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How to significantly reduce the incidence of cervical cancer?

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In Taiwan, cervical cancer is the ninth most common cancer in women and the eighth leading cause of female cancer mortality. Since 1995, the national health insurance (NHI) of Taiwan has made free annual cervical screening available to all Taiwanese women aged ≥ 30 years. The age-standardized incidence of cervical cancer in Taiwan has decreased from 29.09 per 100 000 in 1981 to 7.88 per 100 000 in 2017. The age-standardized mortality decreased from 7.14 per 100 000 in 1981 to 3.20 per 100 000 in 2017. The rate of 6-year Pap smear screening coverage rate has stabilized at 70% for 15 years. Efforts must be made to increase the coverage.

A study for newly diagnosed cervical found that 44.0% of the participants had never had a Pap smear before diagnosis. Stepwise logistic regression identified perceived potential pain, fear of embarrassment as independently associated with the number of previous Pap smears (0 versus ≥ 1). The need for developing more comfortable and privacy-assured methods of screening is highlighted. Education strategies should be focused on improving access to never-users.

The fact that HPV testing is useful in primary screening for cervical neoplasms is widely accepted in medical community. In a population-based study (Taoyuan-CGMH cohort), the overall HPV prevalence was 10.8%. The sensitivity of the Pap smear was 81.9%, which improved to 97.2% with combined Pap and HPV testing. Co-test should be offered for those Pap under-users. A study invited women who have not attended Pap smear in the past 5 years to HPV testing by self-sampling. Only 305 (2.85%) with informed consent and HPV test

samples were returned. Primary screening using self-sampling vaginal specimens has not been registered in US Food and Drug Administration (FDA) or Taiwan FDA (TFDA) so far. A breakthrough of cervical screening coverage rate is promising if HPV testing using self-sampled vaginal specimen and reflex Pap can be proven non-inferior to Pap for primary cervical screening.

Identify cancer precursors can secondary prevent the occurrence of invasive cervical cancer, while HPV vaccination is the primary prevention. Again, the coverage is important. Prophylactic HPV vaccines have been available since 2007, however only a few cities or counties are providing HPV vaccination of 12 to 13 year-old girls by public funding. National program of HPV vaccination for 7-grade girls has been implemented since 2018 in Taiwan. According to Health Promotion Administration, the coverage rate was 76.6% in 2018 and 86.9% in 2019. A catch-up 16-18 year-old girls vaccination should be considered see the impact will be greater using multiple age cohort vaccination strategy.

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Real world experience after NHI reimbursement of bevacizumab— Recurrent ovarian cancer

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In OCEANS trial for platinum-sensitive (PS) recurrent epithelial ovarian cancer (EOC), progression-free survival (PFS) was significantly increased in chemotherapy plus bevacizumab (BEV) when compared with chemotherapy alone among patients with progression-free interval (PFI) 6– 12m (12.5 m vs 7.4 m; hazard ratio [HR] 0.36, 95% CI 0.25– 0.53). However, overall survival (OS) did not differ between the two treatment groups. In MITO-16B trial for PS EOC with prior BEV-containing therapy, the median PFS for chemotherapy plus BEV vs chemotherapy alone were 9.8 vs 7.9 m (HR 0.50, 95% CI 0.33– 0.74). OS data is not yet mature.

We have provided real world experience in treatments for 65 recurrent EOC, tubal cancer (TC), primary peritoneal cancers (PPC). Of those treated with various chemotherapy regimens, 39 (60.0%) received adjuvant platinum-based chemotherapy and 22 (33.8%) had prior BEV use. BEV dosage was 7.0– 12.6 mg/kg and 7.9– 11.6 mg/kg for patients with the first and ≥2 relapses, respectively; the mean number of treatment cycles was 5.3 and 6.5, respectively. Thirty-nine patients (60.0%) had serous histology, 10 (15.4%) had clear cell carcinoma histology, 6 (9.2%) had endometrioid histology, and 4 (6.2%) had mucinous histology. During follow-up, 39 patients (60.0%) developed progressive disease, and 29 (44.86%) died. Twenty-one (32.3%) had PFI <6 m, 21 (32.3%) had PFI of 6-12 m, and 23 (35.4%) had PFI ≥12 m. Patients with PFI ≥6 m after primary therapy had a significantly better OS and PFS2– PFS than those with PFI <6 m ($P < 0.001$ and $P < 0.001$, respectively). Patients with a longer PFI had more favourable survival.

Bevacizumab is now covered under the Taiwan national health insurance for patients with PFI of 6-12 m. With more promising data, we believe more patients with PS EOC/TC/PPC will be treated with chemotherapy plus BEV and BEV continuation to achieve a longer PFI and survival.

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Real world experience after NHI reimbursement of bevacizumab— Dosage and adverse events

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Targeted therapy has been a new option for gynecological patients since the publication of GOG218 and ICON7 in the New England Journal of Medicine in 2011. Ever since then, multiple indications of bevacizumab usage emerged in the field of gynecology oncology.

There were two important trials that aimed to resolve unmet needs. One for advanced cervical cancer, and the other was for platinum sensitive recurrent ovarian cancer. In 2014, Tewari et al published the landmark trial GOG240, demonstrating overall survival benefits with the addition of bevacizumab to two chemotherapy regimens combined in advanced cervical cancer patients. An increased incidence of hypertension, thromboembolic events, and gastrointestinal fistulas were noted in the bevacizumab containing arm. In 2017, Dr. Robert Coleman published the results of the bevacizumab component of GOG213, also demonstrating a survival benefit in platinum sensitive recurrent ovarian cancer in the chemotherapy group. The most frequently reported adverse events of these in the chemotherapy plus bevacizumab group compared with the chemotherapy group were hypertension, fatigue, and proteinuria.

Gynecological patients in Taiwan had limited resource other than chemotherapy in the past few years. After the usage of targeted therapy in our institution, we investigated adverse events and outcomes in patients treated with bevacizumab for ovarian cancer patients and showed that there were different kinds and higher cumulative incidences of adverse events observed compared to those reported in previous clinical trials. Moreover, bevacizumab doses showed cumulative toxicity and plateau effects on hypertension and proteinuria.

Starting from the third quarter of 2020, two indications were reimbursed in national health insurance for gynecological patients. One for partially platinum-sensitive recurrent ovarian cancer patient, and the other was for advanced cervical cancer patients. How are our patients performing and what are the experiences regarding dosage and adverse events? We give a brief report regarding this topic.

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Real world experience after NHI reimbursement of bevacizumab— Recurrent cervical cancer

Most of the recurrent cervical cancer is incurable, except those of local/regional recurrence. Chemotherapy is the major treatment for recurrent cervical cancer. Compared with cisplatin alone, cisplaltin + topotecan was the first regimen proven to have survival benefit to recurrent cervical cancer by GOG 179. GOG 240 compared combination chemotherapy (carboplatin + paclitaxel or paclitaxel + topotecan) with or without bevacizumab, and showed longer progression-free survival (PFS, 2-side) and overall-survival (OS, 1-side). Reimbursement of bevacizumab + carboplatin + paclitaxel was passed in June 2020 in Taiwan. Here we reported the preliminary results of the response of recurrent cervical cancer to the new regimen as a light of real-world experience. From June 2020 to Feb. 2021, 70 patients with recurrent cervical cancer were approved for use of bevacizumab + carboplatin + paclitaxel. In 47 patients who had used more than 3 cycles, 11 patients (23.4%) obtained complete response, 24 (51.1%) partial response, 5 (10.6%) stable disease. The overall response rate was 74.5% and disease control rate was 85.1%. Toxicity was also reported in our first-in-Taiwan real-world experience.

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Onco-fertility in gynecologic cancers – guidelines-- Cervical Cancer

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As screening progresses, more and more patients with cervical cancer are diagnosed at a young age. In American, almost 40% of women with cervical cancer are diagnosed between the ages of 20 and 44 years, with disease confined to the cervix in approximately 46% of cases. The radical trachelectomy procedure is now recognized as an alternative to radical hysterectomy for young women with lesions <2 cm who wish to preserve fertility as National Comprehensive Cancer Network (NCCN) guidelines. It is reassuring that a recent Surveillance, Epidemiology, and End Results (SEER) data analysis shows that uterine preserving surgery such as cone/trachelectomy is not associated with a higher risk of death compared with non-uterine preserving surgery (hysterectomy).

Conization and radical trachelectomy are standard methods of fertility preservation for patients with early-stage cervical cancer. Cervical conization can be performed for stage IA1 or IA2 cervical cancer. Sanghoon et al reported combined results of multiple studies showed in Korean studies, the rate of recurrent cervical cancer was 3.5% (22 of 619) and that of mortality was 1.9% (12 of 619) in a total of 619 patients with cervical cancer who underwent trachelectomy. Among the 619 patients, 236 patients successfully became pregnant, but 20% of these patients had a miscarriage in the first trimester, and 8% (20 of 236) had a miscarriage in the second trimester. Eventually, 66% of the pregnant patients had a delivery in the third trimester (157 of 236), 15% before the 32nd week of pregnancy and 85% after the 32nd week of pregnancy.

There are also many fertility-sparing treatment studies for cervical cancer with large tumor size (> 2 cm), and for more conservative surgery (large conization , simple trachelectomy after neoadjuvant chemotherapy). We wish to further confirm the safety and feasibility of reproductive preservation in patients with early-stage cervical cancer. The ultimate objective in medicine is not only how to survive, but also how to live better.

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Onco-fertility in gynecologic cancers – guidelines-- Endometrial Cancer

Endometrial cancer is one of the most common gynecologic cancer worldwide. About 5% of the patient are under 40 years of age. Fertility-sparing treatment including involves the use of progestins and/or levonorgestrel-releasing intrauterine devices, which have been shown to be feasible and safe in early endometrial cancer. However, data on the efficacy and safety are based on retrospective studies and randomized clinical trials in younger women are underway.

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Onco-fertility in gynecologic cancers – guidelines-- Epithelial ovarian Cancer

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Epithelial ovarian cancer (EOC) is the seventh most common cancer and the eighth most common cause of cancer death among women worldwide. Although about 75 % patients are diagnosed stage III or IV initially. 10-15 % of patients are with localizes disease in ovary. EOC is most commonly diagnosed after menopause (average age 65 years), although between 3% and 17% of cases are diagnosed in women younger than 40 years.

Standard treatment of advanced ovarian cancer includes bilateral salpingo - oophorectomy, total hysterectomy, omentectomy, peritoneal biopsies or intraabdominal tumor excision, pelvic and para- aortic lymph node dissection, followed by taxane/platinum chemotherapy . However, standard treatment leads to permanent sterility. Fertility issue is important for young women who wish to preserve their childbearing potential in early stage ovarian may benefit fertility sparing surgery (FSS) (uterine and contralateral adnexa preservation).

Fertility sparing surgery may be another option for reproductive patients with early stage ovarian cancer. Patient’ s selection is important about tumor location(unilateral), histology type, grade, genetic mutation and reproductive age. Oncological outcome (recurrent and survival rate) between FSS and radical surgery reveals no significant difference. Embryo, oocyte or ovarian cryopreservation following FSS are tools to elevate reproductive outcomes which may resemble as general population. Although FSS is an option for young age patients, accurate counseling and patient’ s selection are important before treatment.

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Onco-fertility in gynecologic cancers – guideline-- Germ cell ovarian cancer

Introduction

Non-epithelial ovarian tumors are approximately 10% of ovarian cancers. Malignant germ cell tumor (GCT) represents 5% of all ovarian cancers and 80% of preadolescent malignant ovarian tumors. The World Health Organization (WHO) classification of GCTs defines as dysgerminoma, yolk sac tumor, embryonal carcinoma, non-gestational choriocarcinoma, mature teratoma, immature teratoma, and mixed germ cell tumor.

Current diagnosis

Diagnostic work-up should include pelvic ultrasound, abdomino-pelvic computed tomography (CT) scan, chest X-ray and positron emission tomography (PET) scan in selected cases (GCTs)

Treatment guideline

Germ cell tumors are chemosensitive and susceptible to fertility-sparing surgery. The correct pathological diagnosis is essential.

Early-stage Germ cell tumors (60%– 70%) are diagnosed at early stage
fertility. Fertility-sparing surgery is safe with excellent survival and reproductive outcome. Adjuvant chemotherapy with 5-day BEP is the most used regimen.

Advanced-stage and recurrent GCTs Fertility-sparing surgery could still be considered in advanced stages. Adjuvant chemotherapy with 5-day BEP is the most used regimen.

Fertility Outcome After fertility-sparing surgery, the reproductive outcome is promising.

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Genetic testing and PARP inhibitor maintenance in epithelial ovarian cancer after NHI reimbursement--Genetic testing

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Poly(ADP-ribose)polymerase (PARP) inhibitors are targeted therapy for cancers with homologous repair deficiency (HRD) based on its mode of action. They were first approved for ovarian cancer and have changed current treatment strategies. Ovarian cancer with mutations in BRCA1 and BRCA2, breast cancer susceptibility genes are highly sensitive to platinum-based chemotherapy and PARP inhibitors. Taiwan FDA has also approved the reimbursement of the first PARP inhibitor, olaparib (Lynparza), in Nov. 2020 for advanced ovarian, fallopian tube or peritoneal cancer patients with germline or somatic BRCA1/2 mutations who had response to initial chemotherapy as maintenance treatment.

Recent approvals for another PARP inhibitor niraparib (Zejula) encompass patients with ovarian tumors that are HRD positive as well as those with BRCA mutations. However, the clinical challenge in Taiwan is to establish a reliable and affordable assay determining HRD to identify more patients who will benefit from the PARP inhibitors. On the other hand, many clinical trial have shown that even patients without HRD, as assessed by the current tests, still benefited from PARP inhibition. Such findings leave many open questions regarding the clinical utility of HRD testing.

In this talk we will go through current available tests for the indications of PARP inhibitors and discuss the rationale in the choice of tests and PARP inhibitor drugs.

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Genetic testing and PARP inhibitor maintenance in epithelial ovarian cancer after NHI reimbursement--PARP inhibitor maintenance

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gBRCAm, sBRCAm and Homologous recombination repair deficiency (HRD) are frequent features of high-grade ovarian, fallopian tube and peritoneal carcinoma (HGOC) and associated with sensitivity to PARP inhibitor (PARPi) therapy. Now, PARPi maintenance therapy became the standard care of ovarian cancer in patients with BRCAm and also got NHI reimbursement since Nov. 2020. But in patients with HRD & BRCAw, PARPi maintenance still have survival benefit, but didn’ t have NHI-reimbursement.

BRCA tesing or HRD testing provides an opportunity to optimise PARPi use in HGOC but methodologies are diverse and clinical application remains controversial. Today, we will discuss about best practice for BRCA testing and HRD testing in HGOC. The main aims were to (i) define the term 'BRCAm, HRRd and HRD test'; (ii) provide an overview of the biological rationale and the level of evidence supporting currently available HRRm or HRD tests; (iii) provide recommendations on the clinical utility of BRCA, HRD tests in clinical management of HGOC.

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婦科癌症的新標記物-DNA 甲基化
Novel markers for gynecologic cancer-DNA Methylation

近年來的癌症研究中有發現到，腫瘤的形成與 DNA 甲基化（methylation）有相關性；DNA 甲基化是表基因 epigenetics 改變的一種方式，甲基化的機制為 CpG 雙核苷酸上的胞嘧啶(C)在 DNA 合成後，經 DNA 甲基轉移酶（DNA methyltransferase）將甲基作轉移；大部份的甲基化基因會在基因及上游的啟動子區域形成 CpG 島（CpG islands），當發生高度甲基化（hypermethylation）會影響基因的轉錄和表現，導致基因靜默。所以，癌症的發生與不正常 DNA 甲基化有關，特別是抑癌基因 tumor suppressor gene 的高度甲基化。因此，DNA 甲基化具潛力作為生物標記用於癌症的早期診斷。基因組的甲基化的研究可以發現新基因以進行開發和檢測。

目前在婦產科領域來說，已經有甲基化檢驗在子宮頸癌與子宮內膜癌。安蓓(MPap)基因甲基化檢測是結合生物資訊與基因體學，從大量基因資訊中篩檢出多個甲基化基因，再由 370 個臨床檢體，證明該基因甲基化的程度與子宮內膜癌密切相關，可作為癌症診療的指標。其敏感度可達 83.7~96.0%，特異性為 78.7~96.0%。子宮頸癌甲基化基因檢測是由醫師採集子宮頸細胞，以即時聚合酶連鎖反應（Real-time PCR）技術直接檢測細胞內 PAX1 基因的甲基化程度，作為細胞癌化的判定。子宮頸癌甲基化基因的檢測已被認為是新一代能有效篩檢癌症的生物標記和方法。配合子宮頸癌抹片篩檢及人類乳突病毒檢測結果，可提供醫師用以評估婦女是否罹患子宮頸癌的參考。至於卵巢癌目前並沒有好的篩檢方法，開發早期篩檢的有效方法，也是重要議題，目前並未有卵巢癌廣泛基因體的甲基化研究，已經有的依些研究中利用分析 100 個良性與惡性卵巢瘤，與多種生物資訊的方法，比較其甲基化的狀態與臨床指標，以期釐清這些甲基化基因在卵巢癌的臨床用途潛力。

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循環腫瘤細胞– 婦科腫瘤的新標記
Novel Marker for Gynecologic Cancer—Circulating Tumor Cells

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Ovarian cancer is a common cancer among women with extremely poor prognosis. Even with the latest diagnostic technologies, more than half of patients with ovarian cancer are diagnosed at advanced stage. It is usually necessary to wait until after the operation for the definitive diagnosis and cancer staging. Even though tissue biopsy is the gold standard for diagnosing cancer, it is rare for ovarian cancer to use tissue biopsies to confirm the diagnosis before surgery, and it is difficult to use tissue biopsies to track the progress of disease after surgery. Therefore, a new diagnostic tool is urgently needed to assist in preoperative evaluation, detection of minimal residual disease, evaluation of recurrence, evaluation of drug resistance and even selection of therapeutic drugs.

CTCs are cells shed from the primary cancer lesion and enter the peripheral blood circulation, which then have the potential to re-enter and reach a suitable tissue environment to form new tumor foci. Although many mechanisms involved in tumor metastasis are not yet clear, CTCs undoubtedly play an important role in cancer metastasis. We can repeatedly draw blood from patients to detect CTCs as a sort of "real-time liquid biopsies, which can be used to predict tumor recurrence, evaluate potential drug resistance, and even provide information on drug selection.

Currently, CTCs testing has not yet been widely used for clinical practice due to several reasons. First, many testing steps still rely on manual operations, resulting in limited testing volume and unstable testing results. Secondly, only limited information can be provided as most clinical trials were based on enumeration of CTCs. In recent years, the advancement in CTCs detection technology can be attributed to several factors: the development of automated CTC platforms with high cell capture rate and throughput, the great progress in the research of cancer cell markers, and the progress of single-cell gene analysis technologies.

At present, there are several ongoing research projects in the world on the clinical application of CTCs for ovarian cancer, and there is no consensus yet. We reviewed some recent studies and will discuss feasible directions, especially molecular characterization and single cell analysis, for the clinical application of CTCs in gynecological cancers.

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Correlation of Genomic Alterations Between Tumor Tissue and Circulating Tumor DNA by Next-generation Sequencing

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Purpose: Analysis of circulating tumor DNA (ctDNA) offers an unbiased and noninvasive way to assess the genetic profiles of tumors. This study aimed to analyze mutations in ctDNA and their correlation with tissue mutations in patients with a variety of cancers.

Methods: We included 21 cancer patients treated with surgical resection for whom we collected paired tissue and plasma samples. Next-generation sequencing (NGS) of all exons was performed in a targeted human comprehensive cancer panel consisting of 275 genes.

Results: Six patients had at least one mutation that was concordant between tissue and ctDNA sequencing. Among all mutations (n = 35) detected by tissue and blood sequencing, 20% (n = 7) were concordant at the gene level. Tissue and ctDNA sequencing identified driver mutations in 66.67% and 47.62% of the tested samples, respectively. Tissue and ctDNA NGS detected actionable alterations in 57.14% and 33.33% of patients, respectively. When somatic alterations identified by each test were combined, the total proportion of patients with actionable mutations increased to 71.43%. Moreover, variants of unknown significance that were judged likely pathogenic had a higher percentage in ctDNA exclusively. Across six representative genes (PIK3CA, CTNNB1, AKT1, KRAS, TP53, and MET), the sensitivity and specificity of detection using mutations in tissue sample as a reference were 25 and 96.74%, respectively.

Conclusions: This study indicates that tissue NGS and ctDNA NGS are complementary rather than exclusive approaches; these data support the idea that ctDNA is a promising tool to interrogate cancer genetics.

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Novel marker for gynecologic cancer--IsoAAT and ovarian clear cell carcinoma

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Epithelial ovarian carcinoma consisted of mainly four different histology types, including high-grade serous carcinoma (HGSC), mucinous, endometrioid, and clear cell carcinomas (CCC). While HGSC is the most common histotype, CCC has a higher incidence in Asian countries such as Taiwan and Japan than in Western countries. CCCs are mostly diagnosed at early stages but the outcomes of patients with CCC are worse than in those with HGSC. Diagnosis of CCC is difficult because the lesion is often arisen and embedded in endometriosis. Biomarkers in the diagnosis and detection of recurrence in CCC is plausible that attributed partly to its poor prognosis. CA125 is the standard marker in daily practice to distinguish between benign and malignant ovarian tumors but is not a reliable marker for CCC. Alpha1-antitrypsin is a protease inhibitor that chiefly secreted in liver. Isoforms of alpha1-antitrypsin (isoAAT) with a molecular weight of 72 and 68 kDa (V-CHECK®, Taiwan, patent no. US 9,229,012 B2) can be detected in serum samples from gastrointestinal diseases of foals and human, human hepatoma, and cholangiocarcinoma. In addition, isoAAT could be detected in sera of patients with endometriosis. I will present the data of serum isoAAT levels in ovarian tumors.