LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

Reviews covering publications from August 15, 2018 – February 15, 2019

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Supported by ESGO

Issue No. 1 (9) May 2019

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Dear colleagues,

We present to you LiFE 9! It includes reviews of publications in gynaecological oncology dating from August 15, 2018–February 15, 2019. LiFE is an initiative of ENYGO supported by ESGO.

This issue was supported by reports from new authors Ilker Kahramanoglu (Turkey), Paweł Bartnik (Poland), and Begoña Díaz de la Noval (Spain). We welcome them to the LiFE team.

The last 5 years of LiFE have been a great journey, and we have established a novel educational tool for our community. This is not least due to the continuous work of our authors and their enthusiasm for the project. A few weeks ago we asked ENYGO members for their opinions regarding LiFE. Almost 60% of our network read LiFE regularly, and for over 72% this is an important tool helping them in their daily development! We believe that these results are the best evidence of the appreciation of work done by the over 40 authors involved in this project. Congratulations and thank you for your efforts.

Still, we feel it is time to pause and take some time to think. The sustainability of the project is our main focus and, together with our partners, we aim for a product of the highest quality. In order to achieve this, we will revise the concept carefully during the next months.

We hope you will enjoy LiFE 9, find it interesting, and share it with your colleagues!

Please let us know if you have any comments or other feedback.

Stay up to date!

The LiFE team

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Ovarian cancer

Endometrial cancer

Cervical cancer

Vulvar cancer

Surgical management

Miscellaneous

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Pathology/pathogenesis of malignant ovarian tumours

Dogan Vatansever

He et al. systematically identified factors that could be responsible for resistance to PARPi or platinum therapy in BRCA-defective patients with high-grade serous ovarian cancer (HGSOC). They used a genome-scale bacterial clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 knockout (GeCKO) library to identify genes in which loss confers resistance to clinical PARPi and platinum drugs in a panel of patient-derived BRCA1-mutant HGSOC lines. Diminished expression of dynein light chain 1 protein (DYNLL1; also known as LC8 or PIN) significantly correlated with poor progression-free survival after platinum-based chemotherapy of patients with BRCA1-mutated tumours [1].

They also described the mechanism by which DYNLL1 contributes to resistance to PARPi or platinum therapy. Limited DNA end resection is the key to impaired homologous recombination in BRCA1-mutant cancer cells. The loss of DYNLL1 enables DNA end resection and restores homologous recombination in BRCA1-mutant cells, thereby inducing resistance to platinum drugs and PARP inhibitors. They concluded that DYNLL1 is an important anti-resection factor that influences genomic stability and responses to DNA-damaging chemotherapy.

Poillet-Perez et al. investigated the relation of autophagy with a non-essential amino acid, arginine. Some human cancers are defective of argininosuccinate synthase 1 (ASS1) and synthesise arginine from citrulline. Cancer cells silence expression of ASS1 which eventually results in the inability to synthesise arginine and may render tumour cells dependent on exogenous arginine. Autophagy is essential for the transportation of intracellular components to lysosomes and their recycling in order to enable survival during starvation. Autophagy is also very important for the survival for cancer cells. Although deletion of essential autophagy genes impairs the metabolism, proliferation, survival, and malignancy of spontaneous tumours in cancer models, systemic inhibition of autophagy in the host induces greater tumour regression than tumour specific autophagy inhibition. This is linked to the reduction in circulating arginine in the circulation of an autophagy-defective host. Defective autophagy in the host led to the release of ARG1 (arginine-degrading enzyme arginase 1) from the liver and the degradation of circulating arginine, which is essential for tumour growth; this identified a metabolic vulnerability of cancer [2].

Kondrashova et al. studied the BRCA 1 methylation in relation to rucaparib response of ovarian carcinoma. They assessed the response of 12 patient-derived xenografts (PDX) to the PARP inhibitor rucaparib. They observed variable dose-dependent responses in BRCA1/2 mutated patients and did not observe any response in PDX lacking BRCA mutation. Moreover, among BRCA1-methylated PDX, silencing of all BRCA1 copies predicted rucaparib response, whilst heterozygous methylation was associated with resistance. Additional analysis of 21 BRCA1-methylated platinum-sensitive recurrent HGSOC (ARIEL2 Part 1 trial) confirmed that homozygous or hemizygous BRCA1 methylation predicts rucaparib clinical response, and that methylation loss can occur after exposure to chemotherapy. Quantitative BRCA1 methylation analysis in a pre-treatment biopsy could allow identification of patients most likely to benefit and facilitate tailoring of PARPi therapy [3].

Sehouli et al. investigated the prognostic significance of Ki-67 levels and hormone receptor expression in low-grade serous ovarian carcinoma. They evaluated Ki-67 and HR expression evaluated by immunohistochemistry in 68 patients with LGSOC. The results underlined the value of Ki-67 as a prognostic marker in LGSOC. Furthermore, most LGSOCs were positive for HR expression, which is associated with a better PFS [4].

Al Habyan et al. used live imaging of 3D culture models and animal models to investigate the origin and mechanism through which cancer cells form spheroids in ascites fluid. Cancer cells can detach either as single cells or clusters. Clusters were more resistant to anoikis and had a survival advantage against single cells. Multicellular spheroids are formed by collective detachment of cells rather than the aggregation of single cells in the abdomen. These multicellular spheroids have the potential to metastasize intraabdominally and retain the heterogeneity from the primary tumour [5].

Amit et al. developed a method of computerised morphometry of the fimbrial epithelium [7] and compared the fimbriae of patients with endometrial cancer with healthy women [6]. Twenty-four healthy women and 26 patients with endometrial cancer (13 UPSC and 13 endometrioid endometrial cancer) were enrolled in the study. All fimbriae reported by the pathologist as “normal” were subjected to a computerised histomorphometric analysis. Significant differences in the morphometric characteristics of the fimbriae were found when UPSC patients were compared to EEC and healthy patients. The clinical significance of this finding is to date unknown.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	DYNLL1 binds to MRE11 to limit DNA end resection in BRCA1-deficient cells.	He YJ et al.	Nature	https://www.ncbi.nlm.nih.gov/pubmed/30464262
2	Autophagy maintains tumor growth through circulating arginine.	Poillet-Perez L et al.	Nature	https://www.ncbi.nlm.nih.gov/pubmed/30429607
3	Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma.	Kondrashova O et al.	Nature Communications	https://www.ncbi.nlm.nih.gov/pubmed/30266954
4	Prognostic significance of Ki-67 levels and hormone receptor expression in low-grade serous ovarian carcinoma: an investigation of the Tumor Bank Ovarian Cancer Network.	Sehouli J et al.	Human Pathology	https://www.ncbi.nlm.nih.gov/pubmed/30428389
5	Multicellular detachment generates metastatic spheroids during intra-abdominal dissemination in epithelial ovarian cancer.	Al Habyan S et al.	Oncogene	https://www.ncbi.nlm.nih.gov/pubmed/29789717
6	Can morphometric analysis of the fallopian tube fimbria predict the presence of uterine papillary serous carcinoma (UPSC)?	Amit A et al.	Plos One	https://www.ncbi.nlm.nih.gov/pubmed/30818325
7	Evaluation of microscopic changes in fallopian tubes of BRCA mutation carriers by morphometric analysis of histologic slides: A preliminary pilot study.	Amit A et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/28863070

Screening for ovarian and fallopian tube cancer

Lucas Minig

The University of Kentucky Ovarian Cancer Screening Trial was initiated in 1987 to determine the effect of annual transvaginal ultrasonography on stage at detection and ovarian cancer mortality. van Nagell et al. recently reported the stage at detection and long-term survival of patients with type I and type II epithelial ovarian cancer detected by screening in this trial. Mucinous carcinoma, clear cell carcinoma, and low-grade serous and endometrioid carcinoma were classified as type I tumours, and high-grade serous and endometrioid carcinoma, undifferentiated carcinoma, and carcinosarcoma were designated as type II tumours.

Unscreened women with clinically detected epithelial ovarian cancer (EOC) referred to the same centre for treatment between 1995 and 2017 served as the control group (unscreened cohort). In the screening group, annual pelvic ultrasound was prospectively performed in more than 46,000 asymptomatic women. Abnormal ultrasound findings were followed up with tumour morphology indexing, CA 125 testing, and surgery as indicated. Seventy-one invasive EOC and 17 borderline tumours were identified. In the group with EOC, 42% were diagnosed at stage I and 31% at stage II. In the unscreened cohort, however, 30% of patients were diagnosed at stage I and II disease. Follow-up ranged from 9.2 months to 27 years (mean 7.9 years). Disease-specific survival at 5, 10, and 20 years for women with EOC detected by screening was 86±4%, 68±7%, and 65±7%, respectively, vs. 45±2%, 31±2%, and 19±3%, respectively, for unscreened women ($p < 0.001$). Twenty-seven percent of screen-detected malignancies were type I and 73% were type II. The disease-specific survival of women with type I and type II screen-detected tumours was significantly higher than that of women with clinically detected type I and type II tumours and was related directly to earlier stage at detection.

As compared with the unscreened cohort, the screened population had significantly improved disease-specific survival (86±4% vs. 45±2% 5-year disease-specific survival). This survival difference remained true for both the entire cohort as well as those with type I and II malignancies separately and was entirely accounted for by the shift toward earlier stage at diagnosis.

These results, however, should be interpreted with caution. The screened population in this study had a higher percentage of type I tumours (27%) as compared with SEER data (11% of nationally reported ovarian malignancies from 2011 to 2015 were type I tumours), and the specific histology of type I tumours in the unscreened control cohort was not reported. Additionally, data on germline mutations was not available, despite a high percentage of women with a significant family cancer history. These factors could have influenced disease-specific survival rates. In the absence of a randomised design, it is difficult to determine whether the presence of these and other potentially undetected confounding variables account for the differences reported, or whether a true difference in disease-specific survival is present with routine screening. Finally, the screened cohort appeared to represent a population of women at high risk for ovarian cancer, whereas the control cohort's risk is unknown. For these reasons, it is difficult to agree with the authors' conclusion that the ultrasound screening reduced ovarian cancer mortality.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Survival of women with Type I and II epithelial ovarian cancer detected by ultrasound screening.	van Nagell JR Jr., et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/30303916

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Hereditary ovarian cancer (BRCA1/2 mutation, genetic counselling, management)

Sara Giovannoni

PARP inhibitors

Lin et al. published a retrospective translational study focussing on BRCA reversion mutation in BRCA carriers with high-grade ovarian cancer who had progressive disease in the ARIEL2 phase II trial. To estimate the prevalence of BRCA reversion mutation, they performed targeted next-generation sequencing of circulating cell-free DNA from pre-treatment and post-progression plasma of the 112 patients included. BRCA reversion mutations were identified in pre-treatment cfDNA from 18% of platinum refractory and 13% of platinum-resistant tumours, compared with 2% of platinum-sensitive cancers ($p = 0.049$). Patients without BRCA reversion mutation had longer PFS than those with reversion mutation (mPFS 9.0 vs. 1.8 months; $p < 0.0001$). The analysis of BRCA reversion mutations in cfDNA may predict resistance to PARP inhibitors in order to select the best treatment options for patients at disease progression [1].

Bi et al. used a preclinical mice model to study the radiosensitising effects of olaparib. The authors assessed the growth-inhibitory action of olaparib plus radiotherapy in mice bearing BRCA1 deficient high-grade serous ovarian cancer tumours compared with mice without BRCA mutations. Olaparib improved the effect of radiotherapy in BRCA mice. This data may represent a preclinical rationale to design trials including radiotherapy and PARP inhibitors [2].

PALB2 mutation

A Spanish translational study explored the role of PALB2 mutation in ovarian cancer patients without BRCA1/2 mutations. PALB protein is involved in DNA homologous recombination pathway through cooperation with BRCA proteins and RAD51. The authors analysed 60 patients and 320 controls, evaluating four predicted splicing disruption variants and large genomic rearrangements by multiplex ligation-dependent probe amplification.

A frameshift mutation which segregates in an early onset cancer family and four rare missense variants were found. None of the variants tested for a predicted splicing disruption showed an aberrant transcript pattern. Although PALB2 truncating mutations were rarely identified, segregation analysis and early onset cancer suggest a role in high-grade serous ovarian cancer susceptibility in the Spanish population. PALB2 screening may improve genetic counselling, but further trials are needed [3].

Genetic counselling/prophylactic surgery

Vogel et al. conducted a prospective randomised controlled pilot trial to assess the benefits and feasibility of a patient-centred mobile health application in order to motivate for genetic counselling. One hundred and four untested women with ovarian or peritoneal or fallopian tube cancer were included. The mobile application aimed at identifying barriers, increasing motivation, and providing triggers to action in the intervention group. Although improved compared to historical controls, there was no difference in the uptake of genetic counselling between the arms.

The intervention group presented a greater knowledge of hereditary cancer ($p < 0.0001$), and 96% of the women talked with their family about genetic counselling compared with 77% in the control group [4].

A prospective cohort study by Ozanne et al. demonstrated the accuracy and feasibility of the N-TRAC (patient-reported questionnaires based on NCCN guidelines and adapted for affected and unaffected women) in a prospective cohort study of 200 women. Test accuracy for family history was excellent, but it is noteworthy that available risk-assessment tools may identify different groups of patients. The tool seems to be useful in clinical practice in order to identify women at increased risk for hereditary and ovarian cancer [5].

Two papers analysed the quality of life of women with BRCA mutation after prophylactic ovarian surgery. Early onset menopausal symptoms or worsening of postmenopausal symptoms, as well as a decline in sexual functioning, were reported by the women. However, in one study, only 21% of women used any treatment to relieve the symptoms, even though HRT may not mitigate all symptoms either. A two-stage alternative with delayed oophorectomy is currently being studied as an alternative option of risk-reducing surgery [6,7].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	BRCA reversion mutations in circulating tumor DNA predict primary and acquired resistance to the PARP inhibitors rucaparib in high-grade ovarian carcinoma.	Lin KK et al.	Cancer Discovery	https://www.ncbi.nlm.nih.gov/pubmed/30425037
2	Radiosensitization by the PARP inhibitor olaparib in BRCA1-proficient and deficient high-grade serous ovarian carcinomas.	Bi Y et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30025822
3	A PALB2 truncating mutation: Implication in cancer prevention and therapy of hereditary breast and ovarian cancer.	Velázquez C et al.	Breast	https://www.ncbi.nlm.nih.gov/pubmed/30521987
4	A patient-centered mobile health application to motivate use of genetic counseling among women with ovarian cancer: A pilot randomized controlled trial.	Vogel RI, et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30718125
5	Evaluation of National comprehensive cancer network guideline-based tool for risk assessment for breast and ovarian cancer (N-TRAC): a patient-reported survey for genetic high-risk assessment for breast and ovarian cancers in women.	Ozanne EM et al.	J Genet Couns.	https://www.ncbi.nlm.nih.gov/pubmed/30663827
6	Satisfaction and impact on quality of life of clinical and instrumental surveillance and prophylactic surgery in BRCA-mutation carriers.	D'Alonzo M et al.	Clin Breast Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30122348
7	Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a BRCA1 or BRCA2 mutation.	Hall E et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30414741

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Surgical treatment of primary ovarian cancer

Ilker Kahramanoglu

Molecular subtyping

Can molecular subtyping be used in planning ovarian cancer primary treatment? Torres et al. investigated the role of tumour molecular subtype on surgical risks in primary debulking surgery in advanced ovarian cancer. The mesenchymal subtype was an independent predictor of severe postoperative morbidity (OR = 2.14, 95% CI 1.17–3.92; p = 0.01) [1].

Minimal invasive surgery

A retrospective study of prospectively collected data at the MD Andersen Cancer Center evaluated the use of laparoscopic scoring to define which patients should undergo primary surgery. Among 139 patients, overall concordance of laparoscopic scoring and primary surgery was 96%, which varied by anatomic location. The highest concordance was 95% for peritoneal carcinomatosis, and the lowest concordance was 75% for the prediction of bowel infiltration [2].

Lymphadenectomy in advanced ovarian cancer

The LION study, a randomised gynaecologic cancer intergroup trial, studied the role of systematic pelvic and paraaortic lymphadenectomy in advanced ovarian cancer. The study included 647 patients with stage IIB–IV ovarian cancer who underwent complete cytoreduction and had normal lymph nodes. Patients were randomised to either lymphadenectomy or no lymphadenectomy. Even though 56% of the patients in the lymphadenectomy group had subclinical nodal metastases, neither overall survival (HR: 1.06; 95% CI: 0.83–1.34) nor progression-free survival (HR: 1.11; 95% CI: 0.92–1.34) improved. Lymphadenectomy was associated with longer surgery, more blood loss, higher transfusion rates, re-laparotomies, and mortality within 60 days after surgery [3].

Extended procedures

Tseng et al. retrospectively evaluated the surgical paradigm shift in primary cytoreductive surgery at the Memorial Sloan Kettering Cancer Center over a 13-year period. They categorised 978 patients by year of surgery. Between 2001 and 2005, they introduced extensive upper abdominal procedures (Group 1). Over the next four years, the goal of cytoreductive surgery evolved to complete cytoreduction (Group 2). Adjustments over the last four years included: Cardiophrenic nodal resection, use of selection criteria for neoadjuvant chemotherapy, and implementation of earlier operative start times (Group 3). As a result, complete cytoreduction increased from 29% to 40% to 55% for Group 1–3, respectively. The increased radicality also improved survival with five-year overall survival rates of 40%, 44%, and 56%, respectively (p < 0.001). Major complication rates were similar between the groups [4].

Perioperative care

Tanner et al. performed a prospective pilot study of acute normovolemic haemodilution in primary debulking surgery where whole blood is removed and replaced with a crystalloid/colloid mixture. Detailed technical details were presented. Minimum allowable haemoglobin was defined as 8 g/dL, and allowable blood loss was capped at 3 L. They observed a 32% reduction in allogeneic red blood cell transfusion without increasing complication rates. The only shortcoming noted in the study was a 20% risk of delaying the procedure as the next step in the procedure was delayed until blood withdrawal was completed [5].

Cost-effectiveness

The cost-effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) at interval cytoreductive surgery (ICS) to ICS alone was investigated in the United States based on Medicare data, prior published studies, and the financial department of an academic hospital [6]. The study reported that HIPEC at the time of ICS was cost-effective, with an incremental cost-effectiveness ratio of 2,436 US dollars/quality-adjusted life-years, compared to ICS alone. Also, when reversal of ostomies was considered, this ratio did not change substantially.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Mesenchimal molecular subtype is an independent predictor of severe postoperative complications after primary debulking surgery for advanced ovarian cancer.	Torres D et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/m/pubmed/30503050/
2	Concordance of a laparoscopic scoring algorithm with primary surgery findings in advanced stage ovarian cancer.	Hansen JM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/m/pubmed/30366647/
3	A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms.	Harter P et al.	N Engl J Med.	https://www.ncbi.nlm.nih.gov/m/pubmed/30811909/
4	Continuous improvement in primary debulking surgery for advanced ovarian cancer: Do increased complete gross resection rates independently lead to increased progression-free and overall survival?	Tseng JH et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/m/pubmed/30126704/
5	A prospective trial of acute normovolemic hemodilution in patients undergoing primary cytoreductive surgery for advanced ovarian cancer.	Tanner EJ et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30336947
6	Cost-effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) at interval debulking of epithelial ovarian cancer following neoadjuvant chemotherapy.	Lim SL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30718126

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Medical treatment of primary ovarian cancer

Ilker Selcuk and Muhammad Rizki Yaznil

Moore et al. evaluated the efficacy of olaparib as a maintenance therapy in newly diagnosed advanced (stage III or IV) high-grade serous or endometrioid ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma patients with a BRCA mutation and in response to platinum-based chemotherapy. In this international, randomised, double-blind, phase III trial, 391 patients were treated with olaparib tablets (300 mg, twice daily) or placebo. The median duration of follow-up was 41 months. At three years, 60% in the olaparib group were progression-free compared to 27% in the placebo group (HR 0.30, 95% CI: 0.23–0.41, $p < 0.001$). Median progression-free survival (PFS) was not reached in the olaparib group and was 13.8 months for the placebo group. All subgroup analyses (i.e., complete vs. partial response) showed an improved efficacy for olaparib. Analysis of overall survival (OS) with 21% data maturity showed 84% and 80% (HR: 0.95, 95% CI: 0.60–1.53) OS for the olaparib and placebo group, respectively. Median time to first subsequent therapy or death was 51.8 and 15.1 months (HR: 0.30, 95% CI: 0.22–0.40) for the olaparib and placebo groups, respectively. The most common adverse effects of any grade were nausea (77% vs. 38%), fatigue/asthenia (63% vs. 42%), vomiting (40% vs. 15%) and anaemia (39% vs. 10%). Grade 3 or 4 adverse events were detected in 39% vs. 18% of patients, most commonly in the olaparib group with 22% anaemia and 9% neutropenia. There was no difference in quality of life between the groups at the end of the second year. Olaparib as maintenance therapy in patients with a newly diagnosed mBRCA high-grade ovarian cancer provided 70% lower risk of disease progression or death compared to placebo [1].

Olawaiye et al. evaluated the impact of chemotherapy dose modification (DM) (dose adjustment or treatment delay) on PFS and OS for 738 women diagnosed with stage III/IV ovarian/peritoneal cancer included in the GOG-182 study. They also compared PFS and OS in patients who required granulocyte colony stimulating factor (G-CSF) with those of patients who did not. After optimal or suboptimal cytoreductive surgery, patients were randomised to one of five treatments with a platinum doublet or triplet. Carboplatin/paclitaxel (AUC 6) and paclitaxel (175 mg/m^2) was the reference chemotherapy arm, and eight cycles were given in each arm. Patients who completed eight cycles were included in this study. Chemotherapy dose modification was defined as dose reduction or dose delay. Patients were divided into two main groups. Group 1 (n = 229): Patients who received full-dose chemotherapy on-schedule (dose-unmodified, reference group). Group 2 (n = 509): Patients who required DM. After completing eight cycles, HR for disease progression and death in the DM group was 1.43 (95% CI: 1.19–1.72, $p < 0.001$) and 1.26 (95% CI: 1.04–1.54, $p = 0.021$), respectively. The median PFS of dose-unmodified patients was 7.63 months longer than that of dose modified patients ($p < 0.001$). The median OS of dose-unmodified patients was 19.3 months longer than for dose modified patients ($p = 0.021$). The same differences were reported when 6 cycles of chemotherapy were considered. Not surprisingly, the DM group had 263% greater odds receiving G-CSF than in the dose-unmodified group (OR = 3.63, 95% CI: 2.51–5.26, $p < 0.001$) [2].

Bevacizumab

Since the effect of chemotherapeutic and targeted agents may differ by ethnicity, Komiyama et al. evaluated the role of bevacizumab containing first-line chemotherapy in a single-arm prospective observational study in Japan. A total of 293 Japanese patients diagnosed with advanced epithelial ovarian/fallopian tube/primary peritoneal cancer between April 2014 and February 2016 received three-weekly carboplatin/paclitaxel, with bevacizumab (15mg/kg) every three weeks for cycles 2–22. When grade ≥ 3 adverse events were analysed, there was a high rate of hypertension (23.2%) and proteinuria (12.6%), but the incidence of thromboembolic events (1.4%), gastrointestinal perforation (0.3%), and fistula (0.7%) were comparable to GOG-218. Bowel resection was performed in 12.6% of patients, and none of them had a gastrointestinal perforation or fistula after bevacizumab. In this population, previous bowel resection does not seem to be a risk factor for gastrointestinal complications during the use of bevacizumab. The median PFS was 16.3 months (95% CI: 14.5–18.9) and was similar to GOG-218 (14.1 months) [3].

Gonzalez et al. published a post-hoc analysis of the ICON-7 trial. They evaluated the impact of bevacizumab across tumour stages and residual disease (optimal ≤ 1 cm, suboptimal >1 cm). For FIGO stage I–IIA, grade 3 or clear cell histology, treatment with bevacizumab led to longer PFS (HR < 1). For patients of stage IIIB–IV with no visible residual tumour the HR for PFS was 0.77 (95% CI: 0.59–0.99) favouring bevacizumab (24.3 vs. 19.5 months of median PFS). For patients with a visible residual tumour, the HR was 0.81 (95% CI: 0.69–0.95) with a slightly larger gain in PFS (16.7 vs. 12.0 months). A benefit in OS was only detected in stage IIIB–IV patients with residual tumour (40.3 vs. 35.7 months, HR: 0.87, 95% CI: 0.73–1.04) and stage IV disease. Bevacizumab improved PFS irrespective of stage and residual disease. However, the greatest benefit of bevacizumab on PFS and OS was observed in patients with residual disease [4].

Neoadjuvant chemotherapy

Meyer et al. evaluated the use and effectiveness of neo-adjuvant chemotherapy (NACT) in elderly women with advanced epithelial ovarian cancer by analysing the patterns of care, complications, and outcomes in the SEER-Medicare database. Patients age ≥ 66 years who had undergone both surgery and chemotherapy from 2000 to 2013 were included. There was an increase over time in the use of NACT from 16% at 2000 to 35.4% at 2013 in women with stage III/IV ovarian cancer ($p < 0.001$). There were more complications and utilisation of acute care services (30 day) in stage III women who received primary cytoreductive surgery (PCS) compared to those who received NACT (shock, 9.7% vs. 6.4%, $p = 0.03$; respiratory complications, 34.9% vs. 20.9%, $p < 0.0001$; surgical complications, 46.1% vs. 36.4%, $p = 0.0004$; acute renal failure, 6.8% vs. 4.2%, $p = 0.04$). Perioperative morbidity rates were also higher after PCS for stage IV patients. Median OS in women with stage III disease was significantly longer in the PCS group compared to the NACT group (38.8 months vs. 28.0 months, $p \leq 0.0001$). In stage IV, however, there was no difference in OS (29.8 months for PCS vs. 29.4 months for NACT) [5].

Vergote et al. [6] conducted a pooled analysis of the EORTC 55971 and CHORUS trials. After a median follow-up of 7.6 years, no difference in median OS was observed between women who received NACT (27.6 months) and women after PCS (26.9 months) (HR: 0.97 95% CI: 0.86–1.09, $p = 0.586$). In stage IIIC patients, there was no difference in PFS and OS between the NACT and PCS; however, in patients with stage IV disease, NACT resulted in better PFS (10.6 vs. 9.7 months, HR: 0.77, $p = 0.049$) and OS (24.3 vs. 21.2 months, HR: 0.76, $p = 0.048$) compared to upfront surgery.

Medical treatment of primary ovarian cancer

Ilker Selcuk and Muhammad Rizki Yaznil

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer.	Moore K et al.	N Engl J Med	https://www.nejm.org/doi/full/10.1056/NEJMoa1810858
2	Does adjuvant chemotherapy dose modification have an impact on the outcome of patients diagnosed with advanced stage ovarian cancer? An NRG Oncology/Gynecologic Oncology Group study.	Olawaiye AB et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30135020
3	Bevacizumab combined with platinum–taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients (JGOG3022 trial).	Komiyama S et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30030657
4	Exploratory outcome analyses according to stage and/or residual disease in the ICON7 trial of carboplatin and paclitaxel with or without bevacizumab for newly diagnosed ovarian cancer.	Gonzalez MA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30449719
5	Neoadjuvant chemotherapy in elderly women with ovarian cancer: Rates of use and effectiveness.	Meyer LA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29961559
6	Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials.	Vergote I et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30413383

Surgical treatment of recurrent ovarian cancer

Patriciu Achimas-Cadariu

Preliminary data from the DESKTOP III trial [NCT01166737] presented at ASCO 2017 suggested that SCS is a valuable option for recurrent OC patients, since it improves PFS. At ASCO 2018, secondary objective of the GOG 213 trial [NCT00565851] was presented – the impact of secondary surgical cytoreduction: R0 resection statistically improved PFS and OS relative to those with post-operative residual disease; however, relative to chemotherapy alone, R0 was not associated with better OS despite extending PFS. In the overall population, secondary cytoreduction was not associated with an improvement in either PFS or OS compared to no surgery. Compared to the DESKTOP-III trial, where adjuvant and maintenance rate of bevacizumab was close to 20%, the GOG-0213 had a higher rate of 84% and less strict criteria for the inclusion of patients. The SOC 1 trial [NCT01611766] is ongoing, while the SOCceR trial [NTR3337] was stopped due to low accrual.

A retrospective multicentre Italian study of 126 patients with known gBRCA status reported that recurrent ovarian cancer BRCAmut patients (40%) had the best prognosis regardless of SCS ($p = 0.558$). The post-recurrence survival (PRS) in the BRCAwt population was better when complete SCS was performed (5-year PRS of 54% vs. 42%, $p = 0.048$); hence, the incorporation of predictive biomarkers such as BRCA status could help to tailor the surgical approach in recurrent ovarian cancer patients [1]. However, the proportion of patients with germline BRCA mutation highlights the higher risk of selection bias in retrospective studies.

A review published by an Italian group covers the more recent literature on the evidence of secondary cytoreduction in ovarian cancer [2].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	BRCA mutation status to personalize management of recurrent ovarian cancer: A multicenter study.	Marchetti C et al.	Ann Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30128899
2	Secondary cytoreduction in ovarian cancer: who really benefits?	Giudice MT et al.	Arch Gynecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/30255344

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Medical treatment of recurrent ovarian cancer

Ilker Selcuk

Lee et al. analysed the effectiveness of bevacizumab with single-agent chemotherapy in platinum-resistant ovarian cancer patients in Korea. Single-agent weekly paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan were used. Bevacizumab was given for a median five cycles with a median PFS of 6.1m, which is comparable with the AURELIA study. RECIST response rates were highest in the weekly paclitaxel cohort; there was no difference in PFS between the cohorts. In the PLD arm, grade ≥3 adverse events (AEs), especially haematological events, were less frequently observed [1].

Stanley et al. analysed the role of endocrine treatment (ET) in a retrospective study of relapsed high-grade serous ovarian cancer patients following at least one line of previous chemotherapy. A total of 269 patients were analysed (77% letrozole, 18.6% tamoxifen, 2.2% megestrol acetate, 2.2% other). The median duration of ET was 126 days (28–1427), with a clinical benefit rate (PR and SD) of 40.1%. Oestrogen receptor histoscore > 200 and a longer treatment-free interval (>180 days) were independent predictors of duration of response [2].

Niraparib, a PARPi, as a maintenance treatment in recurrent ovarian carcinoma was analysed in patients age ≥ 70 who were included in the ENGOT-OV16/NOVA trial [3]. A total of 61 patients received niraparib 300mg daily, and 34 patients received placebo. After a median follow-up of 17.3m, median PFS was not reached in the niraparib group. In the placebo group, however, the median PFS was 3.7m, (HR: 0.09, 95% CI: 0.01–0.73). The toxicity profile with thrombocytopenia (34.4%), anaemia (13.1%), and neutropenia (16.4%) was similar to what has been reported for the whole population. In the selected elderly population, niraparib seemed safe.

Friedlander et al. published the mature data of Study 19 of olaparib maintenance monotherapy in 265 patients with platinum-sensitive recurrent high-grade serous ovarian cancer who had received at least two lines of platinum-based chemotherapy and were in complete or partial response. Median follow-up was 77 months. With 79% OS data maturity, a statistically significant advantage in OS was observed for the olaparib arm (29.8 vs. 27.8m; HR: 0.73, 95% CI: 0.55–0.95; p = 0.0213) [4].

In a retrospective MITO study, 27 patients with relapsed epithelial ovarian cancer (EOC) who had received previous PLD either as a single agent or in combination with platinum or trabectedin were re-challenged with PLD [5]. Patients had received a median of three previous chemotherapy lines before re-challenge. At re-challenge, PLD was administered as single agent (48%), in combination with carboplatin (19%) or in combination with trabectedin (33%). The median number of cycles was five (range 3–9). At re-challenge, complete response, partial response, and stable disease were observed in 19%, 30%, and 37% of cases, respectively (combined results of all regimens), resulting in an overall response rate of 49%. Additionally, mean PFS was five months, 13 months, and two months for PLD monotherapy, carboplatin combination, and trabectedin combination, respectively. PLD may be particularly active in HRD-deficient patients, but BRCA status was only available for 19 patients; four of these had a BRCA germline mutation. The most frequently observed grade 3–4 AEs were neutropenia (19%) and thrombocytopenia (7%). Cardiac toxicity (grade 1) was only observed in two patients (7%). Re-treatment with PLD in previously treated EOC patients showed a safe profile with favourable anti-tumour activity.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Real-world effectiveness of bevacizumab based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA): A Korean Gynecologic Oncology Group study (KGOG 3041).	Lee JY et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30409490
2	Endocrine treatment of high grade serous ovarian carcinoma; quantification of efficacy and identification of response predictors.	Stanley B et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30501904
3	Efficacy and safety of niraparib as maintenance treatment in older patients (≥ 70 years) with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial.	Fabbro M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30638768
4	Long-term efficacy, tolerability and overall survival in patients with platinum--sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy.	Friedlander M et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30353045
5	Pegylated liposomal doxorubicin re-challenge in patients with ovarian cancer relapse: a multicenter retrospective study.	Tripodi E et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640698

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Emerging molecular-targeted therapies or early preclinical trials in ovarian cancer

Anna-Maria Schütz

During the six months since the last review, several phase I (avelumab, afuresertib) and phase II (alisertib, cediranib and olaparib, cabozantinib) chemotherapy trials for ovarian cancers have been published. In addition, a pharmacokinetic study on PARP inhibitors and a study on a newly developed PI3K/MTOR dual inhibitor have been published.

Phase I

Disis et al. investigated avelumab, an anti-programmed death-ligand 1 agent, in 125 patients with previously treated recurrent or refractory ovarian cancer in a phase Ib study to evaluate efficacy and safety. Avelumab was given at a dose of 10 mg/kg every two weeks until disease progression or unacceptable toxic effects.12 patients (9.6%) responded, one of them (0.8%) with complete response. The one-year PFS rate was 10.2%, and median OS was 11.2 months. An evaluation of avelumab in combination with pegylated liposomal doxorubicin is ongoing [1].

Blagden et al. reported on outcomes of a phase Ib dose escalation and expansion study of afuresertib, an AKT inhibitor, in combination with carboplatin and paclitaxel in recurrent platinum-resistant ovarian cancer and primary platinum-refractory ovarian cancer. The aim of this study was to determine whether the preclinically demonstrated outcome of platinum resensitisation could be reproduced. Part I was a 3+3 dose escalation study. Afuresertib was given at a dosis of 50–150 mg/day orally together with paclitaxel at a dosis of 175 mg/m^2 and carboplatin every three weeks for six cycles, followed by a maintenance therapy with afuresertib at a MTD of 125 mg/day. In part II, the activity of this combination was evaluated. Patients received afuresertib in combination with carboplatin + paclitaxel for six cycles, followed by maintenance afuresertib. Three dose-limiting toxicities of grade 3 rash were reported. The overall response rate in part II was 32% by RECIST 1.1 and 52% by GCIG CA125 criteria. Median progression-free survival was 7.1 months [2].

Phase II

This phase I / II study carried out by Falchook et al. reported on the efficacy and safety of alisertib in combination with weekly paclitaxel in patients with breast (phase I) and ovarian cancer (phase I and phase II). In all, 73 patients were randomised to alisertib plus paclitaxel and 69 to paclitaxel alone (n = 142). Alisertib was given 40 mg twice per day orally and three days on and four days off for three weeks. Median PFS was 6.7 months with alisertib plus paclitaxel vs 4.7 months with paclitaxel. The most common adverse events in the alisertib plus paclitaxel arm were neutropenia (77% in the combination arm vs. 10% in the paclitaxel arm), stomatitis, and anaemia [3].

In another randomised, open-label, phase II trial, Liu et al. reported on the OS and PFS of patients with relapsed platinum-sensitive ovarian cancer who received either cediranib, an oral anti-angiogenic, in combination with olaparib or olaparib alone. Ninety patients were enrolled and randomised to receive either 30 mg of cediranib daily and 200 mg of olaparib twice daily or 400 mg of olaparib twice daily until disease progression. Median PFS was significantly longer with cediranib/olaparib compared to olaparib alone. A statistically significant improvement in PFS in gBRCA wild-type/unknown patients was reported, although OS was not statistically different in the overall study population. PFS and OS appeared similar between the two arms in gBRCAm patients [5].

Matulonis et al. published a randomised phase II study on cabozantinib, a receptor tyrosine kinases inhibitor, vs. weekly paclitaxel in the treatment of patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. One arm received 60 mg of cabozantinib orally per day, the other arm was given paclitaxel 80 mg/m^2 weekly for three out of four weeks. Median PFS was 5.3 months for cabozantinib and 5.5 months for weekly paclitaxel. Also, overall survival (7% for cabozantinib vs. 24.1% for weekly paclitaxel) and event-free survival (3.5 months in the cabozantinib arm compared to 5.0 months in the paclitaxel arm) showed that cabozantinib did not perform as well as weekly paclitaxel. The overall response rate was also less for cabozantinib compared to weekly paclitaxel (7% vs. 24.1%). In summary, treatment with cabozantinib at this dose and schedule cannot be recommended as a treatment for recurrent ovarian cancer [6].

Preclinical trials

Sund et al. performed a comparative pharmacokinetic study on PARP inhibitors that demonstrated favourable efficacies of niraparib in preclinical BRCAwt tumour models. Tumour exposure to niraparib was 3.3 times greater than plasma exposure in tumour xenograft mouse models, whereas, tumour exposure to olaparib was less than observed in plasma. Also, niraparib did cross the blood-brain barrier and showed good sustainability in the brain; however this effect could not be observed with olaparib. Niraparib achieved more tumour growth inhibition than olaparib in BRCAwt models and an intracranial tumour model at maximum tolerated doses. These findings demonstrate better antitumor effects of niraparib in BRCAwt tumours [9].

Choi et al. reported on the effect of a newly developed PI3K/MTOR dual inhibitor, CMG002, on chemoresistant ovarian cancer cells in combination with paclitaxel or cisplatin. In vivo studies that were carried out in a xenograft mouse model showed toxicity against chemoresistant ovarian cancer cells and re-sensitised these cells to chemotherapeutic agents and could lead to a reduction in tumour growth. This novel inhibitor might be a new therapeutic strategy for chemoresistant ovarian cancer [10].

Emerging molecular-targeted therapies or early preclinical trials in ovarian cancer

Anna-Maria Schütz

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: Phase 1b results from the JAVELIN solid tumor trial.	Disis ML et al.	JAMA Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30676622
2	Phase IB dose escalation and expansion study of AKT inhibitor afuresertib with carboplatin and paclitaxel in recurrent platinum-resistant ovarian cancer.	Blagden SP et al.	Clin Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/30563934
3	Alisertib in combination with weekly paclitaxel in patients with advanced breast cancer or recurrent ovarian cancer: A randomized clinical trial.	Falchook G et al.	JAMA Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30347019
4	Overall survival and updated progression-free survival outcomes in a randomized phase 2 study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer.	Liu JF et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30753272
5	A randomized phase II study of cabozantinib versus weekly paclitaxel in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study.	Matulonis UA et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30587441
6	A comparative pharmacokinetic study of PARP inhibitors demonstrates favorable properties for niraparib efficacy in preclinical tumor models.	Sund K et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/30647846
7	A novel PI3K/mTOR dual inhibitor, CMG002, overcomes the chemoresistance in ovarian cancer.	Choi HJ et al.	Gynaecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30686552

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Treatment of ovarian sex cord stromal and germ cell tumours

Anna Dückelmann

The American National Cancer Database was used to analyse 276 patients with advanced stage malignant ovarian germ cell tumours (MOGCT). Macroscopic residual disease following cytoreductive surgery was not associated with worse prognosis [1].

An analysis of six OGCT trials (3 = paediatric, 3 = adult) showed no difference in event-free or overall survival between platin-based (carboplatin vs. cisplatin) regimens for advanced-stage dysgerminoma. Patients diagnosed with dysgerminoma have an excellent overall survival (OS) across all age groups, and carboplatin should be investigated further to minimise treatment-related toxicities [2].

An interesting paper by Iemura et al. on the histopathological characterisation of the neuroglial tissue within ovarian teratoma showed a significant difference between the anti-N-methyl-D-aspartate (NMDA) receptor encephalitis-associated cases compared to the control cases. NMDA receptor (+) small neuronal clusters with proliferative activity are characteristically present in those cases [3].

A large retrospective cohort study in the National Cancer Database on patients diagnosed with malignant ovarian non-granulosa cell (GC) sex cord-stromal tumours (SCSTs) suggested a possible clinical benefit of adjuvant chemotherapy for patients with advanced stage disease (median OS: 34.96 vs. 15.51 months, p = 0.013). No clear benefit was shown for patients with early stage disease, confirming that postoperative treatment is controversial [4].

The review by Young provides a comprehensive histomorphological overview of ovarian SCSTs [5].

An experimental study by Gogola et al. showed that mixtures of persistent organic pollutants present in follicular fluids may promote GC tumour progression by acting as mitogenic factors in granulosa cells [6].

Zhao et al. investigated MR imaging of 42 ovarian SCSTs to differentiate benign from malignant SCSTs. Malignant SCSTs showed higher signal intensity on T2 and diffusion-weighted (DW) imaging. The combination of T2, DW and dynamic contrast-enhanced imaging permitted the distinction with an accuracy of 88.0% [7].

In the case series on imaging by Xu et al., Sertoli–Leydig cell tumours (SLCT) of the ovary were characterised by a solid or mixed solid-cystic mass on CT/MR scans and showed marked or moderated heterogeneous and constantly enhancement upon postcontrast study [8].

Two studies performed whole-exome and cancer gene panel sequencing of AGCT. AGCTs are characterised by the transcription factor FOXL2 somatic mutation, although the presence of this hotspot mutation is not prognostic. In a small study by Alexiadis et al. (22 cases of AGCT), the TERT promoter mutation was the only recurrent mutation (~40% of cases), which is associated with more aggressive disease [9]. Hillman et al. (79 AGCTs), however, identified for the first time KMT2D-truncating mutations as a significantly mutated gene in AGCT. Those mutations exhibited a statistically significant enrichment in recurrent (10/43, 23%) compared to primary AGCTs (1/32, 3%; p = 0.02). A much larger series will be required to formally evaluate KMT2D inactivation as an independent risk factor for recurrence [10].

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No	Title	Authors	Journal	Link to abstract
1	Prognostic significance of residual disease in advanced stage malignant ovarian germ cell tumors.	Nasioudis D et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30700566
2	Is carboplatin-based chemotherapy as effective as cisplatin-based chemotherapy in the treatment of advanced-stage dysgerminoma in children, adolescents and young adults?	Shah R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29884437
3	Histopathological characterization of the neuroglial tissue in ovarian teratoma associated with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis.	Iemura Y et al.	Pathol Int	https://www.ncbi.nlm.nih.gov/pubmed/30427104
4	Role of adjuvant chemotherapy in the management of non-granulosa cell ovarian sex cord-stromal tumors.	Nasioudis D, Orfanelli T et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30740951
5	Ovarian sex cord-stromal tumors: Reflections on a 40-Year experience with a fascinating group of tumors, including comments on the seminal observations of Robert E. Scully, MD.	Young RH	Arch Pathol Lab Med	https://www.ncbi.nlm.nih.gov/pubmed/30500284
6	Persistent endocrine-disrupting chemicals found in human follicular fluid stimulate the proliferation of granulosa tumor spheroids via GPR30 and IGF1R but not via the classic estrogen receptors.	Gogola J et al.	Chemosphere	https://www.ncbi.nlm.nih.gov/pubmed/30414542
7	The value of MRI for differentiating benign from malignant sex cord-stromal tumors of the ovary: emphasis on diffusion-weighted MR imaging.	Zhao SH et al.	J Ovarian Res	https://www.ncbi.nlm.nih.gov/pubmed/30165895
8	Sertoli-Leydig cell tumors of ovary: A case series.	Xu Q et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/30334998
9	Mutational landscape of ovarian adult granulosa cell tumors from whole exome and targeted TERT promoter sequencing.	Alexiadis M et al.	Mol Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/30166312
10	KMT2D/MLL2 inactivation is associated with recurrence in adult-type granulosa cell tumors of the ovary.	Hillman RT et al.	Nat Commun	https://www.ncbi.nlm.nih.gov/pubmed/29950560

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Treatment of ovarian tumours of low malignant potential (borderline ovarian tumours)

Aleksandra Strojna

Conservative treatment

Jia et al. conducted the largest series on the patients with endometrioid borderline ovarian tumours (eBOTs), including 59 patients with eBOTs. The report is the first to be specifically dedicated to fertility results following the conservative treatment of eBOTs. The mean age of the patients at diagnosis was 41.7 years (range, 23–81 years). Of 47 women aged ≤50 years at diagnosis, 29 (69.2%) had a conservative procedure, leaving the uterus and some intact ovarian tissue in situ. Of these, eight patients (20.5%) retained the involved ovary by cystectomy. Compared with the radical group, patients undergoing conservative surgery were younger and more likely to be nulliparous ($p < 0.001$). The median follow-up time was 30 months (range, 6–177 months). Nine patients (15.3%) developed 13 recurrences; 6–137 months after the initial surgery (median interval, 25 months), including five patients with seven recurrences in the conservative group and four patients with six recurrences in the radical group. The patients who underwent conservative surgery showed a tendency for earlier recurrence, with a high recurrence rate (17.2% vs. 13.3%); this difference was not significant ($p = 0.45$). The median age of the nine patients with recurrence was 35 years (range, 23–47 years). During the initial management, four patients had complete staging surgery, and five patients received additional platinum-based chemotherapy. All patients had FIGO stage I except for one with stage IIIB. In the radical group, the pelvic peritoneum was the most common (75.0%; n = 3/4) recurrent site, whereas in the conservative group, the most common site of recurrence was the ipsilateral ovary (60.0%; n = 3/5) that had been preserved at the initial surgery. Multivariate analysis showed that a younger age of the patients at diagnosis (HR = 0.86, 95% CI: 0.76–0.98, $p = 0.021$) was significantly associated with recurrence rate [1].

Fertility preservation and pregnancy

Patients with BOT are often young and have not yet completed their childbearing. Fertility-preserving surgery is associated with an increased risk of recurrence. The same study mentioned by Jia et al. confirmed that conservative management of endometrioid borderline ovarian tumours was significantly associated with high recurrence rate. Forty-seven patients under age 50 participated in the study. Twenty-nine patients (61.7%) underwent conservative procedures, leaving the uterus and some intact ovarian tissue in situ. Of 20 (69.0%) patients who had attempted to conceive at the time of the data extraction, eight (40.0%) received unilateral cystectomies with/without contralateral ovarian biopsies. There were three pregnancies among two patients (10%) that resulted in two live births, even though four women had tried infertility treatments (two with ovarian stimulations and two with IVF-ET). Eleven women developed endometrial disorders (seven with endometrial endometrioid carcinoma and four with endometrial intraepithelial neoplasia) at a median of 18 months of follow-up (range, 0–177 months), and six patients experienced disease recurrence (two invasive and four borderline) at a median of 29 months of follow-up (range, 8–177 months). The data suggest that conservative management can be proposed in young women with eBOTs to preserve their fertility and obtain spontaneous pregnancies, but patients should be warned about the high risk of disease recurrence. The authors highlighted the need for a careful evaluation of the endometria in conjunction with the high prevalence of synchronous endometrial disorders. Moreover, the reproductive result was not satisfactory, and an exhaustive oncofertility counselling is advocated [1].

Fang et al. conducted retrospective analysis on borderline ovarian tumours (BOT) including 92 young patients aged < 40 years. In all, 54 patients (59%) had undergone fertility-sparing surgery and 38 (41%) received radical surgeries. The majority of patients in the fertility-sparing surgery group were of FIGO stage I (78%, including 57% of stage IA), a few cases were of stage II (1.9%), and the remaining cases were of stage III/IV (20%). Serous borderline ovarian tumours (n = 26, 48%) were the most common pathological type, followed by mucinous (n = 25, 46%), endometrioid (n = 2, 3.7%), and serous/mucinous (n = 1, 1.9%). Among these patients, 11 (20%) had micropapillary lesions, five (9.3%) had microinvasion lesions, and two (3.7%) had invasive implants in uterovesical peritoneal reflection and sacral ligament. This retrospective analysis showed that five factors were distinctly associated with DFS, including an advanced stage (≥FIGO stage II)) (HR = 2.589, 95% CI = 1.017– 6.591, $p = 0.046$), a serous type (the mucinous) (HR = 0.184, 95% CI = 0.053–0.636, $p = 0.007$), the presence of bilateral lesions (HR = 3.135, 95% CI = 1.230–7.989, $p = 0.017$), micropapillary lesions (HR = 3.575, 95% CI = 1.446–8.838, $p = 0.006$) and the type of fertility-preserving surgeries (cystectomy-including surgeries) (HR = 3.3, 95% CI = 1.338–8.140, $p = 0.01$) were associated with a higher recurrence rate and a shorter recurrence interval after conservative surgery. The borderline ovarian tumour patients associated with the above characteristics should be more careful in choosing fertility-sparing surgery and should attempt to achieve pregnancy as soon as possible [2].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Safety and fertility outcomes after the conservative treatment of endometrioid borderline ovarian tumours.	Jia SZ et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30470202
2	The impact of clinicopathologic and surgical factors on relapse and pregnancy in young patients (≤40 years old) with borderline ovarian tumors.	Fang C et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30463533

Pathology in endometrial cancer (prognostic factors, EIN, EIC)

Santiago Scasso and Joel Laufer

The cell adhesion molecule L1 (L1CAM) is highly expressed in several human carcinomas and has more recently been described as a new important marker for endometrial cancer (EC).

In the period covered by the 9th edition of LiFE, Klat et al. investigated how positivity for L1CAM was associated with outcome and relapse pattern in patients with FIGO stage IA–IB EC. Tumour samples from 312 patients were analysed for L1CAM by immunohistochemistry. L1CAM positivity was significantly more common in grade 3 compared to grade 1–2 carcinomas ($p = 0.02$). L1CAM positivity was associated with distant metastasis and patients more commonly experienced disease progression ($p = 0.01$) [1]. Yen et al. analysed the clinical significance of ARID1A loss during tumour progression from complex atypical hyperplasia to EC. EC was identified in the hysterectomy specimen of 94% of patients with complex atypical hyperplasia and loss of ARID1A in the endometrial sampling specimen ($p < 0.0001$). The authors highlighted that ARID1A immunostaining may correlate with malignant transformation and the presence of concurrent EC in patients with complex atypical hyperplasia identified at pre-hysterectomy endometrial sampling [2].

Another important issue highlighted during this period was the clinical significance of isolated tumour cells (ITC) and micrometastasis (MM) in low-grade, stage I EC. Piedimonte et al. evaluated the impact of ITC and MM on the outcome of these patients. Grade 1 to 2 stage I endometrioid EC patients with nodal ITC ($n = 11$) or MM ($n = 12$) between 2012 and 2018 were retrospectively compared to a matched group of lymph node negative ($n = 18$) patients. More ITC/MM patients received RT and chemotherapy (91.7% vs. 18.4%; 70.8% vs. 4.5%, respectively; $p < 0.01$) without significant difference in treatment-related toxicities (25% vs. 27.3% grade 1%–2% and 20.8% vs. 9.1% grade 2–3; $p = 0.538$) or PFS (29.2 vs. 25 months; $p = 0.828$). With adjuvant treatment, ITC/MM in otherwise well-differentiated stage I endometrial cancer had similar outcomes to matched lymph-node negative patients [3].

The TransPORTEC consortium was established to refine the prognostic classification and identify novel therapeutic strategies in high-risk endometrial cancer. The current TransPORTEC high-risk endometrial cancer cohort included 45% stages III/IV and mainly high-risk histologies (85% grade 3 endometrioid, serous or clear cells). Auguste et al. refined the classification of high-risk EC based on DNA damage response biomarkers which offers both prognostic as well as molecular subtype specific therapeutic strategies. Their findings have led the TransPORTEC prognostic classification of high-risk endometrial cancer into five distinct subgroups by integrating DNA damage response biomarkers and identified molecular subtype-specific therapeutic strategies. From best to worst prognosis: group 1 "POLE mutated/microsatellite unstable" > group 2 "no specific molecular profile with no DNA damage" > group 3 "TP53 mutated/Non Homologous End-Joining negative" > group 4 "no specific molecular profile with high DNA damage" > group 5 "TP53 mutated/Non Homologous End-Joining positive"; $p = 0.0002$). Actionable targets were also different among subsets. Group 3 had significantly higher infiltration of PD-1+ immune cells ($p = 0.003$), segregating with group 1. Group 2 had frequent PI3K pathway mutations and ER positivity. While group 5, with the worst prognosis, had high DNA damage and PARP-1 expression providing a rationale for PARP inhibition [4].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	L1CAM as a negative prognostic factor in endometrioid endometrial adenocarcinoma FIGO stage IA-IB.	Klat J et al.	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/30591489
2	Clinical significance of isolated tumor cells and micrometastasis in low-grade, stage I endometrial cancer.	Piedimonte S et al.	J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30353577
3	Loss of ARID1A expression in endometrial samplings is associated with the risk of endometrial carcinoma.	Yen TT et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30126589
4	Refinement of high-risk endometrial cancer classification using DNA damage response biomarkers: a TransPORTEC initiative.	Auguste A et al.	Mod Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/29955143

Screening for uterine cancer/Hereditary uterine cancer

María de los Reyes Oliver Pérez

In the period covered in this edition of the LiFE report, one retrospective study [1], nine clinical trials [2–10], and two literature reviews [11,12] have been selected for discussion.

Screening for uterine cancer

Clarke et al. published a systematic review of the prevalence and the risk of EC in women with postmenopausal bleeding (PMB). The prevalence of PMB among women with EC was 91% (95% CI: 87%–93%) and the pooled risk of EC was 9% (95% CI: 8%–11%). The authors concluded that early detection strategies should focus on women with PMB [1].

New potential biomarkers of early-stage EC were also evaluated. Cymbaluk-Ploska et al. determined the lipocalin-2 levels in patients with EC compared to those with normal endometrium or mild endometrial pathologies [2]. Wang et al. investigated serum adiponectin, visfatin levels and their ratio [3], while Jiang et al. examined an autoantibody against a novel tumour-associated antigen derived from human DNA-topoisomerase I and peripheral blood surviving-expressing circulating cells in patients with early-stage EC [4]. All seem to be promising in early detection of EC.

Finally, Han et al. verified the feasibility of endometrial samplers for screening EC using a new endometrial sampler – Li Brush. They performed a self-controlled trial of 293 women comparing the cytopathology diagnosis from Li Brush and the histopathology diagnosis from hysterectomy. The sensibility and specificity of the test was 92.73% and 98.2%, respectively [5].

Hereditary uterine cancer

Despite increases in genetic testing (GT), many high-risk women remain unidentified. Populations who do not access genetics services are at risk of missing opportunities for cancer prevention. Lee et al. performed a retrospective review of 184 women diagnosed with EC who had risk factors for Lynch Syndrome (LS). Only 58% of them were given genetic counsel and only 35% underwent GT [6]. Hinchcliff et al. published a very interesting review about the current guidelines for genetics evaluation of patients with gynaecologic cancers and current barriers to GT [7]. Fulk et al. explored the germline mutation spectrum and prevalence among 1,650 women with breast (BC) and uterine (UC) cancer compared to a control group. These women were significantly more likely to test positive than individuals with BC only ($p < 0.001$), UC only ($p < 0.01$), or unaffected controls ($p < 0.001$) [8].

Lynch Syndrome

Regarding a new genetic test in LS, Salvador et al. described the results of paired tumour/germline testing performed on a large cohort of patients (n = 702) with colorectal cancer and EC. Paired testing identified a cause for mismatch-repair-deficient of tumours in 76% and 61% of patients without and with prior LS germline testing, respectively [9]. Also, Libera et al. examined the mutational profiles of a well-characterised series of sporadic and LS-related ECs, performing exonic targeted sequencing of 16 genes mainly involved in microsatellite instability of ECs. The authors concluded that this model provides useful insights into disease biology and diagnostic classification of these tumours [10].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Association of endometrial cancer risk with postmenopausal bleeding in women: A systematic review and meta-analysis.	Clarke MA et al.	JAMA Intern Med.	https://www.ncbi.nlm.nih.gov/pubmed/30083701
2	The role of lipocalin-2 serum levels in the diagnostics of endometrial cancer.	Cymbaluk-Ploska A et al.	Cancer Biomark.	https://www.ncbi.nlm.nih.gov/pubmed/30829613
3	Clinical significance of serum adiponectin and visfatin levels in endometrial cancer.	Wang Z et al.	Int J Gynaecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/30702161
4	Clinical significance of plasma anti-TOP048 autoantibody and blood survivin-expressing circulating cancer cells in patients with early stage endometrial carcinoma.	Jiang XH et al.	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/30341503
5	An efficacious endometrial sampler for screening endometrial cancer.	Han LS et al.	Front Oncol.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6389657/
6	Missed opportunities: Genetic counseling and testing among an ethnically diverse cohort of women with endometrial cancer.	Lee J et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30077346
7	Disparities in gynecologic cancer genetics evaluation.	Hinchcliff EM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30711300
8	Women with breast and uterine cancer are more likely to harbor germline mutations than women with breast or uterine cancer alone: A case for expanded gene testing.	Fulk K et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30612783
9	Comprehensive paired tumor/germline testing for Lynch Syndrome: Bringing resolution to the diagnostic process.	Salvador MU et al.	J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30702970
\	Targeted gene sequencing of Lynch syndrome-related and sporadic endometrial carcinomas.	Libera L et al.	Hum Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/30420047

Treatment of endometrial hyperplasia

Elko Gliozheni

Kitson et al. performed a multicentre, double-blind, placebo-controlled trial in which they randomised women with atypical hyperplasia or endometrioid endometrial cancer (EC) to receive metformin or placebo for 1–5 weeks before surgical treatment. They concluded that short-term treatment with standard diabetic doses of metformin does not reduce tumour proliferation in women with EC awaiting hysterectomy, thus this study does not support a biological effect of metformin in EC and casts doubt on its potential application in the primary and adjuvant treatment settings [1].

Knowing that after successful progestin therapy for endometrial hyperplasia (EH) the risk of relapse remains, Sletten et al. aimed to retrospectively assess if immunohistochemical (IHC) expression of progesterone receptor isoforms (PR-A and PR-B) in endometrial glands and stroma was related to relapse of EH. They concluded that low PR-A in endometrial glands ($p = 0.013$) and stroma ($p < 0.001$), and high PR-B in endometrial glands ($p = 0.001$) in pre-treatment endometrial biopsy were associated with relapse of EH. A pre-treatment ratio of PR-A:PR-B ≤ 1 was associated with a higher risk of relapse (71%) compared with women with a ratio of PR-A:PR-B > 1 (19%; $p < 0.001$) [2].

Bahmani et al. performed a randomised, double-blind, placebo-controlled trial among 60 women diagnosed with EH. Folic acid administration for 12 weeks to subjects with EH improved glycaemic control, triglycerides, VLDL-cholesterol and hs-CRP levels but did not influence recurrence and other metabolic profiles [3].

Based on a systematic review with a meta-analysis, Travaglino et al. concluded that PTEN does not seem to be useful as predictive marker of response to the conservative treatment of EH and EC, regardless of how progestins are administered (oral or intrauterine) [4].

Graul et al. published a retrospective series analysis of the role of LNG-IUS in obese women with EH/atypical endometrial hyperplasia (EHA)/EC. In patients with BMIs over 40 kg/m^2, treatment outcomes using LNG-IUS were more varied, and patients were more likely to experience disease progression compared to patients with lower BMI [5].

Wang et al. retrospectively reviewed patients diagnosed with EC/EHA who underwent fertility-sparing treatment. The patients who achieved a complete response were grouped according to the treatment duration. Longer treatment duration was associated with higher rates of complete response while longer treatment duration (> 9 months) was not associated with a decrease in success rates of pregnancy [6].

Raffone et al. assessed the value of the pretreatment assessment of estrogen (ER; oestrogen) and progesterone receptors (PR) expression in EH and EEC treated with progestins. ER and PR expressions were significantly predictive of response in EH and EEC treated with levonorgestrel-intrauterine device, but not with oral progestins [7].

Yang et al. retrospectively included patients with EAH or well-differentiated EC which received constant oral progestin combined with hysteroscopic evaluation and lesion resection every three months until achieving complete response (CR). This strategy seemed to be an effective and safe fertility-sparing therapy for these patients, while endometrial lesion size ≤ 2 cm was correlated with a shorter treatment period to achieve CR [8].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	PRE-surgical Metformin In Uterine Malignancy (PREMIUM): a multi-center, randomized double-blind, placebo-controlled phase 3 trial.	Kitson S et al.	Clin Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/30563932
2	Significance of progesterone receptors (PR-A and PR-B) expression as predictors for relapse after successful therapy of endometrial hyperplasia: a retrospective cohort study.	Sletten ET et al.	BJOG.	https://www.ncbi.nlm.nih.gov/pubmed/30548528
3	The effects of folic acid supplementation on recurrence and metabolic status in endometrial hyperplasia: A randomized, double-blind, placebo-controlled trial.	Bahmani F et al.	Arch Iran Med.	https://www.ncbi.nlm.nih.gov/pubmed/30415553
4	PTEN as a predictive marker of response to conservative treatment in endometrial hyperplasiaand early endometrial cancer. A systematic review and meta-analysis.	Travaglino A et al.	Eur J Obstet Gynecol Reprod Biol.	https://www.ncbi.nlm.nih.gov/pubmed/30342311
5	Conservative management of endometrial hyperplasia or carcinoma with the levonorgestrel intrauterine system may be less effective in morbidly obese patients.	Graul A et al.	Gynecol Oncol Rep.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6148728/
6	Impact of treatment duration in fertility-preserving management of endometrial cancer or atypical endometrial hyperplasia.	Wang Y et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30826750
7	Should progesterone and estrogens receptors be assessed for predicting the response to conservative treatment of endometrial hyperplasia and cancer? A systematic review and meta-analysis.	Raffone A et al.	Acta Obstet Gynecol Scand.	https://www.ncbi.nlm.nih.gov/pubmed/30779338
8	Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrialcancer.	Yang B	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30674421

Surgical treatment of primary uterine cancer

Piotr Lepka

Lymphadenectomy (LND) in endometrial cancer (EC)

Polan et al. retrospectively evaluated major complication rates among women with EC treated with minimally invasive surgery according to the extent of LND. In all, 3,282 patients with EC were evaluated and divided into subgroups: no LND (62.4%), traditional LND (33.2%), and sentinel LND (4.4%). The results showed that traditional LND had the highest rate of major complications (3.6%) compared with sentinel LND (2.0%) and no LND (2.0%). In addition, the traditional LND group had the longest surgery time and this cohort also had twice the odds of major complications and need for readmission compared to the sentinel and no-LND groups [1].

Sari et al. retrospectively evaluated 280 patients with surgically endometrioid-type EC with positive lymphovascular space invasion according to the lymph node involvement. Out of 88 patients (31.4%) with positive LN, factors such as elevated baseline serum CA125, deep myometrial invasion (MMI), adnexal involvement, and positive cytology were found to be independent markers of LN metastasis. Deep MMI together with elevated baseline serum CA 125 were found in 46.8% women with LN metastasis [2].

Ørtoft et al. retrospectively evaluated the role of LND in high-risk patients with EC defined as grade 3, > 50% myometrial invasion or serous/clear/undifferentiated stage I–IV EC. In this cohort of 390 patients after LND, 31 were upstaged from I to IIIC and 19 from II to IIIC. Cancer-specific survival in high-risk stage I patients LN-negative and upstaged patients from I to III C were almost comparable: 81% and 77%, respectively. Excluding stage I patients, LND patients had significant higher overall survival as compared with non-LND. However, LND did not significantly affect cancer-specific survival, progression-free survival, recurrence rate risk of local, distant, or LN recurrence [3].

Postoperative outcomes

Volpi et al. retrospectively evaluated patients with EC who underwent hysterectomy with pelvic and paraaortic LND according to the postoperative lymphocele and lower extremity lymphoedema incidence. In total, 249 patients were evaluated: 198 with pelvic LND and 51 with both pelvic and paraaortic LND. In total, 36.9% (n = 92) patients developed lymphoedema and 17.3% (n = 43) developed lymphocele. The risk of lymphoedema was significantly correlated with radiotherapy and positive lymph nodes and lymphocele was correlated with removal of circumflex iliac nodes [4].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Extent of lymphadenectomy and postoperative major complications among women with endometrial cancer treated with minimally invasive surgery.	Polan et al.	American Journal of Obstetrics and Gynecology	https://www.ncbi.nlm.nih.gov/pubmed/30521798
2	Risk factors for lymph node metastasis among lymphovascular space invasion-positive women with endometrioid endometrial cancer clinically confined to the uterus.	Sari et al.	Oncol Res Treat.	https://www.ncbi.nlm.nih.gov/pubmed/30419557
3	The effect of introducing pelvic lymphadenectomy on survival and recurrence rates in Danish endometrial cancer patients at high risk: a Danish Gynecological Cancer Group study.	Ørtoft et al.	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/30640686
4	Long term complications following pelvic and para-aortic lymphadenectomy for endometrial cancer, incidence and potential risk factors: a single institution experience.	Volpi et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30718312
5	Sexual function following hysterectomy for endometrial cancer: A five-year follow up investigation.	Buckingham et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30420200

Surgery in recurrent endometrial cancer

Arun Kalpdev

Gallotta et al. reported a case of recurrent endometrioid endometrial adenocarcinoma in a 55-year-old woman, who presented with recurrence of the disease twice (vaginal cuff and intraparenchymal lesion in spleen) after primary surgery successfully treated with surgery and subsequent chemotherapy lines. [1].

Amant et al. published a summary of management of endometrial cancer as a part of the FIGO cancer report. In this report, the authors suggested that "large" recurrences should be evaluated for surgery and followed by radiotherapy. In patients who have had prior radiation therapy, extended surgery may be considered. Similarly, for central recurrences, pelvic exenteration should be considered in properly selected cases (e.g., central recurrences without signs of distant spread) [2]. there seems to be a role of surgery in recurrent endometrial cancer in carefully selected patients.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Robotic splenectomy for isolated splenic recurrence of endometrial adenocarcinoma.	Gallotta V et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29128439
2	Cancer of the corpus uteri.	Amant F et al.	Int J Gynaecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/30306580

Medical treatment of recurrent endometrial cancer

Ewa Surynt

Connor et al. nicely reviewed currently available data for the management of recurrent endometrial cancer (REC), with a focus on systemic treatment. They discussed the available evidence for first-line, second-line, and subsequent systemic therapy and also discussed emerging therapeutic targets, including their biologic plausibility and early clinical data [1].

Iwase et al. retrospectively analysed the recurrence patterns, treatments, and prognoses of 112 REC patients who were primarily treated in Japan, where chemotherapy has become a standard adjuvant treatment after primary surgery. Approximately 78% of patients received adjuvant chemotherapy and 85/112 patients (76%) experienced recurrence within 2 years after the initial treatment; therefore, a more aggressive strategy should be used for patients at high risk to improve their prognoses. The prognosis of patients with recurrence within regional LN and/or vagina was significantly better than of patients with distant recurrent lesions. A multivariate analysis indicated that positive peritoneal cytology, a disease-free interval of less than 12 months, recurrent lesions in two or three localizations, and treatment excluding surgery or radiotherapy were independent predictors of poor prognosis after recurrence [2].

Finally, Cottu et al. presented results of an open-label, multicentre, randomised, parallel-group, phase I study where 52 heavily pre-treated patients with recurrent tumours (12 with REC) positive for type I progesterone receptor were treated with onapristone, a type I progesterone receptor antagonist. Onapristone was exceptionally well tolerated, with no dose limited toxicity reported. Tumour assessments strongly suggested anticancer efficacy. Nine of the 52 patients had a clinical benefit lasting at least 24 weeks, and 11 additional patients experienced stable disease as best response [3].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Management strategies for recurrent endometrial cancer.	Connor EV et al.	Expert Rev Anticancer Ther.	https://www.ncbi.nlm.nih.gov/pubmed/29972650
2	The clinical features of recurrent endometrial cancer in Japan: Chemotherapy instead of radiotherapy as postoperative adjuvant treatment.	Iwase H et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30095709
3	Phase I study of onapristone, a type I antiprogestin, in female patients with previously treated recurrent or metastatic progesterone receptor-expressing cancers.	Cottu PH et al.	PLoS One.	https://www.ncbi.nlm.nih.gov/pubmed/30304013

Uterine sarcoma

Marcin Bobiński

Treatment and follow-up

A meta-analysis of 17 studies including 786 patients on ovarian preservation in low-grade endometrial stromal sarcoma treatment was published by Nasioudis et al. The conservative approach was associated with higher recurrence rate, which suggests the role of hormones in carcinogenesis of endometrial stromal sarcoma. If such an approach is chosen, patients need to be informed about this risk [1]. An interesting review of literature regarding leiomyosarcoma (LMS), was prepared by Roberts et al. [2].

Diagnostic tools

Nishigaya et al. analysed a combination of clinical markers such as D-dimer, LDH, and CRP in distinguishing uterine LMS and leiomyoma, considering it a potentially useful tool [3]. A novel approach to differentiation between malignant and benign myometrial lesions was proposed by Malek et al. By using machine learning to analyse MRI results, they achieved an accuracy of 91.7%, sensitivity of 100%, and specificity of 90% [4]. A similar approach was presented by Nakagawa et al., who compared the accuracy of differentiation between leiomyoma and sarcoma using MRI and PET analysed by machine-learning algorithms, and proved the superiority of MRI [5]. Takeuchi et al., reported that intra-tumoral haemorrhage on an MRI scan was an important diagnostic feature in the diagnosis of myometrial lesions [6].

Molecular and basic research

An initial report assessing the usefulness of ctDNA in uterine LMS was released by Hemming et al. The authors reported a correlation between cfDNA and tumour size and progression of the disease, considering it a potentially useful diagnostic tool [7]. An interesting analysis of BRCA2 gene alteration among patients with soft-tissue sarcomas based on 1,236 cases was published by Seligson et al. The incidence of BRCA2 mutation in the entire group was 1%, but in the subgroup of uterine LMS it was found in 9% of cases. The data suggested that patients with uterine LMS should be considered for somatic BRCA2 profiling; clinical trials assessing the efficacy of PARP inhibitors among such patients are also needed [8].

The analysis of 84 cancer-related miRNAs expression in uterine leiomyosarcoma was performed by Gonzalez Dos Anjos et al., confirming the association of several miRNAs with DFS, metastasis, and disease relapse [9].

Varia

A rare case of conservative treatment of endometrial stromal sarcoma with sparing of the uterus was reported by Michael Straughn et al. [10].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Ovarian preservation for low-grade endometrial stromal sarcoma: a systematic review of the literature and meta-analysis.	Nasioudis D et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30640694
2	Uterine leiomyosarcoma: A review of the literature and update on management options.	Roberts ME et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30244960
3	Diagnostic value of combination serum assay of lactate dehydrogenase, D-dimer, and C-reactive protein for uterine leiomyosarcoma.	Nishigaya Y et al.	J Obstet Gynaecol Res.	https://www.ncbi.nlm.nih.gov/pubmed/30152048
4	A machine learning approach for distinguishing uterine sarcoma from leiomyomas based on perfusion weighted MRI parameters.	Malek M et al.	Eur J Radiol.	https://www.ncbi.nlm.nih.gov/pubmed/30599861
5	A multiparametric MRI-based machine learning to distinguish between uterine sarcoma and benign leiomyoma: comparison with 18F-FDG PET/CT.	Nakagawa M et al.	Clin Radiol.	https://www.ncbi.nlm.nih.gov/pubmed/30471748
6	Clinical utility of susceptibility-weighted MR sequence for the evaluation of uterine sarcomas.	Takeuchi M et al.	Clin Imaging.	https://www.ncbi.nlm.nih.gov/pubmed/30340078
7	Detection of circulating tumor DNA in patients with leiomyosarcoma with progressive disease.	Hemming ML et al.	JCO Precis Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30793095
8	BRCA 1/2 functional loss defines a targetable subset in leiomyosarcoma.	Seligson ND et al.	Oncologist.	https://www.ncbi.nlm.nih.gov/pubmed/30541756
9	Could miRNA signatures be useful for predicting uterine sarcoma and carcinosarcoma prognosis and treatment?	Gonzalez Dos Anjos L et al.	Cancers (Basel).	https://www.ncbi.nlm.nih.gov/pubmed/30200635
10	Treatment of low-grade endometrial stromal sarcoma in a nulligravid woman.	Michael Straughn J Jr et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29887484

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Emerging therapies in endometrial cancer

Zoia Razumova

Precision medicine in cancer treatment is developing fast in gynaecological oncology. In 2018, the FDA approved pembrolizumab, PD-1 inhibitor, as immunotherapy in MSI high advanced endometrial cancer (EC). Other molecular biomarkers in EC could also help to identify targets for therapeutic strategies in the future.

Long non-coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs) is a member of a new noncoding RNAs class. Their role in EC is currently unknown.

Ravo et al. explored lncRNAs as possible molecular biomarkers. Some lncRNAs was differentially expressed in EC and normal endometrial tissues. Moreover, deregulation of small and long RNAs was associated with EC, representing a group of cancer markers that can be used in diagnosis, follow-up, and targeted therapy [1]. Chen et al. studied lncRNA testis developmental related gene 1 (TDRG1) in EC and normal endometrial tissues in human. lncRNA TDRG1 was strongly overexpressed in EC. Furthermore, lncRNA TDRG1 effected on cell proliferation, invasion, migration, and apoptosis. The possible mechanism is positively targeted VEGF-A [2]. Li et al. investigated the role of lncRNA prostate cancer gene expression marker 1 (PCGEM1) in EC. PCGEM1 expression was outstandingly high in EC. PCGEM1 stimulated the proliferation, migration, and invasive features of EC cells; overexpression could result in tumour growth in vivo. Also, lncRNA PCGEM1 inhibited apoptosis. PCGEM1 also promoted STAT3 expression, which influenced the expression of survivin, vascular endothelial growth factor A, matrix metalloproteinase-2, and B-cell lymphoma-2. Hence, PCGEM1 could affect the development of EC by upregulating the expression of STAT3 [3].

SQ1274 – a novel microtubule inhibitor

SQ1274 is an analogue of bifidenone. It disrupts microtubule dynamics as paclitaxel. Also, it could be a robust chemotherapeutic candidate. Mills et al. compared the effects of SQ1274 expression and paclitaxel in EC cell lines in vitro and in vivo. SQ1274 had a much lower half-maximal inhibitory concentration than paclitaxel in ARK1 cancer cell line, decreased expression of AXL, and caused cell-cycle arrest and apoptosis compared to paclitaxel. Also, SQ1274 better inhibited cancer growth in vivo in comparison to paclitaxel [4]. Thus, SQ1274 may be alternative chemotherapeutic drug to paclitaxel in EC treatment.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Identification of long noncoding RNA expression patterns useful for molecular based classification of type I endometrial cancers.	Ravo M et al.	Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/30483802
2	LncRNA TDRG1 enhances tumorigenicity in endometrial carcinoma by binding and targeting VEGF-A protein.	Chen S et al.	Biochim Biophys Acta Mol Basis Dis	https://www.ncbi.nlm.nih.gov/pubmed/29920344
3	The relationship between lncRNA PCGEM1 and STAT3 during the occurrence and development of endometrial carcinoma.	Li Q et al.	Biomed Pharmacother	https://www.ncbi.nlm.nih.gov/pubmed/30257404
4	SQ1274, a novel microtubule inhibitor, inhibits ovarian and uterine cancer cell growth.	Mills KA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30190114

Cervical pre-invasive disease

Geanina Dragnea

Screening

In an observational study, 578,547 women underwent cervical screening in England between 2013 and 2014, with follow-up until 2017; 183,970 (32%) were screened with hrHPV testing. Baseline hrHPV testing and early recall (at 12 and 24 months) required approximately 80% more colposcopies but detected substantially more CIN than LBC (1.49 for CIN2+, 1.44 for CIN3+) and cervical cancer (1.27). At the incidence screen (at three years), the 33,506 women screened with hrHPV testing had substantially less CIN3+ than the 77,017 women screened with LBC (0.14). This finding supports extending the hrHPV screening interval [1].

HPV testing on self-collected versus clinician-collected samples was evaluated in a randomised, non-inferiority trial, on 187,473 women. HPV testing had similar accuracy on self-collected and clinician-collected samples in terms of the detection of CIN2+ or CIN3+ lesions. These findings suggest that HPV self-sampling could be used as a primary screening method in routine screening [2].

In a study on 1,416 women who underwent screening with HPV testing and LBC, those with HPV-positive results received further tests using DNA-based genotyping, E6/E7 oncoprotein detection targeting HPV16/18 (E6 (16/18) Test) or HPV16/18/31/33/35/45/52/58 (E6/E7 (8 types) Test), respectively. Among HPV-positive women, E6/E7 (8 types) oncoproteins had lower positivity (17.37%) compared to DNA-based genotyping for the same eight types (58.30%) and LBC with ASC-US threshold (50.97%). HPV16 was the genotype showing the highest frequency (8.49%) for oncoprotein detection. For detection of CIN3+, E6/E7 (8 types) test had similar sensitivity (100.00%), superior specificity (85.94%) as well as positive predictive value (PPV, 22.22%) compared to both LBC and DNA-based genotyping (8 types); for detection of CIN2+, E6/E7 (8 types) test was less sensitive (67.74%) but still more specific (89.47%) and risk predictive with PPV of 46.67%. E6/E7 (8 types) test remarkably decreased the number of colposcopies needed to detect one CIN2+ and CIN3+ (2.14 and 4.50), making colposcopy referrals more efficient [3].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Primary cervical screening with high risk human papillomavirus testing: observational study.	Rebolj M et al.	BMJ	https://www.ncbi.nlm.nih.gov/pubmed/30728133
2	Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial.	Polman NJ et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30658933
3	Eight-type human papillomavirus E6/E7 oncoprotein detection as a novel and promising triage strategy for managing HPV-positive women.	Rezhake R et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29943809

Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Matteo Morotti

Cibula et al. analysed the oncological outcomes of 231 patients with lymph node (LN) negative and "intermediate risk" (based on GOG-92) cervical cancer patients. Data were pooled from three different institutions. One hundred and twenty-seven patients were treated with tailored radical surgery and compared to a control group of 104 patients who had surgery followed by adjuvant radiotherapy. Tumour size more than 4 cm was the only significant adverse prognostic factor for disease-specific survival (DSS) in the surgery-only group. In the whole cohort, a tumour between 2–4 cm in size and adeno-squamous histotype were significant prognostic variables. Recurrence, DSS, and overall survival rates were similar between the two groups. There were fewer distant and combined recurrences in the surgery-only group. The authors concluded that surgery alone can be an option in selected 1B1-2 cervical cancer patients; however, further studies are warranted to define those subgroups who will benefit from adjuvant radiotherapy [1].

Yuan et al. assessed the accuracy of detecting pathological parametrial involvement (PMI) by clinical and radiological modalities in stage IIB cervical cancer patients who underwent surgery in Fudan University between 2004–2015. The accuracy of MRI or PET-CT in detecting PMI was significantly lower compared to physical examination. The authors concluded that, given the high percentage of "pseudo" PMI among patients with FIGO stage IIB cervical cancer, they should be given individualised treatment (also surgical option). However, due to the long study period and the lack of information regarding the type of surgery, radiological technologies, and availability of radiotherapy, it is difficult to extrapolate these results to other clinical settings [2].

Chen et al. randomised 101 patients with Ia2-Ib1 cervical cancer < 2 cm in receiving a) laparoscopic Piver-Rutledge class I or b) class III radical hysterectomy. There was no significant differences in terms of pathologic findings, adjuvant treatment, and clinical outcomes between the groups. Postoperative complications were higher in the class III group. The authors suggested that reducing surgical radicality in early cervical cancer patients (< 2 cm) might be safe. Unfortunately, the study had major limitations. Pelvic lymphadenectomy was done, and patients were excluded if no lymph node (LN) metastasis were found at quick paraffin sections. Thus, it is not clear if the LN were then analysed for frozen section or were paraffin-embedded and analysed retrospectively. Moreover, no data on randomisation procedures or LN findings were provided [3].

Tortorella et al. analysed 137 patients who underwent pelvic exenteration (PE), total, anterior or posterior at the Mayo Clinic between 2004–2016. Total PE was performed in 32.6%, anterior PE in 37.7%, and posterior PE in 29.7% of the patients. Among 137 patients, 92 (67.2%) had a postoperative complication within 30 days of surgery. Surgical complexity in terms of the type and level of PE was a major predictor of severe postoperative complications, increasing from 5% (posterior), to 30.8% (anterior) and 42.2% for total PE. In all, 27% of the patients developed severe complications. The independent predictors of severe complications in this sub-cohort were anterior or total PE, pre-operative haemoglobin ≤10 mg/dL and presence of 3+ comorbidities [4].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Surgical treatment of "intermediate risk" lymph node negative cervical cancer patients without adjuvant radiotherapy—A retrospective cohort study and review of the literature.	Cibula D et al.	Gynecol Oncol	https://doi.org/10.1016/j.ygyno.2018.10.018
2	Feasibility of radical hysterectomy in women with FIGO stage IIB cervical cancer: an observation study of 10-year experience in .a tertiary center.	Yuan L et al.	Onco Targets Ther	http://dx.doi.org/10.2147/OTT.S173208
3	Class I hysterectomy in stage Ia2-Ib1 cervical cancer.	Chen L et al.	Videosurgery Miniinv	https://doi.org/10.5114/wiitm.2018.76832
4	Prediction of short-term surgical complications in women undergoing pelvic exenteration for gynecological malignancies.	Tortorella L et al.	Gynecol Oncol	https://doi.org/10.1016/j.ygyno.2018.10.036

Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

A GOG study from Boardman et al. examined the feasibility and tolerability of four cycles of additional carboplatin/paclitaxel after extended field radiation together with concomitant cisplatin for patients with para-aortal node-positive cervical cancer. If PET, fine needle aspiration or surgical assessment were necessary to confirm PA node involvement. If a boost was given to the para-aortic region, was not clear from the publication. Four to six weeks after chemo-radiation, escalating doses of carboplatin three-weekly paclitaxel were started. Of the 11 patients, two did not complete chemo-radiation. At dose level two (AUC = 5), three out of six patients completed all cycles. A CR of 50% and a PR of 10% were reported, as well as median PFS of > 46 months (60% PFS at 12 months). Dose level 2 with paclitaxel 135 mg/m^2 and carboplatin AUC 5 was identified as the maximum tolerated dose, but with a considerable number of grade 3 events, mainly haematological toxicity [1].

The results of the randomised phase III OUTBACK study are eagerly awaited, although extended field radiation is not allowed in that study, due to concerns regarding toxicity.

Treatment of locally advanced disease

In LiFE 8, we discussed the Ferrandina et al. publication on NACT followed by chemoradiation and radical surgery in stage IB2–IVA disease. Here, we discuss their approach with dose-dense NACT followed by radical surgery in the same patient population. In all, 44% had positive pelvic lymph nodes. OR after NACT was 75%, but overall pathological response was only 16.1%. Some 23/36 (64%) of the patients received adjuvant treatment after surgery [2]. The study was closed prematurely due to ethical concerns. The EORTC55994 phase III trial will hopefully help to clarify the role of NACT in LACC, but until then, any such undertaking in light of the results with contemporary chemoradiation alone is to be considered experimental.

Treatment of advanced/recurrent disease

Capecitabine (1250 mg/m^2 twice daily continuously from day one to day 14 of a 21-day cycle) was studied in a retrospective series of 35 patients with recurrent disease after platinum-based chemotherapy. OR was 34.2% with a clinical benefit rate including stable disease of 57%. Only 8.5% of the patients reported grade 3 toxicity [3].

In LiFE 8, the addition of S1 (oral fluoropyrimidine-based anticancer agent) was discussed in addition to cisplatin. Now, Mabuchi et al. published the results of a phase II study in combination with irinotecan. A response rate of 29% was observed, with 15.7% grade 3–4 toxicity, mainly haematological toxicity and diarrhoea [4]. The response rates are similar to what has been reported for S1 alone (Katsumata et al. Ann Oncol. 2011 Jun;22(6):1353-7).

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	A Phase I evaluation of extended field radiation therapy with concomitant cisplatin chemotherapy followed by paclitaxel and carboplatin chemotherapy in women with cervical carcinoma metastatic to the para-aortic lymph nodes: An NRG Oncology/Gynecologic Oncology Group Study.	Boardman CH et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30174176
2	Dose-dense paclitaxel/carboplatin as neo-adjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer: a prospective phase II study.	Ferrandina G et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30506402
3	Capecitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma: a retrospective study.	Maltese G et al.	Cancer Chemother Pharmacol.	https://www.ncbi.nlm.nih.gov/pubmed/30636709
4	A phase II study of irinotecan combined with S-1 in patients with advanced or recurrent cervical cancer previously treated with platinum based chemotherapy.	Mabuchi S et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30833436

Radiotherapy in management of recurrent cervical cancer

Erbil Karaman

Kim et al. conducted a retrospective study on the feasibility and benefit of RT, particularly intensity-modulated RT (IMRT), for salvage treatment of recurrent cervical cancer. 125 patients received salvage RT for the recurred or metastatic tumour mass. The median follow-up period was 5.5 years (range, 10.8 months to 41 years). The five-year local failure-free survival (LFFS) and progression-free survival (PFS) rates were 63.9% and 39.6%, respectively. The five-year overall survival (OS) rate was found to be 66%; 10-year OS reached 51%. They observed late complications in 12 patients (12/125, 9.6%). They concluded that salvage RT is safe and effective against recurrent cervical cancer. IMRT seemed to be a safe and effective salvage modality for these patients, including those requiring re-irradiation [1].

Qu et al. studied the efficacy of image-guided radioactive 125I seed (IGRIS) implantation for pelvic-recurrent cervical cancer (PRCC) after external beam radiotherapy (EBRT) and analyzed the influence of clinical and dosimetric factors on efficacy. In all, 36 patients with PRCC received IGRIS. They evaluated local progression-free survival (LPFS) and overall survival (OS). The median follow-up was 11.5 months. The one- and two-year LPFS rate was 34.9% and 20%, respectively. They investigated the independent factors affecting LPFS and found that recurrence site (central or pelvic wall) (HR = 0.294; 95% CI: 0.121–0.718), lesion volume (HR = 2.898; 95% CI: 1.139–7.372), D90 (HR = 0.332; 95% CI: 0.130–0.850) as the independent factors. The dosimetric parameters of 33 patients mainly included D90 (128.5±47.4 Gy), D100 (50.4±23.7 Gy), and V100 (86.7%±12.9%). When D90 ≥105 Gy or D100 ≥55 Gy or V100 ≥91%, LPFS was extended significantly, but no significant difference for OS was found. IGRIS implantation could be a safe and effective salvage treatment for PRCC after EBRT, which could markedly release the pain [2].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Radiotherapy is a safe and effective salvage treatment for recurrent cervical cancer.	Kim HJ et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30195468
2	Efficacy and dosimetry analysis of image-guided radioactive 125I seed implantation as salvage treatment for pelvic recurrent cervical cancer after external beam radiotherapy.	Qu A et al.	J Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30479093

Emerging molecular-targeted therapies or early preclinical trials in cervical cancer

Marcin Mardas

Sin et al. examined tumour-suppressive functions of TROP-2 in cervical cancer cells in vitro and in vivo. Functional assays showed that overexpression of TROP-2 significantly inhibited the oncogenicity of cervical cancer cells while knockdown of TROP-2 exhibited opposite effects. Human Phospho-Receptor Tyrosine Kinase Array showed that the activity of IGF-1R and ALK was stimulated by TROP-2 knockdown. These results supported that TROP-2 exhibits tumour suppressor functions in cervical cancer through inhibiting the activity of IGF-1R and ALK [1].

Trybus et al. examined the effect of emodin, a natural compound present in the roots and rhizomes of Rheum palmatum, on the induction of mitotic catastrophe in cervical cancer cells. HeLa cells were treated with different emodin concentrations for 48 hours. Emodin induced an increase in the number of polymorphonuclear cells, giant cells, cells with micronuclei, cells with abnormal mitosis, and ones with damaged spindle. The reorganisation of F-actin depended on the concentration of emodin. With the increase in emodin concentration an inhibition of mitotic activity was also demonstrated, which was manifested by a decrease in the mitotic index mainly in metaphase of the mitotic process and an increase in the number of cells inhibited in the G2/M phase. At the same time, an increase in the number of apoptotic cells was found [2].

Chen et al. fabricated biodegradable AG-loaded nanofibrous membranes to inhibit the progression of cervical cancer. AG is a labdane diterpenoid that has been isolated from the stem and leaves of Andrographis paniculata and has been traditionally used to treat infections and certain diseases. Two different membranes were prepared via electrospinning technology and tested on 12 mice divided into three groups: A as the control, B treated with pure mats without AG, and C treated with AG-loaded nanofibrous membranes. The animal test results showed that while the tumour size for rats in the control and in the group receiving pure PLGA mats grew with time, the tumour size in rats implanted with AG-eluting mats decreased over time until day 25. Thereafter, the tumour recurred. This might be attributable to the fact that the drug-loaded nanofibers released high concentrations of AG for up to three weeks, after which the drug concentration gradually dropped to 1,000 μg/mL at the fourth week. Tumour cells thus regenerated with the decrease of drug concentration [3].

Shao et al. examined luteoloside in treating the cervical cancer HeLa cell line and investigated its effects on cell morphology, proliferation, apoptosis, and related proteins. The study demonstrated that luteoloside could inhibit proliferation remarkably; promote apoptosis and cytochrome C release; decrease the mitochondrial membrane potential and reactive oxygen species level; upregulate the expression of Fas, Bax, p53, phospho-p38, phospho-JNK, and cleaved PARP; downregulate the expression of Bcl-2 and phospho-mTOR; activate caspase-3 and caspase-8; change the nuclear morphology and fragmentate DNA in Hela cells. Authors concluded that these findings provide support for the further investigation of luteoloside as a therapeutic agent for cervical cancer [4].

Wang et al. studied the effect of mitofusin 2 (mfn2) on cervical carcinoma HeLa cells and on a cervical carcinoma mouse model. Authors demonstrated that Mfn2 can induce cervical carcinoma HeLa cell apoptosis via the mitochondrial pathway. It activated the pro-apoptotic processes in the mitochondrial apoptosis pathway and inhibited anti-apoptotic protein expression in the mitochondrial pathway. All these features illustrated that Mfn2 may be a promising starting point for the future clinical application of efficient anticancer treatment targets in cervical carcinoma therapy [5].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	TROP-2 exhibits tumor suppressive functions in cervical cancer by dual inhibition of IGF-1R and ALK signaling.	Sin STK et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30429055
2	Emodin induces death in human cervical cancer cells through mitotic catastrophe.	Trybus W et al.	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/30711945
3	Biodegradable andrographolide-eluting nanofibrous membranes for the treatment of cervical cancer.	Chen YP et al.	Int J Nanomedicine.	https://www.ncbi.nlm.nih.gov/pubmed/30666104
4	Luteoloside inhibits proliferation and promotes intrinsic and extrinsic pathway--mediated apoptosis involving MAPK and mTOR signaling pathways in human cervical cancer cells.	Shao J et al.	Int J Mol Sci.	https://www.ncbi.nlm.nih.gov/pubmed/29874795
5	Mitofusin-2 triggers cervical carcinoma cell Hela apoptosis via mitochondrial pathway in mouse model.	Wang W et al.	Cell Physiol Biochem.	https://www.ncbi.nlm.nih.gov/pubmed/29587277

Radiotherapy in primary cervical cancer management

Paweł Bartnik

Li et al. reviewed the National Cancer Database (NCD) and created a cohort of 1,719 patients who between 2004 and 2015 underwent hysterectomy due to cervical cancer (CC) with positive surgical margins and subsequent adjuvant external beam radiation therapy (ERBT). Of these, 778 patients received additional brachytherapy (BT). With a median follow-up of 3.8 years, ERBT with BT were associated with better prognosis than ERBT alone (HR = 0.77; 95% CI: 0.64–0.92; p = 0.003) [1].

Another study by Cushman et al. also analysed 166 patients from the NCD with locally advanced CC who underwent hysterectomy with positive margins, parametrial invasion, and/or positive nodes. Those patients were elderly (age > 70) women, who underwent either an adjuvant chemoradiotherapy (CRT; n = 104) or radiotherapy (RT; n = 62). No differences in overall survival in the median time of observation of 35.3 months were observed depending on CRT or RT [2].

Thamronganantasakul et al. performed a meta-analysis comparing extended-field RT to pelvic RT and extended-field CRT to pelvic CRT in the locally advanced CC. A total of five high-quality studies were analysed. Extended-field CRT may possibly reduce risk of death in comparison to standard CRT (HR = 0.37; 95% CI: 0.14–0.96). In addition, extended-field RT probably reduces the risk of death (HR = 0.67; 95% CI: 0.48–0.94) and para-aortic lymph node recurrence (RR = 0.36; 95% CI: 0.18 = 0.70) in comparison to pelvic RT [3].

One hundred and four patients were analysed in a single-centre study investigating the impact on treatment time depending on imaging method – MRI-based BT and CT-based BT for locally advanced CC. MRI-based BT did not prolong overall treatment time (median treatment time: 50 vs. 53 days; p = 0.781) and significantly shortened BT time alone (median treatment time: 9 vs. 19 days; p < 001) [4].

Another meta-analysis was performed by Sapienza et al. estimating the effectiveness of uterine perforation prevention with an ultrasound-guided applicator insertion in BT for CC. A total of 12 studies including 1,757 insertions and 766 patients were analysed. Ultrasound-guided BT decreased the number of perforations by 90% [5].

Bai et al. performed a meta-analysis of eight studies investigating volumetric-modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) in patients with CC in terms of dosimetric comparison of irradiation of organs at risk (OAC). A significantly lower volume of rectum received a dose of 40Gy was observed in VMAT in comparison to IMRT. No differences were observed in small intestine and bladder irradiated volume [6].

From the EMBRACE 1 study, 1,201 patients who underwent MR based image-guided adaptive brachytherapy (MR-IGABT), were analysed by Serban et al. in order to investigate isodose surface volumes (ISVs) for locally-advanced CC patients in comparison to a standard Point-A therapy. Patients treated with MR-IGABT had improved target dose coverage and decreased ISVs compared classical Point-A based brachytherapy [7].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Survival benefit of adjuvant brachytherapy after hysterectomy with positive surgical margins in cervical cancer.	Li R et al.	Int J Radiation Oncol Biol Phys	https://www.ncbi.nlm.nih.gov/pubmed/29890264
2	Postoperative chemoradiotherapy versus radiotherapy alone for elderly cervical cancer patients with positive margins, lymph nodes, or parametrial invasion.	Cushman TR et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30207105
3	Extended-field radiotherapy for locally advanced cervical cancer.	Thamronganantasakul K et al.	Cochrane Database Syst Rev.	https://www.ncbi.nlm.nih.gov/pubmed/30362204
4	Impact on treatment time of MRI-based brachytherapy in two implants (4 doses) compared with CT-based brachytherapy in five implants for cervical cancer.	Small C et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/30497938
5	Decrease in uterine perforations with ultrasound image-guided applicator insertion in intracavitary brachytherapy for cervical cancer: A systematic review and meta-analysis.	Sapienza LG et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30333082
6	Dosimetric comparison of volumetric-modulated arc therapy and intensity-modulated radiation therapy in patients with cervical cancer: a meta-analysis.	Bai W et al.	Onco Targets Ther	https://www.ncbi.nlm.nih.gov/pubmed/30425510
7	Isodose surface volumes in cervix cancer brachytherapy: Change of practice from standard (Point A) to individualized image guided adaptive (EMBRACE I) brachytherapy.	Serban M et al.	Radiother Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30243671

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Pathology of epithelial and non-epithelial malignant tumours of the vulva and vagina

Kamil Zalewski

HPV prevalence

Based on a systemic database search (26 studies published between 1986 – 2017), Bertoli et al. estimated the overall and type-specific prevalence of human papillomavirus (HPV) in vaginal cancer (VaSCC) (n = 593) and vaginal intraepithelial neoplasia (VaIN) (n = 1,374) to be 66.7% (95% CI: 54.7–77.8) and 85.2% (95% CI: 78.2–91.0), respectively. The most predominant HPV type among the HPV-positive VaSCC and VaIN cases was HPV16, followed by HPV33, and HPV45 (in VaIN) and HPV18, and HPV33 (in VaSCC). In pooled analyses, 89.9% (95% CI: 81.7–94.6) of HPV-positive and 38.9% (95% CI: 0.9–90.0) of HPV-negative vaginal cancers were positive for p16 overexpression [1]. Zhang et al., conducted a systematic review of 33 studies to estimate the prevalence of HPV in vulvar cancer (VSCC) to be 34% (95% CI: 28%-39%) with 45% (95% CI: 28%–64%) in Asian populations and 34% (95% CI: 26%–42%) in Caucasian populations. HPV-positive vulvar cancer was associated with better overall survival (HR = 0.64, 95% CI: 0.47–0.87; p = 0.004) and recurrence-free survival (HR = 0.66, 95% CI: 0.45–0.97; p = 0.03) compared with the HPV-negative counterpart [2].

HPV and radiotherapy

Based on the result of the immunohistochemical staining performed on 25 patient samples, Nwachukwu et al. presented negative p16 expression as an independent predictor of inferior overall survival in patients with primary vaginal cancer treated with definitive radiotherapy. The two-year cumulative incidence of recurrence was 14% for p16-positive tumours compared with 67% for p16-negative tumours (p = 0.07) [3].

In the first study of its kind and based on the results of 73 women treated with neoadjuvant or definitive chemoradiation with a median follow-up of 13.4 months, Horne et al. evaluated the impact of p16 on intact VSCC. P16-expressing VSCC, a surrogate of HPV infection, had higher pathologic response rates (53.8% vs 31.4% for p16+ vs p16–, respectively (p = 0.067)) and p16 expressing VSCC had improved local control (75.5% vs. 49.5% for p16– (p = 0.008)) [4].

This was also confirmed in the meta-analysis showing that women with p16 positive vulvar cancers had better survival compared to p16 negative and p53 positive vulvar cancers had a less favourable survival compared to p53 negative. Both p16 and p53 may be clinically useful prognostic markers for vulvar cancer patients [5].

PD-L1 expression in melanomas

Saleh et al. evaluated a series of 13 cases and detected PD-L1 expression in 69% of cases which was not associated with any other molecular alteration (KIT, NRAS, KRAS, and BRAF), tumour stage or morphology. The authors suggested that targeting PD-L1 by selective antibodies may be of benefit in the treatment of these tumours [6]. In another retrospective study, PD-L1 receptor expression was detectable independent of HPV status [7].

Expression of the Sonic Hedgehog receptor

Hedgehog (Hh) pathway dysregulation has been described in cancers associated with high-risk human papillomavirus (HR-HPV) and chronic inflammation, both of which are recognised as independent aetiological factors for VSCC. Yap et al. investigated the status of Hh pathway activity in 91 primary cases of VSCC and examined the associations between Hh pathway activation and clinicopathological criteria. They demonstrated for the first time that 92% of primary VSCC cases over-expressed one or more components of the Hh signalling pathway when compared to the adjacent normal epithelium. Over- or under-expression of PTCH1 was associated with a reduced or increased risk of developing a local disease recurrence, respectively. In VSCC arising on a background of Lichen sclerosus, the risk of local recurrence was also potentiated in cases where PTCH1 was under-expressed. The authors suggested that these results could help stratify patients and inform clinicians of the risk of local recurrence, particularly in cases of VSCC associated with LS [8].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Human papillomavirus and p16 in squamous cell carcinoma and intraepithelial neoplasia of the vagina.	Bertoli HK et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30561092
2	Prevalence of human papillomavirus and its prognostic value in vulvar cancer: A systematic review and meta-analysis.	Zhang J et al.	PLoS One.	https://www.ncbi.nlm.nih.gov/pubmed/30256833
3	Prognostic significance of P16 expression and P53 expression in primary vaginal cancer.	Nwachukwu CR et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/30516621
4	Human papillomavirus infection mediates response and outcome of vulvar squamous cell carcinomas treated with radiation therapy.	Horne ZD et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30082072
5	The prognostic value of p16 and p53 expression for survival after vulvar cancer: A systematic review and meta-analysis.	Sand FL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30415992
6	Frequent PD-L1 expression in malignant melanomas of the vulva.	Saleh B et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/28914674
7	PD-L1 receptor expression in vulvar carcinomas is HPV-independent. Virchows Arch.	Choschzick M et al.	Virchows Arch.	https://www.ncbi.nlm.nih.gov/pubmed/29736798
8	Under expression of the Sonic Hedgehog receptor, Patched1 (PTCH1), is associated with an increased risk of local recurrence in squamous cell carcinoma of the vulva arising on a background of Lichen Sclerosus.	Yap J et al.	PLoS One.	https://www.ncbi.nlm.nih.gov/pubmed/30379908

Preinvasive disease of vulva and vagina (aetiology, diagnosis, management, follow-up)

Kamil Zalewski

5-Flouorouracil and VaIN

In the first meta-analysis to date, Tranoulis et al. studied the efficacy of 5-Flouorouracil (5-FU) on the vaginal intraepithelial neoplasia (VaIN) treatment. After the first 5-FU course 82.18% (95% CI: 69.80%–88.82%) of women had a complete response and 16.42% (95% CI: 7.39%–28.14%) recurred. The summary proportions of women with complete response in the high-grade VaIN, persistent disease, and recurrence subgroups were 77.53% (95% CI: 59.90%–91.15%), 53.92% (95% CI: 34.62%–72.61%), and 72.32% (95% CI: 48.12%–91.05%), respectively [1].

HIV and VaIN

In their observational cohort study of 87 women diagnosed with VaIN for the first time, Bradbury et al. analysed the clinical characteristics, management, and outcomes in HIV-positive patients receiving antiretroviral treatment. HIV-positive women developed VaIN at a younger age compared to HIV-negative women. They are also more often smokers and present with multicentric and multifocal disease at diagnosis. The median time from the diagnosis of HIV to the development of VaIN was 14 years (range = 1–22 years). There were no significant differences in survival outcomes between groups [2].

Vulvar Paget disease

Vulvar Paget disease (VPD) is responsive to immune modulator imiquimod but knowledge about its microenvironment is lacking. Van der Linden et al. investigated (in a retrospective setting and for the first time) the immune infiltration of VPD and compared it to vulvar high-grade squamous cell intraepithelial lesions (HSIL) and healthy controls. They concluded that the epithelium in VPD has fewer immune cells and differs from the healthy skin and vulvar HSIL, whereas the stromal compartment is highly infiltrated by CD4+, CD8+, Foxp3+ T cells, and CD14+ cells [3]. The same authors analysed the data of 113 patients diagnosed with VPD between 1991 and 2016. Seventy-seven percent had non-invasive VPD. Most women underwent surgery (65%). Recurrences were reported in 40%. Of the women with non-invasive VPD, 8% developed invasion. There were no disease-specific deaths reported in women with non-invasive VPD. The five-year DSS was over 98% in non-invasive and micro-invasive VPD, but significantly worse in invasive VPD: 50% ($p < 0.0005$) [4].

Review

Cohen et al. nicely reviewed recent studies that investigated the risks of progression to vulvar malignancy associated with HSIL and differentiated vulvar intraepithelial neoplasia, the prognosis of HPV-dependent and HPV-independent vulvar squamous cell carcinomas and conducted next-generation sequencing mutation analyses to elucidate the genomic profiles underlying vulvar intraepithelial neoplasia [5].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	5-Flouorouracil is an attractive medical treatment in women with vaginal intraepithelial neoplasia: A meta-analysis.	Tranoulis A et al.	J Low Genit Tract Dis.	https://www.ncbi.nlm.nih.gov/pubmed/30132763
2	Vaginal intraepithelial neoplasia: Clinical presentation, management, and outcomes in relation to HIV infection status.	Bradbury M et al.	J Low Genit Tract Dis.	https://www.ncbi.nlm.nih.gov/pubmed/30161052
3	The immune cell infiltrate in the microenvironment of vulvar Paget disease.	van der Linden M et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30274932
4	Vulvar Paget disease: a national retrospective cohort study.	van der Linden M et al.	J Am Acad Dermatol.	https://www.ncbi.nlm.nih.gov/pubmed/30458205
5	Clinical and molecular classification of vulvar squamous pre-cancers.	Cohen PA et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30737358

Primary vulvar cancer treatment

Rubén M. Betoret

Prognostic indicators

Half of vulvar squamous cell cancer (VSCC) patients are aged 70 or older at diagnosis. With life expectancy increasing worldwide and, consequently, rising age-related comorbidities, which seem to be correlated with poor prognosis, an original work by Di Donato et al. evaluated the impact of age-adjusted Charlson Comorbidity Index (ACCI) in predicting outcome among 78 surgically treated patients with vulvar carcinoma. ACCI class was an independent predictor of worse disease-free survival (HR = 3.04; 95% CI: 1.54–5.99; $p < 0.001$), overall survival (OS) (HR 5.25; 95% CI: 1.63–16.89; $p = 0.005$) and cancer-specific survival (HR = 3.79; 95% CI: 1.13–12.78; $p = 0.03$) and could be a useful tool in predicting prognosis in surgically treated VSCC patients [1]. Salcedo et al. retrospectively reviewed 421 patients with invasive VSCC and highlighted the presence of perineural invasion as an independent poor prognostic factor (OS, median 25.5 vs. 94.3 months ($p < 0.001$) and progression-free survival (PFS), median 17.5 vs. 29.0 months ($p = 0.004$), even after adjusting for stage), thus recommending the inclusion of this specific item in all pathologic reports [2]. Polterauer et al. updated their first publication on lymph node (LN) ratio (ratio of positive LN to the total number of resected), completing a retrospective analysis using the AGO-CaRE-1 study multicentre database. In a setting of 1,047 surgically treated patients, including inguinal lymph node resection, these are stratified into three subgroups (lymph node ratio (LNR) of 0%, LNR of > 0% – < 20% and LNR of > 20%), finding statistically significant differences between groups in terms of three-year OS (89.7% vs. 65.4% vs. 41.9%) and three-year PFS (75.7% vs. 44.2% vs. 23.1%), even outperforming nodal status and number of positive nodes in survival analyses [3].

Sentinel lymph node biopsy

Inguinal lymph node involvement is still considered the most important prognostic risk factor for survival in VSCC. Nica et al. retrospectively reviewed the management of 159 VSCC patients at a single institution who underwent sentinel lymph node (SLN) biopsy and found no difference in recurrence rates (5%) between negative SLN without inguinofemoral lymph node dissection (IFL) and positive micrometastasis (under 2 mm) without IFL and subsequently treated by radiotherapy. The groin recurrence rate was slightly higher (9%) in patients with tumour size bigger than 4 cm, discouraging its use in this particular subgroup [4].

Neoadjuvant therapy

Chemoradiation, causing high morbidity, is currently the only alternative treatment strategy for locally advanced VSCC. Amant et al. reported two cases of locally advanced disease (IVA and II), treated with neo-adjuvant chemotherapy (NACT) based in three-weekly paclitaxel (175 mg/m^2)- carboplatin (5xAUC) and with partial responses after four and six cycles, allowing in both cases the subsequent completion of radical vulvectomy and IFL, with OS of 42 and 20 months at the end of follow-up, the latter with no evidence of disease. This publication is proposed to encourage multicentre trial to further explore the role of NACT in VSCC patients [5].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	The age-adjusted Charlson comorbidity index as a predictor of survival in surgically treated vulvar cancer patients.	Di Donato V et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30479090
2	Perineural invasion (PNI) in vulvar carcinoma: A review of 421 cases.	Salcedo MP et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30396690
3	Lymph node ratio in inguinal lymphadenectomy for squamous cell vulvar cancer: Results from the AGO-CaRE-1 study.	Polterauer S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/m/pubmed/30760408
4	Sentinel lymph nodes in vulvar cancer: Management dilemmas in patients with positive nodes and larger tumors.	Nica A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30454877
5	Brief report on 3-weekly paclitaxel carboplatin efficacy in locally advanced or metastatic squamous vulvar cancer.	Amant F et al.	Gynecol Obstet Invest	https://www.ncbi.nlm.nih.gov/pubmed/30227411

Vulvovaginal adenocarcinoma/melanoma/sarcoma

Anna Dückelmann

Al-Obaidy et al. analysed 22 cases of extramammary Paget's disease (EMPD) in the vulva and scrotum. In all, 81% (n = 13) of the 16 vulvar EMPD were positive for p16; however, none of the scrotal or vulvar cases showed positive reactivity for human papillomavirus (HPV) either by immunohistochemistry or in situ hybridisation. EMPD of vulva and scrotum does not appear to be related to HPV [1].

Broggi et al. reported a rare case of intestinal-type adenocarcinoma of the vagina (ACV), arising from a villous adenoma. The main clinico-pathologic features of the only 19 cases of intestinal-type ACV reported in literature are summarised. Clinical and radiologic features as well as the presence of an adenomatous precursor are helpful in differentiating between primary and metastatic tumours.

Saleh et al. detected PD-L1 expression in 69% of 13 cases of malignant melanomas of the vulva, which is not associated with any other molecular alteration, tumour stage or morphology. Targeting PD-L1 may be of benefit in the treatment of these uncommon tumours.

Neff et al. described the rare case of dermatofibrosarcoma protuberans (DFSP) in a 57-year-old patient presenting with a large, bleeding vulvar mass. The patient underwent a radical vulvectomy with complex wound closure and is maintained on imatinib without evidence of recurrence for over 12 months. DFSP is a rare, slow-growing, superficial tumour, often locally aggressive, with a high risk of local recurrence, but a lower risk of distant metastatic spread.

Jahanseir et al. presented a series of 11 cases of DFSP. They determined a high frequency (82%) of PDGFB rearrangement in vulvar DFSP which can be useful in diagnostically challenging cases.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	P16 expression in extramammary Paget's disease of the vulva and scrotum Is not human papillomavirus related.	Al-Obaidy KI et al.	Int J Surg Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/29745285
2	Intestinal-type adenocarcinoma of the vagina: clinico-pathologic features of a common tumor with a rare localization.	Broggi G et al.	Pathologica.	https://www.ncbi.nlm.nih.gov/pubmed/30546144
3	Frequent PD-L1 expression in malignant melanomas of the vulva.	Saleh B et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/28914674
4	Dermatofibrosarcoma protuberans: A rare and devastating tumor of the vulva.	Neff R et al.	Gynecol Oncol Rep.	https://www.ncbi.nlm.nih.gov/pubmed/30733992
5	PDGFB rearrangements in dermatofibrosarcoma protuberans of the vulva: a study of 11 cases including myxoid and fibrosarcomatous variants.	Jahanseir K et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/29140881

Treatment of vaginal cancer

Elis Ismail

Although VC is more common in postmenopausal women, an increase in young women being diagnosed with primary VC has been reported, especially in countries with a high HIV prevalence. A review published as a part of the FIGO Cancer Report 2018, discussed the issues related to diagnostics, staging, and treatment of this disease [1]. Guerri et al. systematically reviewed data on the role of definitive radiotherapy in the management of VC. In this retrospective study, the majority of all the 793 patients were treated with a combination of external beam RT and brachytherapy (74.2%). The five-year local control rates and five-year overall survival ranged between 39% and 79% and 34% and 71.0% (median, 63.5%), respectively. The authors concluded that a brachytherapy boost should be delivered, especially in patients with higher-stage disease, and the addition of concurrent weekly cisplatin should be considered in most patients [2].

Case reports

Jain et al. reported a case of a 64-year old post-menopausal woman who had received radiation therapy 32 years before she was diagnosed with (positive for HPV-16 DNA) vaginal squamous cell carcinoma. The association of human papilloma virus (HPV) in cervical cancers is well established and these patients might have a higher risk of HPV-induced vaginal cancers. The authors concluded that HPV DNA testing during follow-up may facilitate early recognition of HPV-related lower genital tract cancers [3].

Zhang et al. presented a 45-year-old woman with an adenoid cystic carcinoma of the vagina. Although she was proposed to start treatment with a surgical excision, the patient preferred chemoradiotherapy alone and is alive and well 13 months after the initial diagnosis [4].

Chloroma (granulocytic sarcoma or myeloid sarcoma) is a rare malignancy of the vagina. It is an extra-medullary neoplasm of myeloid precursor cells and is reported in 2.5%–9.1% of patients with acute myeloid leukaemia and occurs concomitantly following or (rarely) antedating the onset of systemic bone marrow leukaemia. Madabhavi et al. presented a rare case of chloroma in a 38-year-old female patient who was given induction chemotherapy with the "3+7" regimen, including daunorubicin and cytarabine followed by high-dose cytarabine as consolidation therapy, and stayed asymptomatic at 12 months of follow-up. The role of local RT as consolidation is still controversial [5].

Primary vaginal melanoma is a rare aggressive tumour with a poor prognosis. The average age at diagnosis is 60, and there are no known risk factors. The establishment of a classification system and treatment protocols challenged by the rarity of the disease. The five-year survival rate is estimated to be no more than 10%. The French authors reported a case of an inoperable primary vaginal melanoma in a 58-year-old woman with metastatic lymph nodes in the lumbo-aortic region, treated with nivolumab as monotherapy. Clinical and radiological regression was observed, and the treatment was well tolerated [6].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Cancer of the vagina.	Adams TS et al.	Int J Gynaecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/30306589
2	Definitive radiotherapy in invasive vaginal carcinoma: A systematic review.	Guerri S et al.	Oncologist.	https://www.ncbi.nlm.nih.gov/pubmed/30139838
3	A report of human papilloma virus-16 associated vaginal carcinoma after thirty-two years of successful radiation therapy for cervical cancer.	Jain G et al.	Virusdisease.	https://www.ncbi.nlm.nih.gov/pubmed/30539058
4	Adenoid cystic carcinoma of the vagina: A case report.	Zhang LZ et al.	Medicine (Baltimore).	https://www.ncbi.nlm.nih.gov/pubmed/30608403
5	Primary vaginal chloroma: A rare case report.	Madabhavi I et al.	Int J Hematol Oncol Stem Cell Res.	https://www.ncbi.nlm.nih.gov/pubmed/30595816
6	Primary malignant melanoma of vagina.	Daix M et al.	Rev Med Liege.	https://www.ncbi.nlm.nih.gov/pubmed/30113785

Sentinel node mapping in gynaecological malignancies

Anton Ilin

Vulvar squamous cell carcinoma (VSCC)

Nica et al. evaluated the rates and patterns of recurrence in invasive vulvar SCC after SLN procedure [1].

Endometrial cancer (EC)

Papadia et al. assessed the impact of different doses of indocyanine green on sentinel lymph node mapping. Two different injection protocols were used (protocol 1): 5 mg/mL and a volume of 8 mL protocol 2): 1.25 mg/mL and a volume of 4 mL). It was found that a larger dose of ICG is associated with a higher number of retrieved SLNs but not with an increased bilateral detection rate [2].

Buda et al. assessed the impact of the type of nodal assessment (SLN-mapping algorithm vs. selective lymphadenectomy, LD) on prognosis in 266 patients with early-stage high-intermediate (HI) and high-risk (HR). The three-year comparison did not show a significant difference between strategy adopted for nodal staging (SLN mapping, LD, and SLN + LD) on both disease-free survival and overall survival [3].

Body et al. evaluated factors associated with poor mapping or false negative results in patients with EC. A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99%, respectively, in cases with at least unilateral detection. The authors described the correlation between detection rate and BMI, tumour factors, SLN location, size of LN and explained reasons for failed dye migration, diffuse smearing, and "swollen lymphatics" [4].

A new two-step SLN mapping strategy was proposed by Kyung et al. The first step was to identify SLNs of the uterine body. In total, 4–6 mL of ICG was injected into the bilateral uterine cornual areas, and lymphatic channels were traced, followed by identification and removal of paraaortic SLNs. The second step was to identify SLNs of the uterine cervix by injecting 4 mL of ICG into the cervix. Detection rates were: 100% (50/50) overall for SLNs; 98.0% (49/50) for pelvic SLNs; 94.0% (47/50) for bilateral SLNs; and 86.0% (43/50) for paraaortic SLNs [5].

Cervical cancer (CC)

Cibula and McCluggage gave a critical overview of key aspects related to this concept, such as a necessity for reliable detection of micrometastases (MIC) in SLN and the requirements for SLN pathologic ultrastaging, low accuracy of intraoperative detection of SLN involvement, and the still-limited evidence of oncological safety of the replacement of PLND by SLN biopsy only in ≥IB1 tumours due to unknown risk of MIC in non-SLN pelvic lymph nodes in patients with negative SLN, and absence of any prospective evidence [6].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Sentinel lymph nodes in vulvar cancer: management dilemmas in patients with positive nodes and larger tumors.	Nica A et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30454877
2	The impact of different doses of indocyanine green on the sentinel lymph-node mapping in early stage endometrial cancer.	Papadia A et al.	J Cancer Res Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30043278
3	The impact of the type of nodal assessment on prognosis in patients with high-intermediate and high-risk ESMO/ESGO/ESTRO group endometrial cancer. A multicenter Italian study.	Buda A et al.	Eur J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30077521
4	Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer.	Body N et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29909967
5	Two-step sentinel lymph node mapping strategy in endometrial cancer staging using fluorescent imaging: A novel sentinel lymph node tracer injection procedure.	Kyung JE et al.	Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30217312
6	Sentinel lymph node (SLN) concept in cervical cancer: Current limitations and unanswered questions.	Cibula D, McCluggage WG	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30318103

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Minimal invasive surgery in gynaecological cancer

Mir Fuad Hasanov

Cervical cancer

Primary data on disease-free survival (DFS) from the LACC Trial were already presented as an abstract at the SGO Annual Meeting 2018 and were included in the previous issue of LiFE. Here, we give the link to the final article published in NEJM. The study randomised 631 patients with cervical cancer stage IA1-IB1 to either open abdominal or minimally invasive surgery (MIS). After a median follow-up time of 2.5 years, 34 patients had had a recurrence (27 in the MIS group and 7 in the open-surgery group). The rate of disease-free survival at 4.5 years was 86.0% with MIS and 96.5% with open surgery. Also, the overall survival was inferior in the minimally invasive group (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI: 1.77–20.30). The trial did not reach its intended accrual due to the safety alert. The trial reached 84% power to declare noninferiority for the primary outcome. There was no clear pattern of recurrences across sites. With the limitation that the trial was not powered to study differences in survival in patients with particular low-risk tumors (i.e., < 2cm, no lymphovascular space invasion). MIS was associated with higher recurrence rates and shorter survival in patients with early-stage cervical cancer [1].

Tjalma discussed different surgical approaches to radical hysterectomy methods in the post-LACC Trial era, with emphasis on several possible explanations for the adverse oncological outcomes after minimal invasive surgery. The author suggest that patients should be involved in the discussion after careful counselling about a survival benefit at the cost of an increased short-term morbidity after open surgery [2]. The main argument for MIS is reduced morbidity. Bogani et al. compared laparoscopic and abdominal nerve-sparing radical hysterectomy in 35 patients. Laparoscopy was associated with less blood loss (30.5 [±11.0] vs. 190 [90.4] mL; p<0.001) and shorter hospital stay (3.2 [±1.2] vs. 5.4 [2.0] days; p=0.023). Patients undergoing laparoscopy experienced a lower 30-day pelvic floor dysfunction rate than patients after open surgery. Moreover, they experienced shorter recovery of bladder function than patients compared to open procedures (median, 7 vs. 9 days; p=0.004) [3].

Colleagues from Strasbourg showed a standardised method of retroperitoneal lumbo-aortic lymphadenectomy using a vessel-sealing device in 10 steps. The authors emphasised the advantage of the retroperitoneal access allowing direct access to vascular axes, thus avoiding bowel segments [4].

Endometrial cancer

There were a number of publications on the value of robotic surgery in obese patients with endometrial cancer. An Italian group analysed the surgical and oncological outcome of robotic surgical staging with hysterectomy (RH) and pelvic and aortic lymphadenectomy, compared laparoscopic surgery (LH) in obese patients (BMI≥30 kg/m^2) with endometrial cancer in a multi-institutional study including 655 women. The majority (62%) had undergone LH. Patients treated by robotics had statistically significant increased operating time and a decreased conversion rate. In addition, the rate of pelvic lymphadenectomies in robotic surgeries was doubled compared to LPS. A reduction in hospital stay was observed in the robotic group while oncological outcomes did not vary according to the surgical approach. [5]

Patients with endometrial cancer have excellent prognosis and this highlights the importance of quality of postoperative life. In the Robot Assisted Surgery for High Risk Endometrial Cancer (RASHEC) trial, patients with high-risk endometrial cancer were randomly assigned to robot-assisted laparoscopic surgery (RALS) or laparotomy for pelvic and infrarenal para-aortic lymph node dissection. Data on self-reported lower limb lymphedema (LLL), lymphocyst formation, ascites, and long-term serious adverse events 12 months after surgery were published. At 12 months after laparotomy and RALS, 61% and 50% patients, respectively, reported LLL (p = 0.31). No difference was found in serious adverse events and hospital admissions [6].

Ovarian cancer

While the gynae-oncologic community is eagerly awaiting results of AGO Trust Trial on the role of neoadjuvant chemotherapy vs. upfront debulking surgery, Fagotti et al. explored the value of minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy. In December 2016, 20 gyneacological cancer centres were contacted by e-mail to participate in the INTERNATIONAL MISSION study. Five centres participated, with a total of 127 patients undergoing NACT followed by MIS included. All patients had optimal cytoreduction at the time of interval surgery: among them, 122 (96.1%) patients had no residual tumor. Median operative time was 225 min (range 60–600) and median estimated blood loss was 100 mL (range 70–1320). Median time to discharge was two days (1–33) and estimated median time to start chemotherapy was 20 days (range 15–60). Six (4.7%) patients experienced intraoperative complications, with one patient experiencing two serious complications (bowel and bladder injury at the same time). The conversion rate to laparotomy was 3.9 %. Median progression-free survival was 23 months and survival at 5 years was 52 % (95% CI: 35 to 67). The authors concluded that MIS may be considered for the management of patients with advanced ovarian cancer who have undergone neoadjuvant chemotherapy, when surgery is limited to low-complexity standard cytoreductive procedures. [7].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Minimally invasive versus abdominal radical hysterectomy for cervical cancer.	Ramirez PT et al.	N Engl J Med	https://www.nejm.org/doi/full/10.1056/NEJMoa1806395
2	The survival after a radical hysterectomy for cervical cancer by open surgery is significantly better then after minimal invasive surgery: Evidence beats gut feeling!	Tjalma A	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/30115486
3	Minimally invasive surgery improves short-term outcomes of nerve-sparing radical hysterectomy in patients with cervical cancer: a propensity-matched analysis with open abdominal surgery.	Bogani G et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6393638/
4	Retroperitoneal lumboaortic lymphadenectomy using a vessel-sealing device in 10 steps.	Schaub M et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29079464
5	Laparoscopic versus robotic hysterectomy in obese and extremely obese patients with endometrial cancer: A multi-institutional analysis.	Corrado G et al.	Eur J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30245146
6	Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial.	Salehi S et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640688
7	The INTERNATIONAL MISSION study: minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy.	Fagotti A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640676

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Prevention and management of surgical complications

Martina Borghese

Bartl et al. conducted a single-centre retrospective chart review analysing anastomotic leakage (AL) rate and risk factors for AL in 350 patients with advanced epithelial ovarian cancer undergoing cytoreductive surgery: they found that overall AL rate was acceptably low (4.7%) and outweighed perioperative risks when performed in a high-volume institution. AL risk in patients undergoing isolated rectosigmoid resection was even smaller (1.9%), while multiple large bowel anastomoses seemed to be at elevated risk of AL (more than seven-fold compared with patients with sole rectosigmoid resection (OR, 7.23, 95% CI: 1.04–50.39). Since AL seemed to have prognostic implication on PFS and OS (due to a delayed start of adjuvant chemotherapy) and since no factor could be identified to clearly predict AL, extensive procedures comprising multiple bowel resections should be avoided when complete resection cannot be achieved [1].

ERAS represents best clinical practice and should be adopted across gynaecologic surgical specialties. A retrospective cohort study by Boitano et al. evaluated the impact of ERAS on postoperative gastrointestinal function in gynaecologic oncology patients undergoing laparotomy, finding that ERAS decreases ileus rates and length of stay with no increase in readmission rates. Epidural use was associated with higher rates of ileus [2]. Focusing on ERAS but in minimally invasive gynaecologic surgery (MIGS), Kalogera et al. reported in a review that, irrespective of operative approach, ERAS pathways decrease length of stay, improve patient satisfaction, and reduce hospital costs while maintaining low postoperative complication and readmission rates. Controversy still exists over the use of bowel preparation in MIGS [3]. A recent systematic review of the literature did not succeed in proving the superiority of one laparoscopic entry technique over another. Researchers noted an advantage of direct trocar entry over Veress needle entry for failed entry [4]. Gueli Alletti et al. prospectively performed 30 percutaneous stagings for low/intermediate risk endometrial cancer to investigate the safety, feasibility and oncological adequacy of the Percutaneous Surgical System, reporting that this emerging concept of mini-invasive surgery could improve surgical and cosmetic outcomes in hysterectomy patients, with good promises in terms of safety and oncological adequacy (i.e., reduction in port-site metastases) [5].

In the Robot Assisted Surgery for High Risk Endometrial Cancer (RASHEC) trial, Salehi et al. found no differences in self-reported lower limb lymphoedema or severe adverse events between laparotomy and robot-assisted surgery after one-year follow-up [6].

The application of fibrin sealant was associated with difference in the incidence of lymphocele (overall or symptomatic) in the study by Prodromidou et al., even if it seemed to reduce the duration and volume of drainage after lymphadenectomy [7]. A recent cohort study by Tortorella et al. reported high rates of postoperative morbidity and mortality in patients undergoing pelvic exenteration, in the absence of well-defined preoperative selection criteria to identify eligible patients. In 138 patients, the overall 30-day complication rate was 67%, including 27% severe complication rate, and postoperative 90-day mortality of 2.2%. The most common were urinary reconstruction complications, wound dehiscence, organ system failure, and infections [8]. The introduction of a PONV guideline for the management of PONV in female patients undergoing gyn surgery resulted in a significant reduction in PONV incidence [9].

A study by van Esch et al. reported that laryngeal mask airway can be suitable for use in general anaesthesia for gynaecological cancer operation, resulting as better than endotracheal intubation in keeping more stable hemodynamics and producing less anaesthetic complications from general anaesthesia [10].

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No	Title	Authors	Journal	Link to abstract
1	Predictive and prognostic implication of bowel resections during primary cytoreductive surgery in advanced epithelial ovarian cancer.	Bartl T et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30371563
2	Impact of enhanced recovery after surgery (ERAS) protocol on gastrointestinal function in gynecologic oncology patients undergoing laparotomy.	Boitano TKL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30244961
3	Enhanced recovery after minimally invasive gynecologic procedures with bowel surgery: A systematic review.	Kalogera E et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/30366117
4	Laparoscopic entry techniques.	Ahmad G et al.	Cochrane Database Syst Rev	https://www.ncbi.nlm.nih.gov/pubmed/30657163
5	Technological innovation and personalized surgical treatment for early-stage endometrial cancer patients: A prospective multicenter Italian experience to evaluate the novel percutaneous approach.	Gueli Alletti S et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/30731335
6	Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial.	Salehi S et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640688
7	The application of fibrin sealant for the prevention of lymphocele after lymphadenectomy in patients with gynecological malignancies: A systematic review and meta-analysis of randomized controlled trials.	Prodromidou A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30660344
8	Prediction of short-term surgical complications in women undergoing pelvic exenteration for gynecological malignancies.	Tortorella L et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30414740
9	Implementation of postoperative nausea and vomiting guidelines for female adult patients undergoing anesthesia during gynecologic and breast surgery in an ambulatory setting.	Tabrizi S et al.	J Perianesth Nurs	https://www.ncbi.nlm.nih.gov/pubmed/30718165
10	Comparison of laryngeal mask airway vs tracheal intubation: a systematic review on airway complications.	van Esch BF et al.	J Clin Anesth	https://www.ncbi.nlm.nih.gov/pubmed/28183554

Cancer in pregnancy

Michael J. Halaska

Bae et al. evaluated neoadjuvant chemotherapy in breast cancer within the Korean breast cancer registry. They compared 411 pregnancy-associated breast cancer (PABC) patients with 83,381 patients and found an increasing trend in the application of NAC in PABC throughout recent years and no difference in overall survival rates [1].

Epidemiological data were presented by Cottreau et al. from an U.S. population. In all, 846 pregnancy-associated cancers were identified, with an estimated incidence of 109 per 100,000 pregnancies, and an increasing trend within recent years. The most common cancers were breast cancer (24%), thyroid cancer (19.9%), hematologic malignancies (10%), and cervical cancer (8.7%) [2].

Hartnett et al. evaluated timing between conception and previous cancer. They found an elevated risk of preterm birth in women who conceived within one year after the administration of chemotherapy (RR 1.9, 95% CI: 1.3–2.7), after chemotherapy with radiotherapy (RR 2.4, 95% CI: 1.6–3.6) compared to conception after one year [3]. No difference was found between an interval of one or two years. This information is especially important, since most of the recommendations propose an interval of two years, which is often unacceptable for the patients.

Song et al. performed a review of cervical cancer patients who received a platinum derivate during pregnancy. In a set of 88 patients, one child was diagnosed with rhabdomyosarcoma and one child had acute myeloid leukaemia [4]. Currently, potential ototoxicity is being evaluated by the INCIP group.

Rodolakis et al. published two cases of abdominal radical trachelectomy performed at the 14th week of pregnancy in stage IB1 patients. Blood loss of 1800 and 2000 mL occurred during surgery. One patient delivered at the 36th week of pregnancy and the second at the 32nd week of pregnancy due to unexpected bleeding [5]. Radical trachelectomy performed during pregnancy is usually accompanied by severe complications and should only be performed with highest caution.

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Neoadjuvant chemotherapy and prognosis of pregnancy-associated breast cancer: A time-trends study of the Korean breast cancer registry database.	Bae SY et al.	J Breast Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30607164
2	Pregnancy-associated cancer: A U.S. population-based study.	Cottreau CM et al.	J Womens Health	https://www.ncbi.nlm.nih.gov/pubmed/30307780
3	Pregnancy after cancer: Does timing of conception affect infant health?	Hartnett KP et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30403424
4	Efficacy of neoadjuvant platinum-based chemotherapy during the second and third trimester of pregnancy in women with cervical cancer: an updated systematic review and meta-analysis.	Song Y et al.	Drug Des Devel Ther	https://www.ncbi.nlm.nih.gov/pubmed/30587930
5	Abdominal radical trachelectomy for early-stage cervical cancer during pregnancy: A provocative surgical approach. Overview of the literature and a single-institute experience.	Rodolakis A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30376483

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Immunotherapy in gynaecological cancers

Zoltan Novak

Clinical trials and case reports

A pilot study investigated adoptive cell therapy with tumour-infiltrating lymphocytes in six metastatic platinum-resistant ovarian cancer patients. In the six patients, OR rate was 80%; progression was due to new lesions while target lesions remained stable or in regression. However, the efficacy of the treatment was suboptimal, and the authors raised the role of the involvement of the inhibitory immune checkpoint pathways [1]. Another paper reported the results of a retrospective study with 646 EOC patients, 72 of whom received chemotherapy and sequential immunotherapy, and the control group of 574 patients receiving only chemotherapy. The immunotherapy consisted of at least four cycles of cytokine-induced killer cell transfusion. No serious side effects were observed. The overall survival was longer in the immunotherapy group; univariate and multivariate analyses indicated that adjuvant cytokine-induced killer cell therapy was an independent prognostic factor for the overall survival of the studied patients. This retrospective study showed that this kind of immunotherapy might produce clinical benefit for advanced stage ovarian cancer patients following surgery [2]. The results of a phase I study were published where the researchers used α-particle emitting astatine-211 conjugated to MX35, the antigen binding fragments of a mouse monoclonal antibody. This α-particle immunotherapy was administered intraperitoneally in 12 relapsed ovarian cancer patients following successful chemotherapy. Most toxicities were low-grade and likely related to the treatment procedure. Four patients had a survival > six years, one of whom did not relapse. Overall median survival was 35 months with a five-year survival of 50%. The authors proposed that further optimisation is advisable to increase the efficacy of this treatment [3].

Immune checkpoint inhibitors

Researchers reported the result of a phase Ib study, Keynote-028, which evaluated the safety, tolerability, and antitumour activity of pembrolizumab monotherapy in recurrent programmed death ligand 1 (PD-L1)-expressing advanced ovarian cancer patients. After a median follow-up duration of 15.4 months; overall response rate was 11.5% (one complete response, two partial responses); seven patients (26.9%) achieved stable disease. A phase II evaluation is ongoing [4]. An important retrospective study addressed the problem of early discontinuation with immune checkpoint blockade (ICB) therapy, because delayed responses present a challenge for patients with ovarian cancer and patients who risk early symptomatic disease progression requiring treatment discontinuation. Cut-offs for early and very early discontinuation due to disease progression were defined at 12 and eight weeks, respectively. Forty-six (51.7%) patients discontinued therapy early, 30 of whom (33.7%) discontinued therapy very early and eight patients (9.0%) died within 12 weeks of ICB initiation from disease progression. The authors defined the clinical variables associated with early discontinuation: bulky peritoneal disease (OR: 4.94), parenchymal metastases (OR: 8.08), and high neutrophil-to-lymphocyte ratio (OR: 3,54). The authors proposed caution when giving ICB to these patients [5].

Varia

Authors from M.D. Anderson Cancer Center reported their experience and proposed how to safely implement targeted- and immunotherapy programs in gynae-oncologic academic centres [6]. Two reviews were cited in the present summary: one paper reviewed the topic of immunotherapies in gynaecological oncology [7], the other summarised the current knowledge on the role of PD-1/PD-L1 inhibitors in cervical cancer [8].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Adoptive cell therapy with tumor-infiltrating lymphocytes in patients with metastatic ovarian cancer: a pilot study.	Pedersen M et al.	Oncoimmunology	https://www.ncbi.nlm.nih.gov/pubmed/30524900
2	Retrospective analysis of the efficacy of adjuvant CIK cell therapy in epithelial ovarian cancerpatients who received postoperative chemotherapy.	Zhou Y et al.	Oncoimmunology	https://www.ncbi.nlm.nih.gov/pubmed/30713783
3	Intraperitoneal alpha-emitting radio immunotherapy with Astatine-211 in relapsed ovarian cancer; long-term follow-up with individual absorbed dose estimations.	Hallquist A et al.	J Nucl Med	https://www.ncbi.nlm.nih.gov/pubmed/30683761
4	Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028.	Varga A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30522700
5	Early disease progression and treatment discontinuation in patients with advanced ovarian cancer receiving immune checkpoint blockade.	Roland JL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30470581
6	A practical guide for the safe implementation of early phase drug development and immunotherapy program in gynecologic oncology practice.	Jazaeri A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30213435
7	Immunotherapy in ovarian cancer: fake news or the real deal?	Marth C et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640705
8	PD-1/PD-L1 Inhibitors in cervical cancer.	Lyu Y et al.	Front Pharmacol	https://www.ncbi.nlm.nih.gov/pubmed/30774597

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Imaging in gynaecological malignancies

Tanja Nikolova and Natasha Nikolova

Endometrial cancer

Eriksson et al. analysed women with endometrioid endometrial cancer (EEC) and assessed the presence or absence of the microcystic elongated and fragmented (MELF) pattern on ultrasound. The presence or absence of MELF did not affect the accuracy of preoperative ultrasonography in the assessment of myometrial invasion (MI). MELF pattern was associated with MI ≥ 50% ($p < 0.001$), cervical stromal invasion ($p = 0.037$), more advanced stage (≥ IB) ($p < 0.001$), and lymphonode metastases (LNM) ($p = 0.011$). Tumours with MELF pattern were more than twice as likely to have more advanced stage (≥ IB) and LNM [1].

Cervical cancer

Zheng et al. analysed women with stage IIA2–IVB cervical cancer (CC) and compared contrast-enhanced ultrasound (CEUS) to MRI for evaluating local invasion of CC. Results showed that MRI and CEUS were strongly correlated in the three dimensions: left-right $r = 0.84$, craniocaudal $r = 0.86$, and anteroposterior $r = 0.88$. Vaginal and parametrial invasion were detected by both MRI and CEUS with moderate concordance, and invasion of uterine corpus, bladder, and rectum with good concordance [2].

Ovarian cancer

Prader et al. evaluated the pattern of cardiophrenic lymph node (CPLN) metastases in epithelial ovarian cancer (EOC) patients, their predictive value, and the potential role of CPLN resection on overall survival (OS). In patients with postoperative residual tumour, enlarged CPLN had no impact on survival. In patients with complete resection and radiologically negative CPLN, a five-year OS was 69%, and in patients with radiologically positive CPLN, five-year OS was 30%. In cases with CPLN resection, the matched-pair case-control analysis did not demonstrate any significant impact on survival. The role of CPLN resection for survival therefore remains uncertain. [3].

Breast cancer

In a group of 177,164 women and 499,251 digital mammograms, Posso et al. assessed the effect of breast density over the screen-detected and interval cancers rates. Breast density was classified according to the BIRADS system. The performance of digital mammography was negatively affected by breast density falling to a lower sensitivity and positive predictive value, and higher interval cancer rate as breast density increases. Women aged 60–69 with > 75% glandular breasts had the worst results and therefore may be candidates for screening using other technologies [4].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Clinical and ultrasound characteristics of the Microcystic Elongated and Fragmented (MELF) pattern in endometrial cancer according to the International Endometrial Tumor Analysis (IETA) criteria.	Eriksson LSE et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30640693
2	Contrast-enhanced ultrasonography vs MRI for evaluation of local invasion by cervical cancer.	Zheng W et al.	Br J Radiol.	https://www.ncbi.nlm.nih.gov/pubmed/30028181
3	Pattern and impact of metastatic cardiophrenic lymph nodes in advanced epithelial ovarian cancer.	Prader S et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30463683
4	Mammographic breast density: How it affects performance indicators in screening programmes?	Posso M et al.	Eur J Radiol.	https://www.ncbi.nlm.nih.gov/pubmed/30599878

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Treatment of elderly patients with gynaecological cancers

Alex Mutombo

Gynaecological cancer management in older people is a current challenge. One study discussed the importance of overcoming undertreatment of elderly patients because they are more fragile and have a lower life expectancy than their younger counterparts [1].

Van Walree et al. investigated treatment choices and outcomes, comparing elderly (≥ 75 years) and younger patients (< 75 years) in a single-centre retrospective analysis of patients diagnosed with ovarian cancer between 2010 and 2015. Elderly patients were less frequently treated in accordance with treatment guidelines. Median survival was lower in the elderly and in patients receiving best supportive care [2].

Taylor et al. conducted a study to determine correlation between race and receipt of optimal treatment for ovarian cancer and the impact of this on overall survival. According to their results, non-white women are less likely to receive the standard of care treatment for ovarian cancer and are more likely to die from their disease than white women [3].

In a cohort of patients ≥ 66 years old diagnosed between 2000 and 2013 with stage III–IV epithelial OC who were treated with surgery and platinum/taxane chemotherapy for primary treatment, survival outcomes were similar for patients with stage IV disease after NACT compared to primary debulking surgery (PDS). For patients with stage III disease, PDS performed better. [4].

Elderly patients with cervical cancer are less likely to undergo surgical management and had a decreased overall survival, even when controlling for use of surgery and stage of disease [5]. In the SEER database, increasing age predicts poor cervical cancer prognosis with a subsequent effect on treatment and overall survival [6]. The study of 46350 women also showed a significant benefit of the use of brachytherapy in elderly, even if administered alone. Careful patient selection is paramount to balance treatment-related toxicity risks with theoretical outcome benefits in this category of patients [7, 8].

An NRG oncology group/gynecologic oncology group study aimed to evaluate whether a pre-operative GA-GYN score derived from a predictive model that used components of an abbreviated geriatric assessment. Results showed this score was not predictive of major post-operative complications in elderly patients undergoing primary open cytoreductive surgery [9].

A study conducted by Koual M. at Hôpital européen Georges-Pompidou (Paris, France) from January 2002 to December 2015 found that the management of elderly (≥ 75 years old) women with endometrial cancer was not optimal. They encouraged the development of specific treatment guidelines to improve prognosis [10].

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No	Title	Authors	Journal	Link to abstract
1	Management of endometrial, ovarian and cervical cancer in the elderly: current approach to a challenging condition.	Vitale SG et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/30542793
2	Treatment decision-making in elderly women with ovarian cancer: an age-based comparison.	van Walree IC et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640699
3	Disparities in treatment and survival among elderly ovarian cancer patients.	Taylor JS et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30253875
4	Neoadjuvant chemotherapy in elderly women with ovarian cancer: Rates of use and effectiveness.	Meyer LA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29961559
5	Assessment of treatment factors and clinical outcomes in cervical cancer in older women compared to women under 65 years old.	Diver EJ et al.	J Geriatr Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29503115
6	Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment and overall survival.	Quinn BA et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/30361045
7	Postoperative chemoradiotherapy versus radiotherapy alone for elderly cervical cancer patients with positive margins, lymph nodes, or parametrial invasion.	Cushman TR	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30207105
8	Can Vulnerable Elders Survey-13 predict the impact of frailty on chemotherapy in elderly patients with gynaecological malignancies?	Ferrero A et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/30278504
9	Pre-operative assessment and post-operative outcomes of elderly women with gynecologic cancers, primary analysis of NRG CC-002: An NRG oncology group/gynecologic oncology group study.	Ahmed A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29807694
10	Endometrial cancer in the elderly: does age influence surgical treatments, outcomes, and prognosis?	Koual M et al.	Menopause	https://www.ncbi.nlm.nih.gov/pubmed/29762198

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Epidemiology of gynaecological cancers

Kemal Güngördük

Endometrial cancer (EC)

A large population-based study of 2,882,847 participants demonstrated that infertility was associated with a higher incidence rate of ovarian (adjusted hazard ratio [aHR] = 1.53, 95% CI: 1.38–1.71) and endometrial cancer (aHR = 1.25, 95% CI: 1.11–1.40). Ovulatory disturbances were associated with higher ovarian cancer risk among nulliparous women, and with higher endometrial cancer risk overall. Endometriosis was associated with a higher risk of ovarian cancer but not of endometrial cancer [1]. A recent meta-analysis by Webb et al. showed that use of standard-dose aspirin or other NSAIDs might reduce (approximately 15%) the risk of endometrial cancer among overweight and obese women, (OR = 0.86 [95% CI: 0.76–0.98] and (OR = 0.86, 95% CI: 0.76–0.97), respectively, for aspirin; (OR = 0.87, 95% CI: 0.76–1.00) and (OR = 0.84, 95% CI: 0.74–0.96), respectively [2]. Lu et al. reported that higher dietary intake of several key nutrients involved in folate-mediated one-carbon metabolism—in particular, total folate, natural folate, B2 (HR = 1.27, 95% CI: 1.07–1.50), methionine (HR = 1.26, CI: 1.07–1.48), B6, and B12 (HR = 1.38, CI: 1.17–1.63) were associated with EC risk among women who were overweight/obese [3].

A UK Women's Cohort Study showed that a high consumption of processed meat and total meat (HR = 2.19, 99% CI: 1.34–3.60; HR = 1.53, 99% CI: 1.04–2.24) was associated with an increased risk of endometrial cancer. High intakes of tomatoes (HR = 0.87, 99% CI: 0.75–1.00) and dried fruits (HR = 0.60, 99% CI: 0.37–0.97) were associated with a reduced risk of endometrial cancer. Mushroom intake was associated with a higher risk of ovarian cancer (HR = 1.57, 99% CI: 1.09–2.26) [4]. In contrast, long-term OC use (≥10 years) reduced endometrial cancer risk by 34% (95% CI: 0.56–0.78); the most pronounced reductions were among long-term OC users who were smokers (HR = 0.47, 95% CI: 0.25–0.88), were obese (0.36, 95% CI: 0.25–0.52), and who exercised rarely (HR = 0.40, 95% CI: 0.29–0.56) [5]. In addition, coffee, caffeinated coffee, and caffeine were inversely associated with risk of endometrial cancer (HR = 0.88, 95% CI: 0.79–0.95; HR = 0.88, 95% CI: 0.80–0.96; and HR = 0.93, 95% CI: 0.87–0.99; respectively) [6]. According to the recent meta-analysis, any use of bisphosphonates was associated with a significant 27% reduction in the risk of endometrial cancer (RR = 0.73, 95% CI: 0.58–0.93), but the reduction in the risk of ovarian cancer (RR - 0.81, 95% CI: 0.58–1.14) was not significant. The protective effects of the use of bisphosphonates against endometrial cancer are mainly found in postmenopausal women (RR = 0.53, 95% CI: 0.34–0.93) or in those who have taken bisphosphonates for longer than one year (RR = 0.57, 95% CI: 0.35–0.93) [7].

Ovarian cancer (OC)

Aspirin use was associated with lower ovarian cancer risk (OR = 0.78, 95% CI: 0.55–1.09) [8]. This protection may act through a prostaglandin-independent biologic pathway such as changing the density of M2-type macrophages, which have an immunosuppressive effect on the tumour. Interestingly, Barnard et al. showed an inverse association for low-dose aspirin (100 mg) (HR = 0.77, 95% CI: 0.61–0.96), but no association for standard-dose aspirin (HR = 1.17, 95% CI: 0.92–1.49) [9]. Furthermore, they demonstrated that nonaspirin NSAIDs and use of acetaminophen were not inversely associated with ovarian cancer risk, and heavy use of these medications may be associated with an increased risk for OC. Adiposity changes during peripubertal period are more strongly associated with ovarian cancer risk than adulthood changes. Body mass index (BMI) change between age 10 and 18 was strongly positively associated with ovarian cancer risk (HR per 5 kg/m^2: 1.24, 95% CI: 1.11–1.39), whereas BMI change after age 18 was only slightly associated with risk (HR per 5 kg/m^2 increase: 1.06; 95% CI: 0.99–1.14). These associations were in general stronger for premenopausal cases or non-serous tumours [10].

Methylation at multiple CpG were significantly associated with OC risk through regulation of MAPT, HOXB3, ABHD8, ARHGAP27, and SKAP1 genes expression [11].

Cervical cancer

A meta-analysis showed that vaginal dysbiosis was associated with an increased risk of incident human papilloma virus (RR = 1.33, 1.18–1.50; among young women RR = 1.43, 1.10–1.85), human papilloma virus persistence (RR =1.14, 1.01–1.28), and high-grade lesions and cancer (RR = 2.01, 1.40–3.01) [12]. De Strooper et al demonstrated that a negative FAM19A4/mir124-2 methylation test provides a low cervical cancer risk in HPV-positive women of age 30 and older. The study is a 14 years follow-up of the POBASCAM screening trial and the methylation test is suggested as a adjunct to HPV-based cervical screening programs [13].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	The risk of breast and gynecological cancer in women with a diagnosis of infertility: a nationwide population-based study,	Lundberg FE et al.	Eur J Epidemiol..	https://www.ncbi.nlm.nih.gov/pubmed/30623293
2	Use of aspirin, other nonsteroidal anti-inflammatory drugs and acetaminophen and risk of endometrial cancer: The Epidemiology of Endometrial Cancer Consortium.	Webb PM et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30566587
3	Dietary intake of nutrients involved in folate-mediated one-carbon metabolism and risk for endometrial cancer.	Lu J et al.	Int J Epidemiol.	https://www.ncbi.nlm.nih.gov/pubmed/30544261
4	Diet and risk of breast, endometrial and ovarian cancer: UK Women's Cohort Study.	Dunneram Y et al.	Br J Nutr..	https://www.ncbi.nlm.nih.gov/pubmed/30526696
5	Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers.	Michels KA et al.	JAMA Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29346467
6	Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women.	Arthur R et al.	Cancer Epidemiol..	https://www.ncbi.nlm.nih.gov/pubmed/30075330

Epidemiology of gynaecological cancers

Kemal Güngördük

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
7	Risk reduction of endometrial and ovarian cancer after bisphosphonates use: A meta-analysis.	Zhang XS et al.	Gynecol Oncol..	https://www.ncbi.nlm.nih.gov/pubmed/29960711
8	Antiinflammatory drug use and ovarian cancer risk by COX1/COX2 expression and infiltration of tumor-associated macrophages.	Barnard ME et al.	Cancer Epidemiol Biomarkers Prev.	https://www.ncbi.nlm.nih.gov/pubmed/30377203
9	Association of analgesic use with risk of ovarian cancer in the nurses' health studies.	Barnard ME et al.	JAMA Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30286239
10	Associations of early life and adulthood adiposity with risk of epithelial ovarian cancer.	Huang T et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30576422
11	Genetic data from nearly 63,000 women of European descent predicts DNA methylation biomarkers and epithelial ovarian cancer risk.	Yang Y et at.	Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/30559148
12	Vaginal dysbiosis and the risk of human papillomavirus and cervical cancer: systematic review and meta-analysis.	Brusselaers N et al.	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/30550767
13	Cervical cancer risk in HPV-positive women after a negative FAM19A4/mir124-2 methylation test: A post hoc analysis in the POBASCAM trial with 14 year follow-up.	De Strooper LMA et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29663363

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Gestational trophoblastic disease management

Joanna Kacperczyk-Bartnik

Management

A systematic review and meta-analysis by Zhao et al. evaluated the effectiveness of total hysterectomy versus uterine evacuation in treatment of patients with hydatidiform mole (HM) beyond the age of 40. The meta-analysis included six cohort studies with total of 291 patients. The authors concluded that total hysterectomy is recommended for this age-specific group of women on the condition that fertility is no longer desired [1].

In a retrospective cohort study, Frijstein et al. analysed management outcomes and prognostic factors of 45 patients with epithelioid trophoblastic tumours (ETTs) and nine patients with mixed placental site trophoblastic tumours (PSTTs)/ETTs selected from the international PSTT and ETT database. The authors recommended surgical treatment of early-stage disease and surgery with multichemotherapy in metastatic disease. Advanced-stage disease and an interval exceeding 48 months since antecedent pregnancy was associated with poor prognosis. More data is awaited from this high qualiy database [2].

A retrospective analysis by Essel et al. aimed to determine the utility of surgery in 69 patients with gestational trophoblastic neoplasia (GTN) treated invasively at a single institution between 1985 and 2015. The authors concluded that complete surgical resection is essential to the optimal outcome of patients with any histology of GTN who undergo surgery as a part of their treatment [3].

In a retrospective study by Kanno et al., treatment outcomes of second-line chemotherapy for patients with low-risk GTN were examined. In all, 114 patients were primarily treated with five-day MTX and 64 patients were treated with five-day ETP. Regimens were repeated every 10–14 days until normalisation of serum hCG levels. Of these, 47 (26.4%) patients required second-line treatment due to severe adverse events (n = 16) and the development of drug resistance (n = 31). The second-line regimens of single-agent chemotherapy were effective. Several patients (n = 8) needed multiple agents and combined chemotherapy to achieve remission [4].

Mangili et al. performed a multicentre retrospective analysis of 176 patients with low-risk GTN treated with methotrexate in two different regimens: MTX 50 mg/day on days 1, 3, 5, 7 with FA 7.5 mg on days 2, 4, 6, 8 (n = 99), repeated every 14 days and MTX 1 mg/kg/day on days 1, 3, 5, 7 with FA 7.5 mg on days 2, 4, 6, 8 (n = 77) repeated every 14 days [5]. Both MTX schedules showed comparable efficacy and acceptable toxicity in the treatment of low-risk GTN.

Follow-up

Earp et al. performed a retrospective evaluation of 9,315 patients with previous HM who underwent hCG screening after one or more subsequent pregnancies. Of these, 8630 patients had an initial hydatidiform mole that did not require chemotherapy. A total of 13,341 pregnancies were screened, resulting in detection of six recurrent GTNs. The recurrence rate for patients with previous HM that did not require chemotherapy was three in 12,329 (risk 1:4410). For patients previously treated for GTN with chemotherapy, the recurrence rate was three in 1,012 (risk 1:337). The authors recommended that patients with the history of GTN treated with chemotherapy should be screened by hCG estimations following any subsequent pregnancy. Screening with uncomplicated HM do not require routine routine post-pregnancy HCG screening [6].

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No	Title	Authors	Journal	Link to abstract
1	Total hysterectomy versus uterine evacuation for preventing post-molar gestational trophoblastic neoplasia in patients who are at least 40 years old: a systematic review and meta-analysis.	Zhao P et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30612545
2	Management and prognostic factors of epithelioid trophoblastic tumors: Results from the International Society for the Study of Trophoblastic Diseases database.	Frijstein MM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30473257
3	Complete Resection Is essential in the surgical treatment of gestational trophoblastic neoplasia.	Essel KG et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30157165
4	Treatment results of the second-line chemotherapy regimen for patients with low-risk gestational neoplasia treated with 5-day methotrexate and 5-day etoposide.	Kanno T et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30207097
5	Does methotrexate (MTX) dosing in a 8-day MTX/FA regimen for the treatment of low-risk gestational trophoblastic neoplasia affect outcomes? The MITO-9 study.	Mangili G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30266260
6	Do we need post-pregnancy screening with human chorionic gonadotrophin after previous hydatidiform mole to identify patients with recurrent gestational trophoblastic disease?	Earp KE et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/30684876

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Follow-up after gynaecological malignancies

Jenneke Kasius

Ferraro et al. evaluated the clinical value of human epididymis protein 4 (HE4) to carbohydrate antigen 125 (Ca 125) in women undergoing surveillance after treatment for ovarian cancer. From March 2014 until February 2017, 43 patients were prospectively followed. Most patients were diagnosed with serous type histology (53.5%) and in 'late stages' (81.4%). In 39.5% of the patients, treatment consisted of chemotherapy without surgery. The cut-off value was set at 35kU/L for Ca 125 and 70/100 pmol/L for HE4. The cut-offs as well as the reference change values were used for assessment. CT, PET, and MRI were used to evaluate clinical remission or relapse. Twenty-one patients died within enrolment of follow-up. Ca 125 above a cut-off of 35 kU/L fully fit the relapse reference criteria while HE4 showed a 4.3% rate of disagreement. Both values were simultaneously over cut-offs only in 46% of samples. In their cohort, Ca 125 appeared the most reliable biomarker and HE4 provided additional information only in a minority of patients [1].

Wu et al. assessed follow-up care instructions after completion of treatment for breast or gynaecologic cancer. In the US, 954 women with breast cancer and 492 women with gynaecologic cancers were included. Patients were asked on the phone if they ever received instructions about where to return for routine cancer check-ups after treatment. 1,029 (71.2%) patients had received follow-up care instructions and 417 (28.8%) had not. Factors associated with receipt of follow-up care instructions in the overall group were as follows: breast cancer (compared to gynaecologic cancer), age > 50 years, income > $50,000, higher education, and higher BMI [2].

Alabed et al. did a retrospective evaluation of the positive predictive value (PPV), costs, and radiation exposure of standard imaging in the follow-up of patients with endometrial cancer. Patients with endometrioid stage III disease or serous or clear cell histology who had surveillance with imaging were included. The median follow-up time was 54 months (9–173), with on average 5.6 scans (2–21) per patient. A scan was found to be true-positive in case of confirmation by histology or follow-up imaging that led to initiation of treatment. The overall PPV was 57.7%. The PPV for CT, PET, and MRI were 54.3%, 86.7%, and 33.3%, respectively. The average cost of 5.6 months of surveillance was $4,205 per patient. The detection of one recurrence was estimated to be $11,452. The average amount of radiation exposure was 109.6mSV [3].

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No	Title	Authors	Journal	Link to abstract
1	Serum human epididymis protein 4 vs. carbohydrate antigen 125 in ovarian cancer follow-up.	Ferraro S et al.	Clin Biochem	https://www.ncbi.nlm.nih.gov/pubmed/30125544
2	Disparities in receipt of follow-up care instructions among female adult cancer survivors: Results from a national survey.	Wu J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29970241
3	Surveillance Imaging in patients with endometrial cancer in first remission.	Alabed YZ et al.	Curr Probl Diagn Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28917433

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Sexual function in gynaecologic cancer patients and survivors

Stamatios Petousis

Endometrial cancer

Buckingham et al. performed a cross-sectional study including 129 endometrial carcinomas. 62.5% of the patients were sexually active after surgical treatment. Sexual function was not significantly impaired for endometrial cancer patients regardless of time from initial treatment. None of the demographic and clinical characteristics had a significant impact on the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) [1].

Papathemelis et al. compared the impact of two different dosing schemes of vaginal brachytherapy on quality of sexual life. No statistically significant difference between dosing schedules of three and four times 5 Gy. However, younger patients (age < 70) rather seem to experience greater reduction in sexual quality of life [2].

Ovarian cancer

Hall et al. performed a prospective observational study on the effect of bilateral salpingo-oophorectomy on sexual function among women with BRCA mutations. They enrolled 140 patients with an average follow-up of 3.5 years. Oophorectomy was associated with a significant decrease in sexual pleasure and increase of discomfort. Administration of hormonal replacement therapy was associated with a slight mitigation of the sexual function impairment [3].

Mayer et al. also performed a retrospective study to assess sexual activity and functioning in patients treated for both breast and ovarian cancer. They assessed patients' sexual function according to the Sexual Activity Questionnaire, Female Sexual Function Index-d, and the EORTC Quality of Life Questionnaire-C30. 56.5% of the patients were sexually active. Ovarian cancer survivors did not present significant impairment of sexual function. Sexually active ovarian cancer patients showed no significant differences in sexual function, QoL and health status compared to controls. The life-threatening disease may chnage the patients perspctive and priorities in life. [4].

Cervical cancer

Conway et al. reported on the patient-reported sexual adjustment after definitive chemoradiation and MR-guided brachytherapy for cervical cancer. A negative impact on quality of sexual intercourse in patients, which was significantly associated with advanced stage of the disease (≥IIB) was observed. However, there was no significant longitudinal changes in patient-reported sexual adjustment [5].

Varia

Donkers et al. performed a prospective cohort study to investigate the association between BMI and sexual function in gynaecological cancer patients. A higher BMI was associated with improved sexual functioning in all kinds of cancer except for cervical cancer patients [6].

Finally, Hay et al. studied gynaecological cancer patients' expectations on quality of sexual life after surgery. 45% of patients reported sexuality as somewhat or very important; importance given to this aspect was significantly associated with age, relationship status, and sexual activity but not type of cancer [7].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Sexual function following hysterectomy for endometrial cancer: A five-year follow up investigation.	Buckingham L et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30420200
2	Quality of life and oncological outcome in endometrial cancer patients after vaginal brachytherapy: comparison of two dosing schemes.	Papathemelis T et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/30357499
3	Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a BRCA1 or BRCA2 mutation.	Hall E et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30414741
4	Sexual activity and quality of life in patients after treatment for breast and ovarian cancer.	Mayer S et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/30386993
5	Patient-reported sexual adjustment after definitive chemoradiation and MR-guided brachytherapy for cervical cancer.	Conway JL et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/30509730
6	Body mass index and sexual function in women with gynaecological cancer.	Donkers H et al.	Psychooncology	https://www.ncbi.nlm.nih.gov/pubmed/30286263
7	Sexual health as part of gynecologic cancer care: What do patients want?	Hay CM et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30358703

Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

In a retrospective study by Chae et al., the authors assessed the effect of fertility-sparing treatment in patients with presumed stage IA, G1-2 endometrial cancer. Treatment involved concurrent medroxyprogesterone and levonorgestrel-release intra-uterine device. The study included 71 patients, of which 49 tried to conceive. A total number of 30 pregnancies was recorded, which resulted in 7 abortions (23.3%), 1 pre-term birth (3.3%) and 20 full-term births (66.6%), with a total live-birth rate of 66.6%. The authors stated that a lower grade might be a positive factor for future pregnancy, while successful pregnancy seemed to prolong time to relapse [1].

Cervical cancer

A retrospective study by Sonoda et al., analysed the efficacy of sentinel lymph node (SLN) biopsy in radical trachelectomy for early-stage cervical cancer. In a total of 610 SLNs, the specificity of both imprint cytology and frozen section was 100%, however, the sensitivity was only 58.6% and 65.5%, respectively. The diagnostic sensitivity proved to be higher in 2 mm slices along the short axis than on bisection along the longitudinal axis. The authors concluded that the accuracy of intraoperative SLN diagnosis requires improvement, especially in the presence of small metastatic foci [2].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Pregnancy and oncologic outcomes after fertility-sparing management for early stage endometrioid endometrial cancer.	Chae SH et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30640687
2	Value of intraoperative cytological and pathological sentinel lymph node diagnosis in fertility-sparing trachelectomy for early-stage cervical cancer.	Sonoda K et al.	Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29136624

Palliative care and quality of life in gynaecological cancers

Engin Celik and Nadja Taumberger

Miller and Nevadunsky reviewed palliative care issues in ovarian cancer patients. Early initiation of palliative care demonstrated an increase of quality of life. Palliative radiotherapy is effective in treating used in vaginal bleeding, bone and brain metastasis. They summarize current treatment strategies for pain, constipation, ascites or pleural effusions, as well as bowel obstruction. Physician-assisted suicide was legal in six states in the United States [1].

Schneiter et al. conducted a retrospective chart review of 204 patients with terminally ill gyneacologic oncology patients in Vanderbilt University Medical Center in Nashville between 2006 to 2016. Patients with palliative care consultations had higher hospice enrolment (OR = 2.55, p = 0,016). Outpatient palliative care consultation was engaged for a longer time before death than inpatient consultation care (106 days vs. 33 days). Twenty-five percent of patients in outpatient palliative care consultation had aggressive medical care at the end of life compared to 44% of the inpatients [2].

The multicentre, prospective cohort study published by Faller et al. investigated patients' supportive care needs at the beginning and the end of a three-week inpatient rehabilitation programme in Germany and whether this improved the Quality of Life (QoL) of the 292 enrolled patients with breast and gynaecological cancer. The EORTC QLQ-C30 functioning subscales for measuring the QoL and a four-point Likert scale to evaluate 12 chosen domains of needs were used. Although all needs declined significantly and the QoL increased at the end of the rehabilitation programm, the patients still had strong needs in some domains [3].

Zandbergen et al. enrolled 395 patients who had survived ovarian or endometrial cancer between 2011 and 2014 in a prospective population-based cohort study to investigate the health-related Quality of life (HRQoL) during the two years after treatment. The HRQoL was measured with the EORTC QLQ-C30 functioning scales immediately and six, 12, and 24 months after treatment. The results differed by subgroups according to the treatment received as well as patients' comorbidities and tumor stage. They suggested individualized and follow-up care for patients after chemotherapy if decrease in HRQoL persisted after six months [4].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	Palliative Care and symptom management for women with advanced ovarian cancer.	Miller D and Nevadunksy N	Hematol Oncol Clin North Am	https://www.ncbi.nlm.nih.gov/pubmed/30390762
2	The earlier the better: The role of palliative care consultation on aggressive end of life care, hospice utilization, and advance care planning documentation among gynecologic oncology patients.	Schneiter MK et al.	Support Care Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30209601
3	Supportive care needs and quality of life in patients with breast and gynecological cancer attending inpatient rehabilitation. A prospective study.	Faller H et al.	Acta Oncologica	https://www.tandfonline.com/doi/full/10.1080/0284186X.2018.1543947
4	Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis.	Zandbergen N et al.	Acta Oncologica	https://www.tandfonline.com/doi/abs/10.1080/0284186X.2018.1560498?journalCode=ionc20

ENYGO ESGO European Network of Young Gynae Oncologists | LiFE report Literature for ENYGO

Nutritional support/status in gynaecological cancer

Begoña Díaz de la Noval

Peri-operative care

Agarwal et al. published a prospective trial that successfully supports the enhanced recovery after surgery (ERAS) programme implementation in patients undergoing surgery for advanced ovarian cancer (patients undergoing bowel resections were excluded). The adoption of the ERAS protocol decreased pain score, post-operative complications, and hospital stay, without increasing the readmission rate [1].

Nutritional supplements and Integrative medicine

Drozdoff et al. surveyed 717 breast- and gynaecological cancer patients undergoing systemic therapy. Three-quarters of respondents reported using biologically based complementary medication (BB-CAM); it was more popular among patients younger than 60. Many of these patients use BB-CAM without any professional advice. The study calls for further research on the safety and efficiency of CAM [2].

Integrative medicine can reduce the adverse effects of conventional cancer therapy. Hack et al. developed a standardised protocol for vitamin and micronutrient infusion and performed a retrospective cross-sectional survey in breast- and gynaecological cancer patients. The aim was the report of side effects and patients' satisfaction. Due to the small number of cases (n = 45) and the short follow-up period, no conclusions can be drawn, but most patients reported an improvement. Further research is needed in order to better investigate the application of multinutrient infusions and their benefits, effects, and safety [3].

Elderly and cancer survivors

Patient frailty must be determined in order to optimise therapeutic decisions in geriatric oncology and also to estimate life expectancy. There is a need for geriatric assessment and prediction tools to estimate the risk of mortality in this group of patients. The study from Boulahssass et al. aimed to develop a predictive model of death at 100 days in elderly cancer patients. A comprehensive geriatric assessment (CGA) was performed on 150 patients (mean age: 82 years). The multimodal approach included a nutritional status assessment using the Mini Nutritional Assessment (MNA). The CGA influenced on 22% of therapeutic decisions and MNA was an independent predictor for an increased risk of death at 100 days (OR 8, 95% CI: 3.7–17.3, $p < 0,001$).

The role of the nutritional status in survival needs further analysis in on-going international external validation studies [4].

Burden et al. conducted a review of dietary interventions for cancer survivors, including breast and gynaecological cancer survivors. Dietary interventions were shown to increase the intake of fruit and vegetables and dietary fibre and improve diet quality. However, due to contradictory findings between studies and cancer sites, it is difficult to estimate the potential benefit [5].

Relevant articles retrieved August 15, 2018 – February 15, 2019

No	Title	Authors	Journal	Link to abstract
1	A prospective study evaluating the impact of implementing the ERAS protocol on patients undergoing surgery for advanced ovarian cancer.	Agarwal R et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30833445
2	Use of biologically-based complementary medicine in breast and gynecological cancer patients during systemic therapy.	Drozdoff L et al.	BMC Complement Altern Med.	https://www.ncbi.nlm.nih.gov/pubmed/30249217
3	Supportive infusions in integrative breast and gynecological oncology - report on patients' satisfaction and self-reported effects and side effects.	Hack CC et al.	Geburtshilfe Frauenheilkd.	https://www.ncbi.nlm.nih.gov/pubmed/30498280
4	Predicting early death in older adults with cancer.	Boulahssass R et al.	Eur J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30014882
5	Dietary interventions for cancer survivors.	Burden S et al.	Proc Nutr Soc.	https://www.ncbi.nlm.nih.gov/pubmed/30563580

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We are also most grateful to Helena Opolecka (Executive Manager, ESGO) for her administrative support, Tomáš Grünwald for design and layout, and Beth Green for proofreading.