risk endometrial cancer (stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative), adjuvant brachytherapy is recommended to decrease vaginal recurrence (LOE I; SOR B). However, adjuvant treatment can be omitted especially for patients aged <60 years because there is no OS gain from adjuvant RT (LOE II; SOR C). For high-intermediate-risk endometrial cancer (stage I, endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status; stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion), adjuvant brachytherapy (LOE III; SOR B) is recommended to decrease vaginal recurrence according to the results of GOG249 study [61]: no PFS benefit of adjuvant chemotherapy over the standard EBRT. High-risk endometrial cancer is a heterogeneous group with different stages and histologic types: stage

I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status; stage II; stage III endometrioid, no residual disease; non-endometrioid histologies (serous or clear cell or undifferentiated carcinoma or carcinosarcoma. Because of high risk of pelvic recurrence and distant metastases and inferior outcomes of this group, historically EBRT is the standard therapy to maximize pelvic control. Thus, the guidelines recommended adjuvant EBRT with limited fields to decrease locoregional recurrence (LOE I; SOR B). Recently, however, several clinical trials studied the efficacy and safety of the addition of chemotherapy (PORTEC-3) or replacement of RT by chemotherapy (GOG258) in high-risk endometrial cancer. Study results of both is coming in the near future, and therefore the guidelines recommended adjuvant chemotherapy as LOE II and SOR C. For stage II high-risk patients, a SEER data analysis with 1,577 stage II patients showed that RT was associated with a survival benefit [66]. Vaginal brachytherapy was recommended to patients with grade 1–2 and LVSI negative (LOE III; SOR B) based on the study results of low 5 year recurrent rates of around 2% after EBRT or vaginal brachytherapy alone [67,68]. However, limited field EBRT was recommended to high-risk patients with grade 3 or LVSI unequivocally positive (LOE III; SOR B). For stage III high-risk patients, EBRT was recommended to decrease pelvic recurrence (LOE I; SOR B). However, based on study results of PORTEC-3, which showed that adjuvant chemoradiation improved PFS and OS compared with RT alone, combined therapy of EBRT and chemotherapy was also recommended as LOE II and SOR B. For non-endometrioid, high-risk patients, chemotherapy was recommended to patients with serous and clear cell carcinoma (LOE III; SOR B). However, patients with stage IA, LVSI negative serous or clear cell carcinoma was recommended vaginal brachytherapy only without chemotherapy (LOE IV; SOR C) on the basis of low recurrence rate of 4%–7% and high 5-year OS rate of 84% after vaginal brachytherapy alone in stage IA disease [69]. The guidelines also included the role of RT in advanced and recurrent endometrial cancer: RT with curative intent in patients with isolated vaginal relapse after surgery (LOE III; SOR A) and RT with chemotherapy in patients with vaginal or pelvic nodal recurrence (LOE IV; SOR C). Other than RT, the guidelines also included multidisciplinary evidence-based approaches in diagnosis, treatment and follow-up of patients with endometrial cancer.

VULVAR CANCER ADJUVANT THERAPY

Because of its rarity (2–4/100,000/year), a well-designed large prospective study of vulvar cancer is very difficult to conduct. Therefore, high level evidence is sparse and there are lots of controversies over preferable treatments in practice guidelines, in particular, the clinical benefit from adjuvant therapy in lymph node-positive patients with vulvar cancer [70]. The AGO-CaRE-1 investigators including doctor Mahner et al. [71] conducted a large retrospective multicenter cohort study of 1,618 patients with primary squamous cell carcinoma of vulva. A total of 1,249 who underwent inguinal lymphadenectomy and knew lymph node status were analyzed. About one-third (n=447; 35.8%) had metastatic lesion at one (n=172; 38.5%) or two (n=102; 22.8%) lymph nodes. As a whole, 3-year PFS (75.2% vs. 35.2%; p<0.001) and OS (90.2% vs. 56.2%; p<0.001) rates were significantly higher in node-negative patients than node-positive patients. The extent of lymph node metastases correlated with 3-year PFS and OS: 47.6% and 72.8% for one, 27.6% and 50.1% for two, 33.1% and 44.8% for three, and 21.2% and 33.0% for four or more positive lymph nodes, respectively. Of those with lymph node metastasis, 244 (54.6%) underwent adjuvant therapy, and most of them (n=183; 84.4%) received radiotherapy at the groins. In these node-positive patients, those who received adjuvant therapy had better PFS (3-year PFS 39.6% vs. 25.9%; HR, 0.67; 95% CI, 0.51 to 0.88;

p=0.004), but similar OS (3-year OS 57.7% vs. 51.4%; HR, 0.79; 95% CI, 0.56 to 1.11; p=0.17) compared with those who did not. These trends remained constant after adjustment for age, performance status, stage, grade, invasion depth, and number of positive nodes. Notably, however, a subgroup analysis with regard to the number of positive nodes showed that significant PFS benefit was observed only in the patients with adjuvant radiotherapy in case of two or more positive nodes (HR [95% CI] for one, two, three, and ≥4 positive nodes: 0.87 [0.53 to 1.42], 0.44 [0.25 to 0.78], 0.37 [0.18 to 0.74], and 0.45 [0.25 to 0.82]). The finding that prognosis of node-positive patients remained poor even after adjuvant therapy suggests a prospective randomized study for the improvement of adjuvant therapy, so far most preferably neoadjuvant or adjuvant chemoradiation, is urgently needed.

TARGETED THERAPY UPDATE IN GYNECOLOGIC CANCER

1. Update of anti-angiogenic drugs in ovarian cancer

GOG218 and ICON7 are two large-scaled phase 3 randomized trials of bevacizumab, an anti-VEGF monoclonal antibody, in first-line settings in women with ovarian cancer, both of which previously demonstrated that the addition of bevacizumab to conventional carboplatin and paclitaxel regimen significantly improve PFS [72,73]. In 2015, Oza et al. [74] reported the final OS results of ICON7. Briefly, a total of 1,528 women with newly diagnosed ovarian cancer either high-risk early stage or more advanced stage diseases were 1:1 randomized into standard chemotherapy (six cycles of tri-weekly intravenous carboplatin [AUC 5 or 6] and paclitaxel 175 mg/m^2 of body surface area) or the same chemotherapy regimen plus bevacizumab 7.5 mg/kg intravenous every 3 weeks, concurrently and continued with up to 12 further cycles for maintenance therapy. Primary endpoint was PFS, however, ICON7 was also powered to detect a difference in OS. On March 31, 2013 when the study ended, median follow-up was 48.9 months (IQR 26.6–56.2). At this time where 714 had died (352 in the chemotherapy alone group and 362 in the bevacizumab group), there was no significant difference of OS between the two groups (restricted mean survival time 44.6 months [95% CI, 43.2 to 45.9] vs. 45.5 months [95% CI, 44.2 to 45.7]; p=0.85). However, in an exploratory analysis of high-risk group (n=502), which was defined as FIGO stage IV disease, inoperable stage III disease, or suboptimally debulked stage III disease with residual tumor >1 cm, significant longer OS in the bevacizumab group than chemotherapy alone group was noted (restricted mean survival time 39.3 months [95% CI, 37.0 to 41.7] vs. 34.5 months [95% CI, 32.0 to 37.0]; HR, 0.78 [95% CI, 0.63 to 0.97]; p=0.03). During the extended follow-up, there was only one further severe (grade ≥3) treatment-related adverse event of gastrointestinal fistula in the bevacizumab group. The study results of OS benefit only in the high-risk population, not in the whole study population, suggested the need of further study for optimum indications of bevacizumab in the treatment of ovarian cancer.

There was an effort to identify correlation between the efficacy of bevacizumab and tumor biomarker expression. In 2015 ASCO annual meeting, Birrer et al. [75] presented the results of five tumor biomarker expression (CD31, tVEGF-A, VEGFR-2, NRP-1, MET) assessed by IHC from GOG-218 population, which comprised 1,873 patients with incompletely resected FIGO stage III and IV ovarian cancer who randomly received three of the followings after surgery: 6 cycles of carboplatin and paclitaxel with placebo (CPP), bevacizumab 15 mg/kg q3w then placebo (CPB15), and bevacizumab for 15 months (CPB15+). Correlations between tumor biomarker levels and survivals were evaluated. There was no prognostic or predictive association for VEGFR-2, NRP-1, or MET. However, in CPB+ group compared with

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CPP group, increased expressions of CD31, which indicated microvascular density (MVD), showed potential predictive value for PFS (>3rd quartile [Q3] MVD HR, 0.38 [95% CI, 0.25 to 0.58]; ≤Q3 MVD HR, 0.69 [95% CI, 0.54 to 0.86]; interaction p=0.018) and OS (>Q3 MVD HR, 0.57 [95% CI, 0.39 to 0.83]; ≤Q3 MVD HR, 1.03 [95% CI, 0.83 to 1.27]; interaction p=0.0169). tVEGF-A also revealed a potential predictive value for OS (>Q3 tVEGF-A HR, 0.62 [95% CI, 0.43 to 0.91]; ≤Q3 tVEGF-A HR, 1.01 [95% CI, 0.82 to 1.25]; interaction p=0.023) when comparing CPB15+ with CPP group. Despite hitherto no predictive plasma biomarkers for efficacy of bevacizumab, this study suggests that tissue expression of tVEGF-A and endothelial cell could predict survival benefit from the addition of bevacizumab in advanced stage ovarian cancer.

Another anti-angiogenic drug, nintedanib, is an oral triple angiokinase inhibitor of VEGF receptors 1-3, fibroblast growth factor receptors 1-3, and platelet-derived growth factor receptors α and β. Added nintedanib to conventional carboplatin and paclitaxel regimen significantly improves PFS for chemotherapy-naive patients with advanced ovarian cancer in randomized, placebo-controlled phase III trial, AGO-OVAR 12 [76], in which a total of 1,366 patients with stage IIB-IV ovarian cancer who underwent upfront debulking surgery 2:1 randomly assigned to receive six cycles of carboplatin (AUC 5 or 6) and paclitaxel 175 mg/m^2 with or without 200 mg nintedanib or placebo twice a day on days 2–21 of every 3-week cycle for up to 120 weeks. Nintedanib group (n=911) had a significantly longer PFS than placebo group (17.2 months [95% CI, 16.6 to 19.9] vs. 16.6 months [95% CI, 13.9 to 19.1]; HR, 0.84; 95% CI, 0.72 to 0.98; p=0.024). Of note, preplanned and post-hoc subgroup analyses of PFS revealed that the efficacy of nintedanib seemed to be particularly notable in patients with stage IIB-III (HR, 0.76; [95% CI, 0.63 to 0.91] vs. stage IV, HR, 1.06; [95% CI, 0.80 to 1.39]), AUC 5 (HR, 0.836; [95% CI, 0.69 to 0.99] vs. AUC 6, HR, 0.91; [95% CI, 0.69 to 1.21]) and non-high risk patient group (HR, 0.74; [95% CI, 0.61 to 0.91] vs. high-risk, HR, 0.99; [95% CI, 0.80 to 1.24]). Non-high risk group, which was the same as that of ICON7 [73], was defined as stage III and postoperative residual tumor <1 cm or stage II disease. Considering that the ICON collaborators [73] did not report any significant benefit in the complementary subgroup of non-high-risk patients with FIGO stage up to III and no or minimum macroscopic residual tumor of less than or equal to 1 cm maximum diameter, du Bois et al. [76] proposed the possibility of the difference of efficacy patterns between anti-angiogenic tyrosine-kinase inhibitors and antibodies. The most common side effects were gastrointestinal including diarrhea (nintedanib group [grade 3, 21%; grade 4, <1%] vs. placebo group [grade 3 only, 2%]).

2. Other promising targeting agents in ovarian cancer

VEGF is known to be markedly elevated in the ascites of ovarian cancer patients, which associated with poor prognosis [77]. Similarly, colony-stimulating factor 1 (CSF-1), a cytokine that regulates the differentiation, growth and function of macrophages, is also known to be elevated in the ascites of ovarian cancer patients, and which associated with poor prognosis [78,79]. On the other hand, anti-VEGF antibody, bevacizumab, has been reported to cause fatal side effects, for example, intestinal perforation in up to 10% of patients in clinical trials [80], Moughon et al. [81] demonstrated that macrophage-targeted treatment with CSF-1R inhibitors lessen the number of pro-tumor macrophages and allow the vessels in the abdomen to become normal again, easing ascites accumulation without any concern about fatal side effects. In an immunocompetent murine model (ID8) of ovarian cancer which mimic late stages of human ovarian cancer with ascites, the macrophage content in the ascites directly correlated with vascular permeability. Immune and vascular

dysregulation were shown to worsen as ovarian cancer progressed. For example, mesentery blood vasculature was shown to be highly disorganized with markedly increased vessel density, vessel width, and number of branch points. The vessel perfusion function in the mesentery capillaries of tumor-bearing mice was significantly decreased, to about 25%. However, CSF-1R inhibition by GW2580, a selective CSF-1R inhibitor, was shown to reverse the abnormal vascular features and reduce vascular dysfunction and in this ID8 model as well as human OVCAR3 xenograft model. Notably, the high 3:1 ratio of M2:M1 macrophage was reduced to approximately 1:1 by GW2580 treatment [81]. Considering the abundant secretion of CSF-1 in many ovarian cancers, this study suggests that malignant ascites derived from vascular dysfunction could be safely controlled by blocking the function of tumor-associated macrophage via selective blockade of CSF-1R.

Rucaparib is a PARP inhibitor being developed for the treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors. Assessment of Rucaparib in Ovarian Cancer Trial (ARIEL) is an integrated translational-clinical program for identifying patients with tumor genotypes associated with benefit from rucaparib therapy. In 2015 ASCO annual meeting, the results of a phase II trial (ARIEL2) was presented by McNeish et al. [82]. ARIEL2 was a single-arm open label study to identify pre-specified tumor characteristics predicting sensitivity to rucaparib using a novel next generation DNA sequencing-based HRD assay and genome-wide loss of heterozygosity (LOH). While at least 50% of HGSC was reported to have homologous recombination deficiency (HRD), germline *BRCA1* and *BRCA2* mutations (*gBRCA*^{mut}) account for up to one third of the patients [82]. Because identification of *BRCA*^{wt} HRD tumors which are likely to respond to rucaparib seems challenging, ARIEL2 was conducted to evaluate clinical activity of rucaparib in 3 pre-defined HRD subgroups: tumor BRCA^{mut}, BRCA^{wt}/LOH^{high} and BRCA^{wt}/LOH^{low}. Clinical activity was assessed by RECIST and GCIG CA125 criteria [83]. Of 206 treated patients, of which 96% were high-grade serous cancer, efficacy data were available for 135. Objective response rates of the three subgroups were 69%, 39%, and 11% in BRCA^{mut}, BRCA^{wt}/LOH^{high} and BRCA^{wt}/LOH^{low} patients, respectively ($p<0.0001$, Cochran-Armitage trend test). There were only 15 (9%) BRCA^{wt} tumors that had a loss-of-function mutation or homozygous deletion in a HR gene. Of the 15, 4 (27%), all of the 4 were LOH^{high}, had alterations in *RAD51C* and responded to rucaparib. Of interest, there was an increase in genomic LOH over time in a subset of tumors.

There were two more 2015 ASCO presentations for promising targeted agents in ovarian cancer. One was AZD1775, a Wee1 inhibitor, and the other was IMGN853, a folate receptor alpha (FRα)-targeting antibody-drug conjugate. First, Oza et al. [84] presented the results of randomized phase II trial of AZD1775 plus paclitaxel and carboplatin for the treatment of women with platinum-sensitive, *TP53*-mutant ovarian cancer. On the basis of synthetic lethality of the combination of genotoxic drugs and Wee1 inhibitor AZD1775 in *TP53*-deficient cell, the researchers evaluated the efficacy of AZD1775 plus paclitaxel and carboplatin compared with paclitaxel and carboplatin alone in women with *TP53*-mutant ovarian cancer. A total of 121 patients with confirmed *TP53* mutations were randomly assigned to receive either AZD1775 (225 mg bid) (n=59) or placebo (n=62) for 2.5 days plus paclitaxel (175 mg/m^2) and carboplatin (AUC5) intravenously on day1 every three weeks until progression or the completion of six cycles. PFS was significantly longer in AZD1775 group than placebo group (enhanced RECIST: HR, 0.63; 80% CI, 0.45 to 0.89; 95% CI, 0.38 to 1.06; p=0.080; median PFS, 34.14 vs. 31.86 weeks; RECIST: HR, 0.55; 80% CI, 0.39 to 0.79; 95% CI, 0.32 to 0.95; p=0.030; median PFS, 42.86 vs. 34.86 weeks). However, there was no significant difference of objective response rates between the two groups (81.4% vs. 75.8%; difference 5.6%; 95% CI

for difference −9.4 to 20.2; p=0.459). There were 36 patients who had serious adverse events (40.7% vs. 20.0%), and 25 (20.3% vs. 21.7%) finally discontinued the drugs. The study results suggest that the addition of AZD1775 to paclitaxel and carboplatin could lengthen the PFS compared with paclitaxel and carboplatin alone with acceptable tolerability in women with *TP53*-mutant ovarian cancer. The last 2015 ASCO study of targeted therapy in ovarian cancer reviewed in this series is a phase I study of IMGN853 (mirvetuximab soravtansine) in patients with ovarian cancer [85]. Mirvetuximab soravtansine comprises a conjugation with a highly potent maytansinoid that induces cell-cycle arrest and cell death by targeting microtubules, in order to specifically target FRα-positive cancer cells [86]. Borghaei et al. [85] demonstrated the results of phase I trial of IMGN853. They evaluated recommended phase 2 dose in total 59 patients with two dosing schedules as (A) once every 3 weeks and (B) days 1, 8, and 15, every 4 weeks. Recommended phase 2 dose was determined as 6.0 mg/kg in 44 patients with (A) schedule, while dose finding in (B) continues. Clinical benefits, which was defined as PR or CR, CA125 response, stable disease ≥6 cycles, were observed 11/44 patients in (A) (4 PR; 2 confirmed CA125 responses; 5 SD, 2 for 10 cycles) and 5/15 evaluable patients in (B) (1 PR; 4 SD, 3 with confirmed CA125 response; 6 remain on study). The authors concluded that IMGN853 showed encouraging clinical activity in heavily pretreated ovarian cancer patients with a manageable side effect profile. Based on these findings, a phase II trial of IMGN853 in adults with FRα-positive advanced ovarian cancer is now underway (NCT02631876).

3. Update of targeted therapy in cervical and endometrial cancer

In this series of last year, we reviewed the promising results of GOG240 trial [61], which was an improvement of 3.7 months in median OS by the addition of bevacizumab to combination chemotherapy for the treatment of recurrent, persistent, or metastatic cervical cancer [87]. Two relevant results from additional analyses of GOG240 were reported in 2015. First one was patient-reported health-related quality of life results which was assessed by the score on the Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index (FACT-Cx TOI) [88]. Participants of this study were assessed before treatment cycles 1, 2, and 5, at 6 and 9 months after the start of cycle 1. There was no significant score difference between chemotherapy alone and chemotherapy plus bevacizumab group (p=0.30). Based on these results, although more severe toxicity profiles were reported in the addition of bevacizumab than chemotherapy alone, the authors concluded that the incorporation of bevacizumab into the treatment of advanced cervical cancer were not accompanied by any significant deterioration in health-related quality of life [88]. Second one was a prospective validation of pooled prognostic factors, also known as the Moore criteria [89], in GOG240 [90]. Five factors that were shown to be prognostic included African-American ancestry, performance status 1, pelvic disease, prior cisplatin, and PFS <1 year. Of those, if the patient had 0–1, 2–3, and 4–5 risk factors, she was categorized into low-, mid-, and high-risk group, respectively. Among all 452 patients, high-risk patients had worse OS (p<0.001). The HRs of death for bevacizumab were 0.96 (95% CI, 0.51 to 1.83; p=0.909), 0.673 (95% CI, 0.50 to 0.91; p=0.0094), and 0.536 (95% CI, 0.320 to 0.905; p=0.0196) in low-, mid-, and high-risk patients, respectively. These findings suggest that the clinical benefit from the integration of bevacizumab to chemotherapy seems to be small in low-risk patients with recurrent, persistent or metastatic cervical cancer. However, clear survival benefit shown in mid-to high-risk patients may well outweigh the toxicity concerns of bevacizumab in this group of patients.

There was a phase II clinical trial which demonstrated the notable clinical benefit with tolerable side effects of the combination therapy of letrozole, an aromatase inhibitor, and everolimus, a mammalian target of rapamycin (mTOR) inhibitor in recurrent endometrial

cancer [91]. Given one of the mechanisms underlying resistance to hormonal treatment in endometrial cancer is PI3K pathway activation, targeting mTOR may overcome the resistance, and therefore could improve the poor survival of recurrent or advanced endometrial cancer. A total of 38 patients with incurable endometrial cancer with measurable disease who treated with up to two prior regimens were enrolled. Everolimus 10 mg/day and letrozole 2.5 mg/day were orally administered until progression, discontinuation due to toxicity, or CR. Clinical benefit rate, which was defined as CS, PR, or SD ≥16 weeks, was 40% (14 of 35). Objective response rate was 32% (11 of 35; 9 CRs and 2 PRs). There was no patients who discontinued treatment because of toxicity. Endometrioid histology and *CTNNB1* mutations were associated with better response, while serous histology were associated with lack of response.

BREAST CANCER

1. Palbociclib in hormone-receptor-positive advanced breast cancer

Palbociclib (Ibrance®; Pfizer, New York, NY, USA), an orally bioavailable small-molecule inhibitor of CDK4 and CDK6, have high activity in hormone-receptor–positive breast cancer and is synergistic in combination with endocrine therapies. In the previous open-label, randomized, phase 2 study involving patients with newly diagnosed metastatic estrogen-receptor–positive breast cancer, palbociclib in combination with letrozole was associated with significantly longer PFS than was letrozole alone [92]. The efficacy of palbociclib and fulvestrant in advanced breast cancer who had progression of disease during prior endocrine therapy was assessed in the PALOMA-3 study [93]. A total of 521 patients were randomized in a 2:1 ratio to receive palbociclib and fulvestrant or placebo and fulvestrant. Premenopausal or perimenopausal women also received goserelin. The primary end point was investigator-assessed PFS. The median PFS was 9.2 months (95% CI, 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; p<0.001). The most common grade 3 or 4 adverse events in the palbociclib–fulvestrant group were neutropenia (62.0% vs. 0.6%), leukopenia (25.2% vs. 0.6%), anemia, thrombocytopenia, and fatigue. But febrile neutropenia was rare (0.6% in both groups). The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo.

2. Oncotype DX Recurrence Score in low-risk breast cancer

A 21-gene expression assay (Oncotype DX®; Genomic Health, Redwood City, CA, USA) have been shown to provide additional prognostic information independent of clinicopathologic features and also to predict benefit from adjuvant chemotherapy in estrogen-receptor–positive disease in prior prospective-retrospective design studies [94-96]. The Trial Assigning Individualized Options for Treatment (TAILORx) is a prospective trial to further validate and refine the clinical usefulness of the 21-gene assay in a specified low-risk cohort of women with hormone-receptor-positive, HER2-negative, axillary node-negative invasive breast cancer, with tumors of 1.1 to 5.0 cm in the greatest dimension (or 0.6 to 1.0 cm in the greatest dimension and intermediate or high tumor grade) who met established guidelines for the consideration of adjuvant chemotherapy on the basis of clinicopathologic features [97]. Patients were assigned to receive endocrine therapy without chemotherapy if they had a recurrence score of 0 to 10, indicating a very low risk of recurrence. Of the 10,253 eligible women enrolled, 1,626 women (15.9%) had a recurrence score of 0 to 10. At 5 years, in this patient population, the rate of invasive disease–free survival was 93.8% (95% CI, 92.4 to 94.9),

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the rate of freedom from recurrence of breast cancer at a distant site was 99.3% (95% CI, 98.7 to 99.6), the rate of freedom from recurrence of breast cancer at a distant or local-regional site was 98.7% (95% CI, 97.9 to 99.2), and the rate of OS was 98.0% (95% CI, 97.1 to 98.6).

3. Regional nodal irradiation to internal mammary, supraclavicular, and axillary lymph nodes in breast cancer

Two publications dealt with issues regarding regional nodal irradiation in breast cancer.

Whole-breast irradiation after breast-conserving surgery reduces the rate of local recurrence in early stage breast cancer. 'Regional nodal irradiation' means irradiation to the chest wall and regional lymph nodes, and is commonly used after mastectomy in women with node-positive breast cancer, as it is proven to reduce locoregional and distant recurrence and improves OS. But it has not been clear whether the addition of regional nodal irradiation to whole-breast irradiation after breast-conserving surgery has the same effect. A total of 1,832 women were randomized to either whole-breast irradiation plus regional nodal irradiation (including internal mammary, supraclavicular, and axillary lymph nodes) (nodal irradiation group) or whole-breast irradiation alone (control group) in the MA.20 study [98]. At the 10-year follow-up, there was no significant difference in survival, which is the primary endpoint, with a rate of 82.8% in the nodal-irradiation group and 81.8% in the control group (HR, 0.91; 95% CI, 0.72 to 1.13; p=0.38). The rates of disease-free survival were 82.0% in the nodal-irradiation group and 77.0% in the control group (HR, 0.76; 95% CI, 0.61 to 0.94; p=0.01). Patients in the nodal-irradiation group had higher rates of grade 2 or greater acute pneumonitis and lymphedema.

The incidence of metastatic involvement of the internal mammary nodes varies between 4% and 9% in patients with axillary node–negative breast cancer and between 16% and 65% in patients with axillary node-positive breast cancer. Surgical dissection of the internal mammary nodes failed to improve survival and was abandoned in the 1970s. Elective irradiation of the regional nodes was widely used until the late 1980s, but it also failed to show survival benefit and was suggested to decrease long-term survival owing to irradiation of the heart. Since then, radiation techniques improved and a favorable effect of postmastectomy radiation was proven. So the authors investigated the effect on OS of whole-breast or thoracic-wall irradiation plus internal mammary and medial supraclavicular lymph-node irradiation (nodal irradiation group) in comparison of whole-breast or thoracic-wall irradiation alone (control group) in EORTC 22922/10925 study [99]. At 10 years, OS was 82.3% in the nodal-irradiation group and 80.7% in the control group (HR for death with nodal irradiation 0.87; 95% CI, 0.76 to 1.00; p=0.06). The rate of disease-free survival was 72.1% in the nodal-irradiation group and 69.1% in the control group (HR for disease progression or death 0.89; 95% CI, 0.80 to 1.00; p=0.04), the rate of distant disease-free survival was 78.0% vs. 75.0% (HR, 0.86; 95% CI, 0.76 to 0.98; p=0.02), and breast-cancer mortality was 12.5% vs. 14.4% (HR, 0.82; 95% CI, 0.70 to 0.97; p=0.02).

4. Cavity shave margins in breast cancer

Margin status is a critical determinant of local recurrence after surgery, and 20% to 40% of patients treated with partial mastectomy have positive margins, eventually requiring a second operation for margin clearance. The authors randomized 235 patients with stage 0 to III breast cancer intraoperatively after surgeons had completed standard partial mastectomy according to their usual practice [100]. Patients were randomized to have further cavity shave margins resected (shave group) or not to have further cavity shave margins resected (no-shave

group). The rate of positive margins was the primary outcome measure; secondary outcome measures included cosmesis and the volume of tissue resected. The rate of positive margins after partial mastectomy (before randomization) was similar in the shave group and the no-shave group (36% and 34%, respectively; p=0.69). After randomization, patients in the shave group had a significantly lower rate of positive margins than did those in the no-shave group (19% vs. 34%; p=0.01), as well as a lower rate of second surgery for margin clearance (10% vs. 21%; p=0.02). There was no significant difference in complications between the two groups.

CONCLUSIONS

In 2015, there were several outstanding research advances in the field of gynecologic oncology. In particular, there surely was a trend toward, so called, precision medicine, which takes into account individual variability in genes, environment, and lifestyle for each person. Many resources are moving on to identifying the best candidates of new therapies. "Who will most benefit from this treatment?" is expected to be the main research topic of near future in gynecologic oncology.

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