賴鴻政
SY12

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New perspective of endometrial cancer screening in women with abnormal bleeding

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Background: The increasing incidence and mortality of uterine cancer in Taiwan and worldwide suggests a need for new strategies. DNA methylation assays from conventional Pap materials used as a triage test may allow women to avoid unnecessary endometrial biopsy.

Methods: We did a multicenter confirmatory study to test the diagnostic accuracy of a standardized DNA methylation assay (MPap™) against results from invasive procedures. Women older than 40 years old with abnormal uterine bleeding underwent a transvaginal ultrasound, MPap™ and endometrial tissue biopsy by suction curettage, dilatation and curettage, or hysteroscopic biopsy. Sensitivities (Sen), specificities (Spe) and accuracies were calculated.

Result: From Jan 2018, we started to enroll patients from 5 centers around Taiwan. A preliminary analysis of 251 women as a training set revealed Sen of 90%, Spe of 75% and accuracy of 90% for the detection of endometrial cancer, which is better than TVUS with accuracy around 65-70%.

Conclusion: The application of DNA methylation-based testing for endometrial cancer detection is promising. MPap™ testing, used as a triage before an invasive endometrial biopsy, may allow women to avoid invasive biopsies by more than 70%, which may reduce the risks and cost of over-diagnosis.

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張廷彰
SY13

Detection of lymph node metastasis in early stage endometrial cancer

子宮內膜前哨淋巴結的偵測與臨床意義

張廷彰 教授

前哨淋巴結偵測已廣泛應用在乳癌、黑色素瘤及會陰癌症的診療，子宮頸癌的前哨的淋巴結於本世紀以來，亦有相當的研究與討論。子宮內膜的前哨淋巴結偵測，近年認為其對於早期子宮內膜癌可能有臨床上的意義。

淋巴轉移是最常見的癌症轉移模式，與癌症的預後有明顯相關。大多數癌症的淋巴轉移是漸進式的，也就是由最靠近腫瘤淋巴出口處的淋巴結開始，向較遠端淋巴結逐漸推進。腫瘤附近的淋巴結如呈變大、變硬甚至與其周邊的組織明顯沾粘，皆為淋巴結轉移的明顯變化。以子宮內膜癌而言，此等明顯變化的淋巴結，應於手術中完整而徹底摘除。然而，如果淋巴結中僅有微小的轉移，並不會引起淋巴結外觀的變化，僅能藉仔細的組織病理檢查確認。為了避免漏失此等顯微轉移，於內膜癌手術時，一般建議進行完整而有系統的淋巴結摘除手術，範圍包括骨盆及主動脈淋巴結，上端至少達下腸系膜動脈水平。

美國婦癌研究組織第 33 題研究(GOG33)發現 621 位術前診斷為第一期的內膜癌患者中，144 位（22%）其病理期別超越子宮的範圍； 9%病患有骨盆淋巴結轉移，5% 有主動脈旁淋巴結轉移。此結果於 1987 年發表後，FIGO 自 1988 年起建議宮內膜癌分期，需完整的骨盆及主動脈旁淋巴結摘除。美國 American Congress of Obstetricians and Gynecologists (ACOG) 2005 年對於宮內膜癌治療的建議，亦包括淋巴結取樣或摘除，除非是希望保留生育能力的年輕婦女或不適合接受此一手術的病患。

對於分化良好或分化中等的內膜癌，如果術前的分期，也就是理學及影像檢查結果為 cT1N0M0 者,其淋巴結轉移的風險，綜合數個大型研究的結果發現：組織病理檢查為分化良好者，3%呈淋巴結轉移，中等分化者為 9%，低度分化者為 18%。高分化或中分化，腫瘤直徑不大於 2cm 且子宮肌層侵襲 50%以下者，沒有發現淋巴結轉移。高分化或中分化且子宮肌層侵襲 50%以上者，或低分化而肌層侵襲 50%以下者約有 15%淋巴結轉移的風險，相對於低分化而肌層侵襲 50%以上者的 40%。若僅就腫瘤直徑而言，直徑不大於 2cm 者，4%呈淋巴轉移，大於 2 cm 者有 15% 轉移的機會，若腫瘤充滿整個宮腔，則有 35%的轉移機會。子宮頸已受波及者，淋巴轉移的機會為 15%。對於淋巴結轉移風險不高的患者施行完整骨盆及主動脈旁淋巴結摘除手術，如果考慮到手術耗費的人力及時間成本，所增加的術中及術後併發症的風險以及最近的隨機分配人體試驗結果顯示完整的淋巴結摘除並沒有提高臨床分期為第一期患者的總體存活率，是否還要對臨床第一期，低風險的患者進行完整的淋巴結手術？有待商榷。前哨淋巴結的偵測是進行或不進行完整淋巴結摘除手術之間的折衷辦法，可以降低傳統淋巴結摘除的成本並提高淋巴結顯微轉移的病理診斷率。本題將以循證醫學為主軸，介紹前哨淋巴結偵測於宮內膜癌的應用及其極限。

陳宇立

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SY14-1

★ Debate: Adjuvant treatment for endometrial cancer after surgery -- RT for early and advanced endometrial cancer, pros and cons (正方主辨)

Endometrial cancer is the most common cancer of the female reproductive tract in developed countries. Surgery is the first treatment for almost all women with endometrial cancer. The tissues removed at surgery are examined to determine the stage of cancer. Depending on the stage of the cancer and surgical pathologic findings, further adjuvant treatments, such as radiation and/or chemotherapy may be recommended.

The prognosis for early-stage endometrial cancer is excellent, but some patients within this group will have risk factors such as age, tumor grade, depth of myometrial invasion, and lympho-vascular space invasion (LVSI) that will place the risk of 5-year disease recurrence as high as 20% to 25%. Several phase III randomized controlled trials (RCTs), including the PORTEC-1,2,3 and GOG 99 defined high-intermediate risk (HIR) group of surgically staged endometrial cancer patients and demonstrated decreasing recurrence rates following adjuvant radiotherapy (RT) in these population without altering overall survival (OS). Furthermore, Gupta et al. evaluated the impact of adjuvant RT on 33,600 patients with high-intermediate risk (HIR) stage I endometrial cancer, and showed that adjuvant RT followed by surgery was associated with a statistically significant 4.1% improvement in 5-year OS compared with surgery alone in stage I HIR endometrial cancer. These data suggested that adjuvant RT could be considered in early-stage endometrial cancer patients with certain pathologic risk factors.

Patients with advanced-stage endometrial cancer have a significant rate of relapse. GOG 122 demonstrated adjuvant chemotherapy significantly improved PFS and OS compared with whole- abdominal irradiation. However, in this trial, residual tumor up to 2cm was allowed, and it has been speculated that low dose RT was not sufficient for macroscopic residual tumor. Maggi et al. showed no OS differences between RT and chemotherapy, but local recurrence rate was lower in RT arms in high-risk patients without residual tumor. Three RCTs, including GOG 249, PORTEC-3, and GOG 258 investigated the effect of RT combined with chemotherapy in high-risk patients. These trials confirmed that RT is an effective, well-tolerated, and appropriate adjuvant treatment in high-risk early and advanced endometrial cancer. Although RT could not improve OS, but it could decrease local recurrence rates and had less adverse effects.

許恒誠

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SY14-2

★ Debate: Adjuvant treatment for endometrial cancer after surgery -- RT for early and advanced endometrial cancer, pros and cons (正方答辨)

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Endometrial cancer is a common cancer in women in Taiwan, ranking sixth in prevalence and with its cancer related death ranking 11. According to the national registry annual report of Taiwan, there were 2128 of cases of endometrial cancer in 2016.

The disease is comprised with mostly early stage disease because of its irregular bleeding symptoms leading to prompt diagnosis. Early stage disease patients have a favorable prognosis. The majority of the early stage cases are treated with surgery, with adjuvant therapy reserved for those with a higher risk of recurrence. Risk of recurrence is categorized by multiple factors according to previous literature.

As with patients with advanced disease, the treatment is surgery with adjuvant therapy. Clinical and pathological factors affect the risk of recurrence include the extent of abdominal and pelvic disease, histologic subtype, nodal involvement, and whether optimal resection was achieved. The optimal treatment for advanced stage endometrial cancer has been in much debate.

There has been much research in how the adjuvant therapy should be done in both early and advanced stages of endometrial cancer. In order to decrease the risk of recurrence, women with high-risk endometrial cancer have been treated with pelvic radiation for decades. Also, there is a higher incidence of pelvic recurrences reported in cases treated with adjuvant chemotherapy alone compared to those with radiation. We share our views in order to show how radiation therapy implementation benefit the patients with a higher risk of recurrence and those with advanced disease.

呂建興(反方主辨)

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SY15-1

許世典(反方答辨)

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SY15-2

★ Debate: Adjuvant treatment for endometrial cancer after surgery -- RT for early and advanced endometrial cancer, pros and cons

For stage I endometrioid adenocarcinoma, NCCN guidelines suggested vaginal brachytherapy for low and intermediate risk disease in the presence of risk factor for recurrence, including age >= 60 years, depth of invasion, LVSI, and possible tumor volume, depth of invasion, and lower uterine segment or surface cervical glandular involvement. However, none of large RCTs proved pelvic and/or vaginal brachytherapy in improving OS of adjuvant irradiation. Moreover, in the meta-analysis of randomized trials, irradation also failed to increased OS. Although vaginal brachytherapy was associated with less complications than pelvic R/T, there were no trials direct comparing vaginal brachytherapy with observation when risk factor exists.

For completely staged II endometrioid carcinoma treated with radical hysterectomy, no adjuvant therapy was suggested for patients without other risk factors other than cervical involvement.

For stage III disease, subgroup analysis from PORTEC III trial which randomized candidate patients to chemoradiation (monthly cisplatin + pelvic RT, then carboplatin + paclitaxel x 4 or to pelvic RT alone, found 5-year overall survival 79% for CCRT, 70% for R/T alone (R 0.71, adjusted p=0.074). 5-year failure-free survival was 69% in CCRT group, and 58% in R/T group (HR 0.66, adjusted p=0.014)

Uterine serous carcinomas, clear cell carcinomas, carcinosarcomas, and undifferentiated/ dedifferentiated carcinomas are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation. Therefore, systemic therapy with (or without) tumor-directed RT is the preferred option.

Accordingly, R/T is not an adequate adjuvant treatment in different clinical situations of endometrial cancer!

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王鵬惠
SY16

卵巢癌嶄新的治療

Novel therapy for ovarian cancer

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The current treatment of EOC is the combination of complete staging surgery with primary debulking surgery (PDS) and postoperative platinum-paclitaxel-based chemotherapy, or the use of sandwich method (chemotherapy-operation-chemotherapy), including preoperative chemotherapy (neoadjuvant chemotherapy-NACT), interval debulking surgery (IDS) and postoperative multi-agent chemotherapy. Under this most popular and well-accepted standard therapy, the outcome is still disappointing because nearly all patients can achieve complete remission, even though they are advanced diseases; however, unfortunately, the majority of patients will relapse with the median progression-free survival (PFS) ranged between 16 and 21 months, and the median overall survival (OS) ranged from 32 to 57 months, and these patients finally will die within several years after initial treatment. All suggest the new modalities are urgently needed to enhance the therapeutic effects and subsequently increase PFS and OS.

Among the promising advance in EOC therapy, such as altered delivery method of chemotherapeutic agents (intravenous or intraperitoneal routes), changed dose and interval of chemotherapy administration (dose-dense chemotherapy), intraperitoneal hyperthermia treatment, and additional new agents (small molecules, monoantibodies, and others), which can target the specific cancer-specific antigens, hint the underlying repair system of cancer cells, block the nutrition or oxygen supply (for example, antiangiogenic drugs), change the interaction between cancer cells and surrounding cells, alter or modify behaviors of cancer cells, enhance immune-clearance ability (for example, immune checkpoint inhibitors, immune system modulators), or enhance the therapeutic effect of the original chemotherapy. These latter new agents can be used in the combination of original chemotherapy or alone, based on their targeted sites and mechanisms. All represent a paradigm shift in cancer treatment.

The current talk serves to update emerging data from research articles or trials evaluating the impact of novel therapy on EOC and briefly introduce the advance and development of therapeutic interventions with the goal to improve outcome of patient with EOC.

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王功亮
SY17

健保採取癌症高價藥物部分負擔政策的建議

NHI reimbursement policy for novel cancer treatment, new proposal

王功亮 院長
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Bevacizumab 及免疫藥物 immune blockade 如 PD-1blockade 與 PD-L1 blockade 於晚期及復發婦癌病人的臨床試驗，顯示此等藥物可以延長病人的疾病無進展存活期及總存活期。此等藥物也已使用於其他的癌症，如 immune blockade 使用於 microsatellite instability high (MSI-H)的腫瘤，HPV 感染相關的腫瘤，及高 tumor mutation burden (TMB)腫瘤，包括 glioblastoma, head and neck cancer, lung cancer, triple-negative breast cancer, esophageal cancer, renal cell carcinoma, bladder cancer 等，較傳統的化療，可以得到較佳的效果；使用於晚期婦科腫瘤，包括呈現 MSI-H 的子宮內膜癌及 HPV 感染相關的子宮頸癌，也有較傳統治療更高的 response rate 及 progression free survival. 目前的臨床試驗結果也發現，合併化療，bevacizumab 及 immune blockade, 較單獨使用這些藥物，有更好的療效。只是新藥物的價格昂貴，2018 年健保只將部分的癌症治療納入給付，其中並不包括婦科腫瘤。

現行健保法規定，藥品沒有差額負擔的機制，只有全有、即全數給付，或是全無 、即完全不給付。因此即使新藥的治療效果佳，婦癌病人必須負擔所有的藥物費用，相對的，頭頸部鱗狀細胞癌，泌尿上皮癌及腎細胞癌病人可以健保使用 pembrolizumab，Bevacizumab 可以健保使用在大腸癌病人，但是卵巢癌病人就必須自費使用。健保的資源有限，折衷方法之一是高貴藥物的部分負擔，也就是目前已有的「差額給付」，就是超出健保基本給付的費用由病人自行負擔，目前支架、人工水晶體等特殊醫材，才有差額給付。今年 4 月間，台灣癌症基金會針對 909 名癌友及其家屬以及 300 名一般民眾進行「新藥與新科技部分負擔民眾願付價格」調查，結果顯示，為了爭取救命的新藥、新科技，多達 72%癌友願意每月負擔 5000 元以上，50%癌友願意負擔 2 萬元以上；另有多達 74%受訪者支持健保費用應有所調漲，以納入更多新藥新科技。

https://www.cna.com.tw/news/ahel/201912080082.aspx

昂貴藥物以部分負擔方式納入保險，除了是醫療有限資源下的一個應變之計外，也將救命的藥物更精準的使用在適用有效的範圍，更可以因此降低新藥物的價格。講者將就我國與世界主要國家醫療保險在此一範圍的政策，做一比較，並提出建議。

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SY18-1

★ Debate: Secondary debulking for recurrent ovarian cancer
二次減積手術於復發性卵巢癌的角色 (正方主辨)

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Secondary debulking in women with recurrent epithelial ovarian cancer is widely practiced and debated, which is safe and feasible in selected patients. The results of these studies may be different because of different clinical practices and different patient populations.

Patients with a positive predictive Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score who underwent a secondary debulking surgery for platinum-sensitive recurrent ovarian cancer (PSROC) first relapsing after at least six months since platinum chemotherapy experienced longer progression-free survival (PFS). AGO DESKTOP I employed a predictive AGO score to identify patients who will have complete tumor resection in secondary surgery, composed of an Eastern Cooperative Oncology Group performance score of 0, complete resection during first-line treatment, and ascites less than 500 ml. Positron emission tomography-computed tomography(PET-CT) scan has more positive findings in patients with suspect recurrence who have rising CA125 levels despite negative results on standard magnetic resonance imaging(MRI) or computed tomography(CT); it can modify the management by accurately mapping the distribution of recurrent disease, and it is definitely associated with a real R0 status after secondary cytoreductive surgery. In the era of personalized medicine, the indication of secondary debulking should be individualized. Secondary debulking increases time to first subsequent therapy (TFST) and post-recurrence survival (PRS) in PSROC patients with $BRCA^{mut}$ candidate for olaparib maintenance after platinum-based chemotherapy. HIPEC following secondary cytoreduction is an alternative approach for patients with the recurrent ovarian disease. A meta-analysis showed better OS rates for patients with recurrent epithelial ovarian cancer when adding HIPEC to secondary debulking and traditional chemotherapy.

Secondary debulking is a clinically beneficial treatment option for selected patients with PSROC. Younger women in good health with a lengthened disease-free interval and isolated tumors are the best candidates for surgery.

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廖正義

SY18-2

★ Debate: Secondary debulking for recurrent ovarian cancer

二次減積手術於復發性卵巢癌的角色 (正方答辨)

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Despite the absence of randomized data showing a survival benefit conferred by primary cytoreductive surgery, meta-analyses support the approach. Theoretically, maximal surgical effort may help overcome intrinsic drug resistance, increase drug perfusion, enhance host immunologic response, increase the growth fraction of tumor cells, and circumvent acquired drug resistance after adjuvant platinum-based and taxane-based systemic therapy. Unfortunately, recurrent disease develops in more than 80% of women. The 10-year rates of disease-free survival among patients with recurrent disease are abysmal and are below 15%

Given the widespread adoption of primary surgical cytoreduction, it is not surprising that the approach is also strongly considered for patients with recurrent disease — particularly those who are considered to be candidates for platinum reinduction (e.g., a prolonged treatment-free interval after platinum therapy) and those with isolated or limited-volume recurrent disease.

Current National Comprehensive Cancer Network list the secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who recur more than 6– 12 months since completion of initial chemotherapy, have an isolated focus (or limited foci) of disease amenable to complete resection, and do not have ascites.

In GOG-0213 trial, secondary surgical cytoreduction in patients with platinum-sensitive, recurrent epithelial ovarian cancer selected according to these criteria appears to be feasible, with acceptable postoperative morbidity, but did not result in longer overall survival than no surgery. The delay in initiation of chemotherapy in the surgery group and the previous residual status after the primary cytoreductive surgery may deliute the benefit of secondary cytoreductive surgery.

周宏學
SY19-1

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★ Debate: Secondary debulking for recurrent ovarian cancer
二次減積手術於復發性卵巢癌的角色 (反方主辨)

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Disease recurrence occurs in most of epithelial ovarian cancer (EOC), and always comes repeatedly afterwards. Salvage treatments include secondary debulking surgery and chemotherapy, or in associated with other adjuvant methods.

Some studies focus on the benefit of secondary cytoreductive surgery. The Gynecologic Oncology Group (GOG) 213 trial randomly assigned 485 patients with recurrent platinum-sensitive ovarian or primary peritoneal cancer who had a complete response to front-line chemotherapy, a treatment-free interval longer than six months, and investigator-determined resectable disease to secondary cytoreductive surgery followed by platinum-based chemotherapy (N=240) or platinum-based chemotherapy alone (N=245) (carboplatin and paclitaxel with or without bevacizumab). Complete gross resection (R0) was achieved in 63% of patients who underwent surgery.

At 48 months median follow-up, the HR for death was similar for both groups (surgery versus no surgery HR 1.29, 95% CI 0.97-1.72), which corresponded to a median overall survival after surgery versus chemotherapy of 50.6 and 64.7 months, respectively. The HR for disease progression or death was also similar (surgery versus no surgery HR 0.82, 95% CI 0.66-1.01), with median progression-free survival after surgery versus chemotherapy of 18.9 and 16.2 months, respectively.

In addition, 9 percent of patients in the surgical group experienced surgical morbidity, and one patient died from postoperative complications.

Therefore, we object secondary cytoreductive surgery to every patient with recurrent EOC.

林 浩
SY19-2

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★ Debate: Secondary debulking for recurrent ovarian cancer
二次減積手術於復發性卵巢癌的角色 (反方答辨)

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The debate over secondary cytoreductive surgery for recurrent, platinum-sensitive ovarian cancer remains an open one, as studies reported over the past year produced disparate results.

The concept of secondary cytoreductive surgery dates first described in the early-1980s based on single-center case series and retrospective cohort studies have supported the concept for well-selected patients. A meta-analysis involving 1,100 patients identified complete surgical resection (R0) as the strongest predictor of survival ($P<0.001$). At the 2017 American Society of Clinical Oncology (ASCO) annual meeting, a large, randomized European study (DESKTOP III) showed significant improvement in progression-free survival (PFS) with secondary surgical debulking. In 2018, a retrospective analysis from Norway showed a strong association between treatment-free interval, complete surgical resection, and both PFS and overall survival (OS), as compared with patients who received only chemotherapy at recurrence. However, at the recent 2018 ASCO annual meeting, a highly anticipated U.S. NRG/Gynecologic Oncology Group (GOG 213) trial showed no survival benefit -- PFS or OS -- for patients who had secondary cytoreductive surgery, followed by chemotherapy, versus those who received chemotherapy alone. Median OS was a year longer for the non-surgical group.

There are possible several reasons that may dilute the surgical effect measured:

1. Patient selection criteria on the prediction of R0 on secondary surgery varied among centers. The question remains, as to which selection criteria should be used? Gynecologic surgeons at MSKCC established a relatively simple patient selection criteria to predict R0 in secondary cytoreductive surgey. The criteria take into account the 1) duration of the

disease-free interval, 2) single or multiple sites of recurrence, 3) the presence or absence of carcinomatosis. Their experience of using this criteria showed a R0 rate of 86%. However, the R0 rate would have dropped to 49% if the patients had been evaluated by the criteria used in the randomized European trial. Patient selection criteria for the European study consisted of 1) >6-month platinum-free interval, 2) good performance status, 3) no residual disease after primary surgery, 4) <500 mL of ascites. Therefore, case selection remains challenging and controversial among many centers.

2. The use of bevacizumab and the selection of highly active chemotherapy may have masked an incremental benefit from surgery, similar to the evaluation of bevacizumab combinations in frontline therapy.
3. Improvements in clinical care and the availability of more effective treatments, particularly those in selected populations (e.g., use of PARP inhibitors in patients with tumors with alterations in BRCA1 or BRCA2). All these may extend postprogression survival and can dilute the secondary surgical treatment effect measured.