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Dear colleagues,

We present to you LiFE 7! It includes reviews of publications in gynaecological oncology dating from August 15, 2017 through February 15, 2018. LiFE is an initiative of ENYGO supported by ESGO.

You may notice the new layout that fits in with the ESGO branding.

Some of the topics have found new authors. We welcome Aleksandra Strojna (Poland), Joanna Kacperczyk-Bartnik (Poland), Engin Celik (Turkey), Nadja Taumberger (Austria), Mir Fuad Hasanov (Germany), and Stamatios Petousis (Greece) to the LiFE team.

We had a fruitful workshop with Prof. Christina Fotopoulou and Prof. Sean Kehoe at the ESGO meeting in Vienna, and it was a pleasure to see many of the LiFE authors there. We are in a continuous process to improve the quality of the report and ensure that it is a useful tool in your professional development.

We are grateful for the continuous collaboration with the International Journal of Gynecological Cancer, which adds to the publicity of our work.

We hope you will enjoy LiFE 7 and find it interesting! Please let us know if you have any comments or other feedback.

And, as there is a constant flow of LiFE authors, please get in touch if you are interested in becoming an author. Send an email to enygo.life.project@esgomail.org.

Stay up to date!

Yours,

The LiFE team

Kristina Lindemann
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Pathology/pathogenesis of malignant ovarian tumours

Dogan Vatansever

Five original research articles were considered relevant.

Jimenez-Sanchez et al. presented an exceptional case report of a high-grade serous ovarian cancer patient who was heavily pre-treated with multiple regimens. Some of the patient's metastatic lesions regressed, while others simultaneously progressed. The progressing metastases were characterised by immune cell exclusion, whereas regressing and stable metastases were infiltrated by CD8+ and CD4+ T cells and exhibited oligoclonal expansion of T cell subsets. This case study provides evidence of divergent tumour genetics, tumour microenvironments, and immune activation within a single patient with advanced ovarian cancer. If this inter-site heterogeneity is more generalisable, it may represent a profound clinical challenge limiting the efficacy of cytotoxic, targeted, and immuno-therapies.

Ducie et al. performed integrated genomic analysis of advanced-stage tumours with and without serous tubal intraepithelial carcinomas (STIC) lesions and normal tissues in a multicentre study. Analyses of the data from copy number alterations, messenger RNA sequencing, and microRNA profiling failed to identify any significant differences between HGSCs with or without precursor STIC lesions. These data provide evidence from a multi-platform genomic perspective that HGSCs with or without STIC lesions originate from a common site of origin. The similarity between HGSC and normal fallopian tube, normal ovary, and normal peritoneum were calculated through molecular barcodes, finding the most likely site of origin in the distal fallopian tube. These comparisons suggest that the distal fallopian tube is most likely the one common biological origin for high-grade ovarian cancer.

Labidi-Galy et al. also studied the hypothesis that fallopian tube cancers may be precursors of HGSOC. Whole-exome sequence and copy number analyses of laser capture microdissected fallopian tube lesions (p53 signatures, STICs, and fallopian tube carcinomas), ovarian cancers, and metastases from nine patients. Many tumour-specific alterations in ovarian cancers were present in STICs, including those affecting TP53, BRCA1, BRCA2 or PTEN. Evolutionary analyses revealed that p53 signatures and STICs are precursors of ovarian carcinoma. They used a mathematical model to estimate the time between the development of the earliest neoplastic clones in the fallopian tube and the development of ovarian and other metastatic lesions. This model would suggest the timing of the progression from STICs to ovarian cancer was on average 6.5 years, but development of metastatic lesions in these patients occurred rapidly thereafter.

Torres et al. retrospectively categorised IP disease dissemination into four mutually exclusive patterns: Upper abdominal (60%), miliary (16%), lower abdominal (15%), and pelvic (9%). Additionally, molecular subtype assignments were derived from expression profiling of tumours from 334 patients. Patients with either miliary or upper abdominal dissemination patterns were less likely to achieve R0, despite higher surgical complexity. Among the subset with molecular subtype data, patients with mesenchymal subtype tumours were more likely to have upper abdominal or miliary dissemination patterns compared to patients with differentiated, proliferative or immunoreactive subtypes, possibly explaining the lower rates of complete resection in this subtype. The authors concluded that these associations at least partially explain the poorer overall survival reported in patients with the mesenchymal subtype.

Garsed et al. identified 96 long-term survivors of high-grade serous ovarian cancer in the population-based Australian

Ovarian Cancer Study and another institutional biobank and evaluated the tumours by immunohistochemistry and genome sequencing. They put the patients into three groups: Long-PFS, Multiple Responder, and Long-Term Survivors. Long-PFS was defined as > 36 months progression-free survival from diagnosis and restricted to cases with macroscopic residual disease after primary cytoreductive surgery. Multiple Responders had complete responses to three or more lines of platinum-based chemotherapy. For response to first-line only, patients with residual disease after surgery were included. Long-Term Survivors had an overall survival period of at least 10 years after histological diagnosis. Collectively, these three patient subgroups are referred to as Exceptional Responders. Pathogenic germline and somatic mutations in genes involved in homologous recombination (HR) repair were enriched in all three groups relative to a population-based series. CD8+ tumour-infiltrating lymphocytes were more commonly present in long-term survivors. Retinoblastoma-1 (RB1) loss was associated with long progression-free and overall survival. HR deficiency and RB1 loss were correlated, and co-occurrence was significantly associated with prolonged survival.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient.	Jimenez-Sanchez A et al.	Cell	https://www.ncbi.nlm.nih.gov/pubmed/28841418
2	Molecular analysis of high-grade serous ovarian carcinoma with and without associated serous tubal intra-epithelial carcinoma.	Ducie J et al.	Nature Communications	https://www.ncbi.nlm.nih.gov/pubmed/29042553
3	High-grade serous ovarian carcinomas originate in the fallopian tube.	Labidi-Galy SI et al.	Nature Communications	https://www.ncbi.nlm.nih.gov/pubmed/29061967
4	Intraperitoneal disease dissemination patterns are associated with residual disease, extent of surgery, and molecular subtypes in advanced ovarian cancer.	Torres D et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/ 28964622
5	Homologous recombination DNA repair pathway disruption and retinoblastoma protein loss are associated with exceptional survival in high-grade serous ovarian cancer.	Garsed DW et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/ 29061645

Screening for ovarian and fallopian tube cancer

Lucas Minig

An updated version of the US Preventive Services Task Force in 2012, regarding recommendations on screening for ovarian cancer, was recently published [1]. The document "recommends against screening for ovarian cancer in asymptomatic women" (D recommendation). These are asymptomatic women who are not known to have a high-risk hereditary cancer syndrome. They conclude with a level D recommendation (moderate certainty), based on a rigorous evaluation of the evidence of benefits and harms of ovarian cancer screening.

The American College of Obstetricians and Gynecologists (ACOG) recently updated the document entitled: "The Role of the Obstetrician–Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk". The committee opinion concludes that: 1) There is no current strategy for early detection of ovarian cancer that reduces ovarian cancer mortality; 2) The use of vaginal ultrasonography and tumour markers (such as CA 125), alone or in combination, for the early detection of ovarian cancer in average-risk women have not been proved to reduce mortality, and harms exist from invasive diagnostic testing (e.g., unnecessary surgery) resulting from false-positive test results; 3) Taking a detailed personal and family history for breast, gynaecologic, and colon cancer facilitates categorising women based on their risk (average risk or high risk) of developing epithelial ovarian cancer [2].

A recursive Markov model was suggested to test the effect of the ROCA algorithm to screen post-menopausal women at average risk of ovarian cancer with the aim of preventing death from ovarian cancer. This model could simulate real-world conditions outside of the UKCTOCS trial and examine the effectiveness of screening with respect to the number of deaths prevented as well as the cost per year of life saved. The study observed an absolute decrease of 6% in ovarian cancer mortality, yielding an increase in life expectancy of 0.0101 years, preventing 55 deaths per 100,000 screened at a cost of $585,946 per life-year. Screening for 30 years reduced mortality from 0.954% to 0.872%, an absolute decrease of 9%, preventing 82 deaths at a cost of $763,970 per life-year. The practical impact of the ROCA algorithm in screening is questioned as, even if costs could be reduced ten-fold, it would only have a marginal impact on mortality from ovarian cancer [3].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	US Preventive Services Task Force. Screening for ovarian cancer: US Preventive Services Task Force recommendation statement.	US Preventive Services Task Force, Grossman DC et al.	JAMA	https://www.ncbi.nlm.nih.gov/pubmed/29450531
2	The role of the obstetrician–gynecologist in the early detection of epithelial ovarian cancer in women at average risk.	The American College of Obstetricians and Gynecologists	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28832487
3	Ovarian cancer screening with the risk of ovarian cancer algorithm (ROCA): Good, bad, or just expensive?	Naumann RW and Brown J	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29398069

Surgical treatment of primary ovarian cancer

Sileny Han

Technique

In a prospective observational study (n = 150), Mukhopadhyay et al. [1] found that lesser sac metastasis and particularly supragastric lesser sac metastasis are present in almost two-thirds of cases of advanced ovarian cancer but are often small in size. This region, therefore, needs careful intraoperative exploration for residual disease to avoid unrecognised incomplete cytoreduction.

In the treatment of advanced ovarian cancer, complete resection to no residual tumour is the most important prognostic factor. Rosendahl et al. studied the predictive value of the peritoneal carcinosis index (PCI) in achieving complete cytoreduction [2]. They hypothesised that specific PCI regions, namely the small intestine with mesentery (regions 9–12) and the hepatoduodenal ligament (region 2), are more predictive of complete resection (R = 0) and survival than the entire PCI. They analysed prospectively collected Danish registry data from 507 patients with stage 3b to 4b EOC who underwent primary surgery with complete cytoreductive intent. Selected PCI regions (9–12 and 2 + 9–12) corresponding to the small intestine and hepatoduodenal ligament were more predictive of complete resection and survival than the entire PCI. Early intraoperative examination of those PCI regions rather than the whole PCI will help to decide if R = 0 is achievable.

Cost-effectiveness

Tran et al. [3] investigated the cost-effectiveness of NACT relative to PCS (primary cytoreductive surgery) for advanced-stage epithelial ovarian cancer (EOC) from the US Medicare perspective. Model outcomes included costs, life-years gained, quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness ratios (ICER), in terms of cost per life-year gained and cost per QALY gained. NACT resulted in a savings of $7,034 per patient with a 0.035 QALY increase compared to PCS; therefore, NACT was superior to PCS in the base case analysis. In the short-term, NACT is a cost-effective alternative compared to PCS in women with advanced stage EOC.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Metastatic involvement of lesser sac in advanced epithelial ovarian cancer.	Mukhopadhyay A et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/9324540
2	Specific regions, rather than the entire peritoneal carcinosis index, are predictive of complete resection and survival in advanced epithelial ovarian cancer.	Rosendahl M et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29324538
3	Cost effectiveness of neoadjuvant chemotherapy followed by interval cytoreductive surgery versus primary cytoreductive surgery for patients with advanced stage ovarian cancer during the initial treatment phase.	Tran AQ et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29273308

Surgical treatment of recurrent ovarian cancer

Patriciu Achimas-Cadariu

While we await the final results of the two ongoing trials (NCT00565851, GOG213 and NCT01166737, DESKTOP III; the latter was discussed in LiFE 6), there is growing evidence that secondary cytoreductive surgery may convey a survival benefit in carefully selected patients.

A retrospective single-institutional cohort study of patients who underwent secondary cytoreductive surgery for recurrent epithelial ovarian cancer published by Katsnelson et al. showed that complete cytoreduction was associated with a longer overall survival compared to optimal (< 1cm) and suboptimal cytoreduction. The factors associated with suboptimal cytoreduction were age > 55 years, serous histology, largest tumour implant size > 4cm, and suboptimal cytoreduction at primary surgery. Still, the surgical outcome of secondary cytoreductive surgery was an independent predictor of survival regardless of the outcome of primary cytoreduction [1].

Another single-institution retrospective study from the Catholic University of the Sacred Heart, Rome, Italy, investigated the feasibility and safety of laparoscopic secondary cytoreductive surgery in a series of 58 patients with platinum-sensitive recurrent ovarian cancer. It concluded that, for carefully selected patients, this is a feasible and safe approach to optimal cytoreduction associated with a 2-year PFS of 58.7%. Larger prospective studies will be needed to confirm the role of minimally invasive surgery [2].

Recently, a review published by Pignata et al. addressed the most debatable issues of a `personalised` approach in recurrent ovarian cancer, including the role of surgery in the ever-changing landscape of this disease [3].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Preoperative predictors that impact the survival and outcome of patients undergoing secondary cytoreduction for ovarian cancer.	Katsnelson M et al.	J Obstet Gynaecol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=29385863
2	Secondary laparoscopic cytoreduction in recurrent ovarian cancer: A large, single-institution experience.	Gallotta V et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=29081384
3	Treatment of recurrent ovarian cancer.	Pignata S et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=29232464

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Medical treatment of primary ovarian cancer

Ilker Selcuk

Adjuvant chemotherapy in early-stage ovarian cancer

Hogen et al. assessed the role of adjuvant chemotherapy in 60 surgically staged patients with stage 1 ovarian clear cell carcinoma. In all, 29 patients received adjuvant chemotherapy and 31 did not. Stage 1c was equally distributed between the groups; however, in the no-chemo group, 84% had unknown cytology compared to 17% in the chemo group ($p < 0.001$). Patients were given platinum-based chemotherapy, with a median follow-up period of 4.96 years. There was no difference in 5 years (73.6% in NACG and 92.8% in ACG; $p = 0.13$) and 10 years (63.1% in NACG and 76.6% in ACG; $p = 0.13$) disease-specific survival (DSS). After adjustment for positive cytology, no adjuvant chemotherapy was statistically significant associated with shorter progression-free survival (PFS) (HR = 4, $p = 0.01$).

Oseledchyk et al. analysed Surveillance, Epidemiology, and End Results (SEER) 2000–2013 data for adjuvant therapy in stage 1 endometrioid and clear-cell epithelial ovarian cancer (EEOC/CEOC). The median follow-up period was 65 months and, in multivariate analysis, adjuvant chemotherapy was associated with improved overall survival (OS) in substage 1c and grade 3 disease for EEOC (HR 0.583; 95% CI: 0.359–0.949; $p = 0.030$); however, for CEOC, chemotherapy was not associated with an improved OS. Only age at diagnosis (HR 1.038; 95% CI: 1.029–1.048; $p < 0.001$) and stage 1c disease (HR 1.353; 95% CI: 1.080-1.694; $p = 0.009$) were independently associated with OS.

IP chemotherapy/HIPEC

The OV21/PETROC study evaluated the role of intraperitoneal (IP) chemotherapy following neoadjuvant chemotherapy (NACT) and optimal debulking surgery in a multicentre, 2 stage, phase II trial of 275 stage 2b–4aA epithelial ovarian cancer (EOC) patients. After NACT and optimal (< 1cm) debulking surgery, patients were randomised to intravenous (iv) carboplatin/paclitaxel (n = 101), ip cisplatin plus iv/ip paclitaxel (n = 72) or ip carboplatin plus iv/ip paclitaxel (n = 102). Characteristics of patients were similar between the groups. Nine-month progressive disease rate (PD9) was similar in the ip carboplatin arm (24.5%, 95% CI: 16.2%–32.9%) compared to iv carboplatin arm (38.6%, 95% CI: 29.1%–48.1%; $p = 0.065$), but statistically significantly lower in the per-protocol population (42.2% in Arm 1 vs. 23.3% in Arm 3, $p = 0.03$). The study was not powered to detect differences in PFS. No statistically significant difference was detected in peripheral neuropathy and gastrointestinal symptoms with regard to QoL.

Van Driel et al. assessed the role of hyperthermic intraperitoneal chemotherapy during IDS with a multicentre, randomised, phase III trial of 245 stage-3 EOC patients. HIPEC was given as cisplatin (100mg/m^2). Patients with a complete or optimal cytoreduction were accepted as feasible for the study and randomised during surgery. HIPEC was associated with longer recurrence-free survival: 10.7 versus 14.2 months in the surgery alone and surgery plus HIPEC groups, respectively. The probability of recurrence-free survival at the end of 3 years was 8% (95% CI: 4–16) versus 17% (95% 11–26), respectively. The median OS was 33.9 versus 45.7 months in the surgery alone and surgery plus HIPEC groups, respectively; additionally, the probability of OS at the end of 3 years was 48% (95% CI: 39–58) and 62% (54–72%), respectively. The percentage of adverse events of any grade was similar between the groups. After HIPEC, patients undergoing bowel surgery were more frequently treated with a stoma (72% vs. 43%), $p = 0.04$). Length of stay was not different.

European Society of Medical Oncology Symposium Article reviewed intraperitoneal (ip) chemotherapy after primary advanced ovarian cancer. Higher toxicity, inconvenience, catheter complications, increased resources, and cost are the downsides of ip therapy.

Endocrine treatment

Fader et al. assessed primary cytoreductive surgery (CRS) followed by endocrine treatment in patients with advanced low-grade serous ovarian carcinoma (LGSC). Twenty-seven stage 2–4 patients were retrospectively evaluated; one had neoadjuvant chemotherapy plus interval CRS before endocrine treatment. No gross residual tumour was achieved in 85.2% of patients and 96% were oestrogen-receptor-positive. Letrozole (55.5%), anastrozole (37.1%), and tamoxifen (7.4%) were administered orally to patients. After a median follow-up of 41 months, 3-year PFS and OS rates were 79.0% and 92.6%, respectively. Phase III evaluation of endocrine treatment as an alternative to chemotherapy is planned.

Heinzelmann-Schwarz et al. prospectively studied letrozole in maintenance after platinum-based chemotherapy in 50 patients with ER-positive high-grade serous ovarian cancers (HGSOC). The stage and level of cytoreduction was similar between the groups. After 24 months, RFS in the letrozole and control group was 60% versus 38.5%, $p = 0.035$. The improvement in the RFS was also demonstrated in patients with residual disease treated with bevacizumab maintenance: 87.5% versus 20.8% of patients were without any recurrence, respectively, irrespective of when letrozole was started. No major side effects were observed.

Neo-adjuvant and primary treatment

Brackmann et al. analysed the first-line chemotherapy regimens for ovarian carcinosarcoma with regard to PFS and OS in a retrospective single-centre study. Thirty-one patients were evaluated, most of them had advanced stage (stage 3–4, n = 24) disease. Paclitaxel-carboplatin chemotherapy doublet had a statistically significant higher PFS than other regimens (17.8 vs. 8.0 months, $p = 0.025$); however, OS was similar between the platinum containing regimens and non-platinum containing regimens (22.7 vs. 19.0 months, $p = 0.323$). Subsequent treatment cross-over during the recurrences may explain the similar OS.

Phillips et al. analysed the effect of the number of cycles given in NACT and residual disease, on survival in a retrospective review of advanced ovarian cancer patients. Patients were analysed in groups of ≤ 4 cycles of chemotherapy (group 1) and ≥ 5 cycles of chemotherapy (group 2). The value of achieving R1 (< 1cm) remains questionable, especially when ≤ 4 cycles of chemotherapy were administered. The best outcomes were observed in patients with R0 disease, independent of the number of cycles given.

Lee et al. retrospectively assessed the impact of time interval from completion of neoadjuvant chemotherapy to initiation of postoperative adjuvant chemotherapy (POAC). The median time interval was 42 days (range 16–178); within that time, 103 patients (53.1%) received POAC within 42 days and 91 patients (46.9%) received it after 42 days. Patient characteristics were similar between the groups. In multivariate analysis, the longer time interval for starting POAC was significantly associated with OS (HR, 2.03; 95% CI: 1.16–3.54, $p = 0.013$), but not with PFS (HR, 1.41; 95% CI: 0.98–2.03; $p = 0.063$). Keeping times short between NACT and start of adjuvant treatment seems important. Not evaluating cancer-specific mortality is the major limitation of this study.

Medical treatment of primary ovarian cancer

Ilker Selcuk

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Is adjuvant chemotherapy beneficial for surgical stage I ovarian clear cell carcinoma?	Hogen L et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28760368
2	Adjuvant chemotherapy in patients with stage I endometrioid and clear cell ovarian cancer in the platinum era: A surveillance, epidemiology, and end results cohort study, 2000–2013.	Oseledchyk A et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28950307
3	OV21/PETROC: a randomized gynecologic cancer intergroup phase ii study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer.	Provencher DM et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29186319
4	Hyperthermic intraperitoneal chemotherapy in ovarian cancer.	Van Driel WJ et al.	N Engl J Med	http://www.nejm.org/doi/full/10.1056/NEJMoa1708618
5	Is intraperitoneal chemotherapy still an acceptable option in primary adjuvant chemotherapy for advanced ovarian cancer?	Monk BJ et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29232474
6	Primary cytoreductive surgery and adjuvant hormonal monotherapy in women with advanced low-grade serous ovarian carcinoma: Reducing overtreatment without compromising survival.	Fader AN et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28768570
7	Letrozole may be a valuable maintenance treatment in high-grade serous ovarian cancer patients.	Heinzelmann-Schwarz V et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29157627
8	Comparison of first-line chemotherapy regimens for ovarian carcinosarcoma: a single institution case series and review of the literature.	Brackmann M et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29426293
9	Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers a survival benefit in advanced ovarian cancer.	Phillips A et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29426779
10	Impact of the time interval from completion of neoadjuvant chemotherapy to initiation of postoperative adjuvant chemotherapy on the survival of patients with advanced ovarian cancer.	Lee YJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29174056

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Medical treatment of recurrent ovarian cancer

Ilker Selcuk

PARP inhibitors

Results from Ariel3 were published. The PARP inhibitor rucaparib was studied in a randomised, double-blind, placebo-controlled, phase III trial of patients with recurrent, platinum-sensitive ovarian cancer responding to the last platinum-based chemotherapy. Patients were randomised in a ratio of 2:1. Median PFS in BRCA-mutated patients on rucaparib was 16.6 months versus 5.4 months in the placebo group (HR: 0.23, 95% CI: 0.16–0.34), $p < 0.0001$. Similarly, in patients with a homologous recombination (HR) deficient carcinoma, PFS was significantly longer on rucaparib: 13.6 versus 5.4 months, respectively, $p < 0.001$. The most common serious adverse effects were anaemia (19% vs. 1%), and increased liver enzymes (10% vs. none). The PARP inhibitor rucaparib, along with olaparib and niraparib, provides an important prolongation of PFS. Patients with bulky disease (≥ 2cm) were also enrolled to this study and the overall response to treatment was 38% and 27% in the mBRCA and HR groups, respectively. The study is also discussed in the report of Sara Giovannoni on hereditary ovarian cancer.

Accompanying the Ariel3 results, Dizon emphasised the need for further studies to better characterise patients potentially benefitting from PARP.

Oza et al. assessed the antitumour activity and safety of PARP inhibitor rucaparib in patients with a relapsed high-grade ovarian carcinoma (HGOC) and germline or somatic BRCA 1/2 mutation after at least two prior chemotherapies. The study is discussed in the report from Sara Giovannoni on hereditary ovarian cancer.

Steffensen et al. evaluated veliparib in a phase I/II study in patients with a platinum-resistant or intermediate sensitive relapse of epithelial ovarian cancer (EOC) and BRCA positive genomic status. The phase I part of the study (2011–2012) showed 300mg veliparib twice daily as a maximum tolerable dose (16 patients). The phase II part of the study (2012–2015) was within 32 heavily pretreated patients. The overall response rate (ORR) was 65% (similar between platinum-resistant and intermediate sensitive patients), and PFS and overall survival (OS) rates were 5.6 months (95% CI: 5.2–7.3) and 13.7 months (95% CI: 10.2–17.3), respectively. Patients with a platinum intermediate sensitive disease had a significantly longer PFS ($p = 0.037$) and OS ($p = 0.02$) than platinum-resistant patients. Fatigue (22%), nausea (22%), and vomiting (9%) were the most common adverse effects; however, only grade 2 toxicity was observed. Veliparib could be an important option in heavily pretreated recurrent ovarian cancer patients.

Moore et al. reviewed PARP inhibitor niraparib with regard to adverse effects during the treatment period.

Dockery et al. assessed the tolerance and toxicity of olaparib in older women (≥ 65 years) with recurrent epithelial ovarian cancer treated in eight completed prospective studies. Patients (n = 398) who received daily oral 400 mg olaparib were analysed due to 5-year intervals by 65 years of age. Of the 398 patients included, 78 were ≥ age 65. Dose reduction rates were 46.9%, 44.7%, 47.8%, and 64.7% for patients aged < 65, 65–69, 70–74, and ≥ 75 years, respectively, $p = 0.62$. With the caveat of small numbers, there does not seem to be a difference in tolerability for elderly women.

Immunotherapy

Kristeleit et al. evaluated IDO1 inhibitor (epacadostat) against tamoxifen in only biochemically recurrent (Ca-125 relapsed) patients following complete remission of first line chemotherapy for advanced epithelial ovarian, primary peritoneal or fallopian tube cancer within a randomised, phase II, open-label study. This study is discussed in the chapter on early preclinical trials in ovarian cancer.

Anti-angiogenic therapy

Miao et al. evaluated apatinib, an anti-angiogenic agent targeting vascular endothelial growth factor receptor 2 (VEGFR2), 500mg daily in a phase II study of patients (n = 28) with recurrent, platinum-resistant, pretreated EOC. Apatinib was administered for a median of 36.8 weeks (13–64.8) and median follow-up time was 12 months. ORR was 41.4%, median PFS and OS were 5.1 months (95% CI: 3.8–6.5) and 14.5 months (95% CI: 12.4–16.4), respectively. Hand-foot syndrome (51.7%) and hypertension (34.6%) were the most common treatment-related adverse effects.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.	Coleman RL et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/28916367
2	PARP inhibitors for targeted treatment in ovarian cancer.	Dizon DS	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/28916370
3	Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.	Oza MA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28882436
4	Veliparib monotherapy to patients with BRCA germ line mutation and platinum-resistant or partially platinum-sensitive relapse of epithelial ovarian cancer: A phase I/II study.	Steffensen KD et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28763368
5	The poly (ADP ribose) polymerase inhibitor niraparib: Management of toxicities.	Moore KN et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29397193
6	Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer.	Dockery LE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29037805
7	A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)–only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer.	Kristeleit R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28698009
8	A phase II study of apatinib in patients with recurrent epithelial ovarian cancer.	Miao M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29248198

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Treatment of ovarian sex cord stromal and germ cell tumours

Anna Dückelmann

Epidemiology/General aspects

Boussios et al. provide a very good overview of the current knowledge on the incidence, clinical presentation, pathology, genetics, therapeutic interventions, survival, and prognostic factors of adult and juvenile granulosa cell tumours (GCT), Sertoli-Leydig cell tumours, and small cell carcinomas of the ovary. Future potential therapeutic targets in these rare cancers are also discussed.

Bownes et al. examine the effect of socioeconomic status (SES) on survival in adolescent and young adults with malignant ovarian germ cell tumours (MOGCT). SES was defined by insurance type, income quartile, and education quartile. Young patients with MOGCT with lower SES presented with more advanced stage disease; however, there was no difference in survival and treatment when results were adjusted for stage.

The standard of care for adult women with ovarian immature teratoma is postoperative platinum-based chemotherapy for all patients except FIGO stage IA, grade 1 tumours. This is in contrast to paediatric series, where surgery alone is curative for completely resected ovarian immature teratomas, regardless of grade. According to an analysis of the malignant germ cell international consortium data set including six paediatric clinical trials and two adult gynaecology clinical trials with 251 patients (Conter et al.), age has no apparent impact on the probability of event or death. This allows paediatric and gynaecologic oncologists to enrol patients onto joint paediatric and adult trials to assess the role of chemotherapy in incompletely resected tumours and its impact on the rate of malignant relapses.

Liang et al. present two cases of teratoma-associated anti-NMDAR encephalitis. For female patients showing symptoms similar to those of virus encephalitis, such as psychosis or seizures, the possibility of anti-NMDAR encephalitis should be considered.

Molecular research

Chang et al. characterised microRNA expression profiles of ovarian germ cell tumours (benign and malignant) and sex cord stromal tumours (SCST). Significant miRNA expression variations among the three tumour groups were observed, suggesting a potential role in tumorigenesis and value as diagnostic markers.

An update of molecular pathogenesis underlying SCSTs by Lim and Oliva concluded that DICER1 mutation is specific for SCSTs and FOXL2 mutation is specific for GCTs.

Individuals with pathogenic germline DICER1 variants are at increased risk for Sertoli-Leydig cell tumour (SLCT) and gynandroblastoma (GAB). Schultz et al. discuss the management guidelines, the risks and potential benefits of screening and surveillance imaging. The authors recommend patient and parent education regarding symptoms and present indications for germline DICER1 genetic testing. In a second paper, they reported that nearly all SLCTs and GAB are DICER1-related, showing the distinct nature of the pathophysiology of SLCT and GAB when compared to germ cell tumours, epithelial ovarian tumours, and even other ovarian SCSTs. DICER1 testing in women with SLCT may facilitate screening of their children for pleuropulmonary blastoma PPB.

Pilsworth et al. performed whole-genome sequencing on 10 adult GCTs. Extension cohort analysis revealed the TERT C228T mutation in 22% of primary adult GCTs, in 41% of recurrent adult GCTs, and in 5% of other SCSTs. Patients with TERT C228T promoter mutation in the primary tumours had worse OS than those without it.

Surgery

According to a retrospective cohort study and meta-analysis by Cheng et al., lymphadenectomy has no statistical significance in improving overall survival in malignant ovarian SCSTs.

Pascual et al. presented a retrospective cohort study of 408 women diagnosed with an ovarian teratoma by ultrasonography. During follow-up, 31.8% women underwent surgery. Surgery was recommended if the patient developed symptoms that could be related to the teratoma, if tumour size increased 10mm or greater, or if ultrasound characteristics changed suggesting malignancy. Surgery was also performed in case of the patient's decision, or concomitant to another surgery. Histologic diagnosis of tumours removed surgically revealed a benign ovarian teratoma in 79.2% of the women; no malignant tumour was found. Expectant management might be a reasonable option for asymptomatic women with ultrasonographic diagnosis of an ovarian teratoma.

Fertility

Nasioudis et al. presented a population-based retrospective study with the longest follow-up, to investigate the safety of fertility-sparing surgery (FSS) for premenopausal women with SCSTs limited to the ovary. Women in the definite surgery group had better cancer-specific survival (CSS (hazard ratio 0.29; 95% CI: 0.1-0.84; $p = 0.015$ from log-rank) However, 5-year, 10-year, and 20-year CSS rates in the definite and FSS groups were 96.3% versus 94.6%, $p = 0.54$; 94.2% versus 87.1%, $p = 0.14$; and 94.2% versus 71.7%, $p = 0.021$, respectively. No significant difference was noted in overall survival (OS). The authors conclude that FSS should be offered after extensive counselling and if SCSTs are confined to the ovary, followed by long-term surveillance.

There are no standard guidelines for fertility management in patients undergoing treatment for MOGCTs. Di Tucci et al. report a good review of the evaluation and preservation of fertility in pre- and post-treatment setting and reproductive outcomes in MOGCT patients.

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1	Ovarian sex-cord stromal tumours and small cell tumours: pathological, genetic and management aspects.	Boussios S et al.	Crit Rev Oncol Hematol.	https://www.ncbi.nlm.nih.gov/pubmed/29198337
2	Socioeconomic disparities affect survival in malignant ovarian germ cell tumors in AYA population.	Bownes LV et al.	J Surg Res.	https://www.ncbi.nlm.nih.gov/pubmed/28988685
3	Ovarian yolk sac tumors; does age matter?	Conter CF et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29194189
4	Teratoma-associated anti-NMDAR encephalitis.	Liang Z et al.	Medicine.	https://www.ncbi.nlm.nih.gov/pubmed/29245365
5	MicroRNA expression profiles in non-epithelial ovarian tumors.	Chang RK et al.	Int J Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29138809
6	Ovarian sex cord-stromal tumours: an update in recent molecular advances.	Lim D, Oliva E	Pathology	https://www.ncbi.nlm.nih.gov/pubmed/29275930
7	DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies.	Schultz KAP et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29343557
8	DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: clinical and genetic findings from the international ovarian and testicular stromal tumor registry.	Schultz KAP et al.	Gynecologic oncology	https://www.ncbi.nlm.nih.gov/pubmed/29037807
9	TERT promoter mutation in adult granulosa cell tumor of the ovary.	Pilsworth JA et al.	Modern pathology	https://www.ncbi.nlm.nih.gov/pubmed/29449679
10	Prognostic significance of lymphadenectomy in malignant ovarian sex cord stromal tumor: a retrospective cohort study and meta-analysis.	Cheng H et al.	Gynecologic oncology	https://www.ncbi.nlm.nih.gov/pubmed/29107349
11	Long-term results for expectant management of ultrasonographically diagnosed benign ovarian teratomas.	Pascual MA et al.	Obstetrics and gynecology	https://www.ncbi.nlm.nih.gov/pubmed/29112653
12	Safety of fertility-sparing surgery for premenopausal women with sex cord -stromal tumors confined to the ovary.	Nasioudis D et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28930803
13	Fertility management for malignant ovarian germ cell tumors patients.	Di Tucci C et al.	Critical Reviews in Oncology / Hematology	https://www.ncbi.nlm.nih.gov/pubmed/29198336

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

Muhammad Rizki Yaznil and Florian Drews

During the six months since the last review, several phase I (veliparib, mirvetuximab soravtansine, intraperitoneal GEN-1) and phase II (paclitaxel with reolysin, cabozantinib, etirinotecan pegol, epacadostat, rucaparib, linsitinib, prexasertib) chemotherapy trials for ovarian cancers have been published. In addition, a phase II trial on intensity-modulated WART as consolidation therapy following successful surgical and chemotherapy treatment in ovarian cancer piqued our interest. The authors attempted to include relevant studies covering the wide field of novel approaches to ovarian cancer treatment.

Phase I trials

Three phase I studies of veliparib, a potent orally bioavailable poly(ADP-ribose) polymerase-1 and -2 inhibitor, were reported. Nishikawa et al. [1] reported on outcomes regarding single-agent veliparib in advanced solid tumours. Eligible patients (n = 16) were assigned to veliparib 200mg or 400mg doses; 14 patients had high-grade serous EOC, one primary peritoneal cancer, and one BRCA-mutated breast cancer. Most frequent adverse reactions included nausea and vomiting, decreased appetite, abdominal pain, diarrhoea, and malaise. Fifty per cent of patients experienced grade ≥ 3 toxicity. 400mg BD was defined as a recommended phase II dose. Veliparib monotherapy showed satisfying tolerability and safety profiles. Nishio et al. [2] studied veliparib in combination with carboplatin and weekly paclitaxel in first line treatment. The recommended phase II dose was 150mg BD; the most common adverse events included neutropenia, alopecia, peripheral neuropathy, anaemia, nausea, and malaise. Veliparib was also studied in combination with carboplatin and gemcitabine in a phase I trial, including 54 ovarian cancer patients [3]. Safety was comparable to carboplatin and gemcitabine alone, with 69% of patients with BRCA-deficient ovarian cancer responding (45% partial, 24% complete responses).

Another phase I dose-escalation study was reported by Moore et al. [4] on mirvetuximab soravtansine (IMGN853), a folate receptor α-targeting (FRα) antibody-drug conjugate in patients with FRα-positive solid tumours. The most common treatment-related adverse events included fatigue, blurred vision, and diarrhoea. Dose-limiting toxicities included grade 3 hypophosphataemia and grade 3 punctate keratitis. Two of 44 patients showed a partial response, both with ovarian cancer.

The NRG Oncology/Gynecologic Oncology study group reported outcomes for a phase I and a phase II trial. Thaker et al. [5] reported outcomes on a phase I trial of intraperitoneal GEN-1 administered with pegylated liposomal doxorubicin (PLD) in recurrent/persistent EOC. A median of 4 cycles was given to 16 patients and no dose-limiting toxicities were found. Adverse effects included grade 4 neutropenia and grade 3 anaemia, abdominal pain and neutropenia. Encouraging clinical benefit (57.1%, 21.4% PR, 35.7% SD) was demonstrated.

Phase II trials

Cohn et al. [6] conducted a randomised phase IIb study that compared weekly paclitaxel +/- oncolytic reovirus (Reolysin) in recurrent EOC to assess its impact on progression-free survival (PFS). Eligible patients (n = 108) had recurrent or persistent EOC with three or fewer prior regimens. Severe adverse events were more common in the combination regimen, including severe neutropenia and respiratory adverse events. A similar median PFS of 4.3 months and 4.4 months (HR 1.11, p > 0.05), respectively, was observed.

Two phase II trials were published on cabozantinib, an orally bioavailable vascular endothelial growth factor receptor-2 and MET inhibitor. Schoeffski et al. [7] investigated the effect of cabozantinib (100mg, once daily) on nine different advanced, recurrent or metastatic tumour types, including ovarian cancer. The highest objective response rate (ORR) among the 526 patients was observed in ovarian cancer. Due to encouraging efficacy results and improved symptoms, randomisation was suspended and patients were evaluated in further expansion cohorts. Vergote et al. [8] reported a median PFS of 5.5 months in 70 patients with an ORR of 21% (1x CR, 14x PR). Most common grade 3/4 adverse events included diarrhoea, palmar-plantar erythrodysaesthesia syndrome, asthenia, hypertension, and neutropenia.

In a multicentre phase II study, Rustin et al. [9] confirmed safety and efficacy of etirinotecan pegol (EP) in recurrent platinum-resistant ovarian cancer (PROC) patients. Of 132 patients, 15.2% achieved an ORR and median PFS and OS were 4.4 months and 10.2 months, respectively. Most common severe side effects included diarrhoea, abdominal pain, vomiting, dehydration, and nausea.

A phase II study by Oza et al. [10] compared intermittent with continuous linsitinib, an oral inhibitor of insulin-like growth factor-1 receptor and insulin receptor, and weekly paclitaxel in recurrent PROC. Amongst the 152 randomised women, neither intermittent (median PFS 2.8 months) nor continuous linsitinib (median PFS 4.2 months) improved PFS, ORR or OS over weekly paclitaxel alone (median PFS 5.6 months). Furthermore, more adverse event rates were found in the linsitinib cohort.

Kristeleit et al. [11] reported on a phase II study of the Indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor epacadostat, a key regulator of immune tolerance in ovarian cancer, versus tamoxifen in biochemically recurrent EOC. Patients with biochemical-only recurrence following complete remission (CR) after 1st line chemotherapy were randomised to 600mg epacadostat or 20mg BD tamoxifen. Due to slow accrual and no evidence of superiority of monotherapy with IDO1 inhibitor, the study was terminated early. Median PFS for epacadostat was 3.75 months versus 5.56 months for tamoxifen (HR 1.34, p = 0.54).

In a single-centre phase II study, Lee et al. [12] reported a first-in-class proof-of-concept on prexasertib, a cell cycle checkpoint kinase-1 and -2 inhibitor in 28 BRCA wild-type recurrent high grade serous ovarian cancer; 79% of them were platinum resistant/refractory. Every 14 days in 28-day cycles, patients received 105mg/m^2 prexasertib intravenously and 29% had PR. Most common grade 3/4 adverse events were neutropenia, reduced white cell count, thrombocytopenia, and anaemia.

The first results of a prospective phase II study on modulated whole-abdominal radiation therapy (WART) following cytoreductive surgery and chemotherapy in advanced ovarian cancer were reported on by Arians et al. [13]. Twenty patients with optimal cytoreduction and complete remission were treated with consolidation therapy in the form of intensity-modulated WART (30Gy in 20 fractions of 1.5Gy). Only one grade 4 haematological toxicity was experienced, while all gastrointestinal toxicities were lower than grade 3. Treatment tolerability and acceptable risk of acute toxicity offer a new therapeutic option for consolidation therapy in advanced ovarian cancer.

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

Muhammad Rizki Yaznil and Florian Drews

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No	Title	Authors	Journal	Link to abstract
1	Phase 1 dose-escalation study of single-agent veliparib in Japanese patients with advanced solid tumors.	Nishikawa T et al.	Cancer Sci	https://www.ncbi.nlm.nih.gov/pubmed/28665051
2	Phase 1 study of veliparib with carboplatin and weekly paclitaxel in Japanese patients with newly diagnosed ovarian cancer.	Nishio S et al.	Cancer Sci	https://www.ncbi.nlm.nih.gov/pubmed/28837250
3	Phase I combination study of the PARP inhibitor veliparib plus carboplatin and gemcitabine in patients with advanced ovarian cancer and other solid malignancies.	Gray HJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29352572
4	Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor α-targeting antibody-drug conjugate, in patients with solid tumors.	Moore KN et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28440955
5	A phase I trial of intraperitoneal GEN-1, an IL-12 plasmid formulated with PEG-PEI-cholesterol lipopolymer, administered with pegylated liposomal doxorubicin in patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancers: An NRG Oncology/Gynecologic Oncology Group study.	Thaker PH et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28802766
6	Randomized phase IIB evaluation of weekly paclitaxel versus weekly paclitaxel with oncolytic reovirus (Reolysin®) in recurrent ovarian, tubal, or peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study.	Cohn DE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28756871
7	Phase II randomised discontinuation trial of cabozantinib in patients with advanced solid tumours.	Schoffski P et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28755607
8	A phase 2 randomised discontinuation trial of cabozantinib in patients with ovarian carcinoma.	Vergote IB et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29059635
9	A multicenter, open-label, expanded phase 2 study to evaluate the safety and efficacy of etirinotecan pegol, a polymer conjugate of irinotecan, in women with recurrent platinum-resistant or refractory ovarian cancer.	Rustin G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28935273
10	Phase 2 study evaluating intermittent and continuous linsitinib and weekly paclitaxel in patients with recurrent platinum resistant ovarian epithelial cancer.	Oza A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29454514
11	A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer.	Kristeleit R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28698009
12	Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study.	Lee JM et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29361470
13	Adjuvant intensity modulated whole-abdominal radiation therapy for high-risk patients with ovarian cancer (International Federation of Gynecology and Obstetrics stage III): First results of a prospective phase 2 study.	Arians N et al.	Int J Radiat Oncol Biol Phys	https://www.ncbi.nlm.nih.gov/pubmed/28870790

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

Sara Giovannoni

Rucaparib

Coleman et al. have published the final results of the ARIEL3 trial [1]. A randomised, double-bind, placebo-controlled trial comparing rucaparib (a poly(ADP-ribose) polymerase inhibitor) versus placebo as maintenance therapy in 564 patients with platinum-sensitive ovarian, peritoneal or fallopian tube carcinoma who received at least two previous platinum-based regimens, responding to their last platinum-based chemotherapy. Patients were included independent of BRCA status. The mPFS in patients harbouring a BRCA mutation was 16.6 months in the rucaparib group versus 5.4 months in the placebo group (HR 0·23 [95% CI: 0·16-0·34]; p < 0·0001). In patients with a homologous recombination-deficient carcinoma, the mPFS was 13.6 months versus 5.4 months (p < 0·0001). The most frequent grade 3–grade 4 adverse events included anaemia and hepatic toxicities. After the NOVA study with niraparib, the ARIEL3 trial confirmed the efficacy of PARP inhibitors in the maintenance setting for patients with platinum-sensitive ovarian cancer relapse, independent of BRCA mutations status. The study is also discussed in 'Medical treatment of recurrent ovarian cancer' by Ilker Selcuk.

The FDA granted accelerated approval of rucaparib for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) after two or more lines of chemotherapy and also approved the FoundationFocus CDx BRCA test (Foundation Medicine, Inc.), to identify patients with somatic BRCA mutation in the tumour. A recent review by Balasubramaniam summarises the FDA review and data supporting rucaparib's accelerated approval [2].

Toxicities with PARP inhibitors

Dockery et al. assessed the tolerability and toxicity of olaparib among older (≥ age 65) patients with recurrent ovarian cancer, enrolled in prospective trials with the standard dose of 400mg BID). There were no statistically significant differences in terms of dose reduction, interruption or in grade 3–4 toxicities between patients ≥ 65 years and < 65 years of age. However, the number of older patients was small, so larger studies are needed [3]. See the report on medical treatment of recurrent ovarian cancer by Ilker Selcuk.

An integrated analysis by Oza et al. investigated the safety profile of rucaparib from the data of the Study 10 and the ARIEL2 trial confirming a manageable safety profile. The most frequently reported side effects were nausea, fatigue, vomiting, and anaemia. The most common grade 3–4 adverse event was anaemia, as confirmed by the ARIEL3 trial [4].

Moore et al. provide an overview of the toxicity profile of niraparib and clinical guidelines about dose reduction/discontinuation and monitoring of the adverse events on niraparib [5].

Risk-reducing salpingo-oophorectomy (RRSO)

The use of hormone replacement in order to reduce endocrine and sexual problems in premenopausal women with high risk of ovarian cancer is still controversial. Vermeulen et al. analysed in a prospective, observational study the efficacy of hormone-replacement therapy after RRSO. In all, 57 of the 178 patients opted for RRSO; of those, 27 used HRT after surgery and 30 did not. Compared to the HRT-users, the HRT-non-users had a significant increase in overall endocrine symptoms ($p = 0.001$, effect size (ES) = -0.40 and $p < 0.001$, ES = -0.59 at T1 – questionnaires filled out before surgery and T2 – questionnaires filled out 3 months after surgery, respectively), and in sexual discomfort ($p < 0.001$, ES = 0.74 and $p < 0.001$, ES = 1.17). Considering an effects size of <0.5 as clinically significant, the results suggest that HRT use in the first year after RRSO has beneficial effects in terms of decreasing endocrine symptoms and sexual symptoms after RRSO [6].

Genetic counselling

The German study AGO-TR-1 [7] analysed the prevalence of deleterious germline variants in risk genes in ovarian cancer patients, testing 16 cancer-risk genes (ATM, BRCA1, BRCA2, CDH1, CHEK2, MLH1, MSH1, MSH2, MSH6, NBN, PMS2, PALB2, RAD51C, RAD51D, STK11, TP53). Of all patients enrolled, 26.4% harbour at least one deleterious variant that could have important implications in risk-reducing surgical ovarian cancer strategy; 5% of the patients with a deleterious variant in established risk genes would be missed if testing involved BRCA1/2 only. Limiting testing to BRCA genes seems not to be enough.

Liang et al. utilised an online survey to assess patients' attitudes and knowledge toward genetic counselling and testing. The results showed 77% of patients wished to obtain genetic information even if the results were not actionable. Providers showed practice differences in the management of patients with deleterious non-BRCA mutation or with VUS (variants of uncertain significance), highlighting the need for training and guidelines in the management these patients [8].

Cicero et al. analysed psychological interviews of 120 women who underwent genetic counselling for breast and/or ovarian cancer. The study underlines the importance of assessing genetic and cancer risk perception in order to avoid an increase in depressive or anxious behaviour [9]. Also, Mella et al. [10] focussed on a retrospective observation study on the emotional impact of BRCA1/2 genetic testing, supporting the need for psycho-emotional monitoring of people receiving genetic test results.

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

Sara Giovannoni

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1	Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.	Coleman RL et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/28916367
2	FDA approval summary: rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer.	Balasubramaniam S et al.	Clin Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/28751443
3	Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer.	Dockery LE et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29037805
4	Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.	Oza AM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28882436
5	The poly (ADP ribose) polymerase inhibitor niraparib: Management of toxicities.	Moore KN et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29397193
6	Hormone replacement therapy after risk-reducing salpingo-oophorectomy minimises endocrine and sexual problems: A prospective study.	Vermeulen RF et al.	Eur J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28818705
7	Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1).	Harter P et al.	PLoS One.	https://www.ncbi.nlm.nih.gov/pubmed/29053726
8	Cancer genetic counseling and testing: Perspectives of epithelial ovarian cancer patients and gynecologic oncolgy healthcare providers.	Liang MI et al.	J Genet Couns.	https://www.ncbi.nlm.nih.gov/pubmed/28785836
9	Risk perception and psychological distress in genetic counselling for hereditary breast and/or ovarian cancer.	Cicero G et al.	J Genet Couns.	https://www.ncbi.nlm.nih.gov/pubmed/28283917
10	Emotional impact on the results of BRCA1 and BRCA2 genetic test: an observational retrospective study.	Mella S et al.	Hered Cancer Clin Pract.	https://www.ncbi.nlm.nih.gov/pubmed/29026449

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

Aleksandra Strojna

Stromal microinvasion

This retrospective multicentre case-control study [1] reported that stromal microinvasion is significantly associated with decreased DFS. Patients with microinvasive borderline ovarian tumours (BOT) had a significantly higher rate of relapse than patients without micronivasive BOT (17.4 vs. 7.8%, OR 3.55, 95% CI: 1.091–11.59, p = 0.03). Microinvasive BOTs were not significantly associated with advanced stage (2–3) disease, lymph node metastasis, peritoneal implants, micropapillary histology, malignant transformation or risk of death (OS).

Fertility preservation

Patients with BOT are often young and have not yet completed their childbearing. Helpman et al. [2] published a retrospective single-centre study, which confirmed that fertility preservation in young women with borderline tumours is associated with a higher risk of recurrence. Fifty out of 234 patients (24%) developed recurrences. Only fertility preservation (HR = 2.57, 95% CI: 1.1-6, p = 0.029) and advanced-stage (HR = 4.15, 95% CI: 2.3–7.6, p < 0.001) were found to be independently associated with recurrence on multivariate analysis. Fertility-preserving treatment did not affect overall survival rate as relapse often was localised and salvaged with surgery. The study highlights the need for appropriate counselling and long-term follow-up.

Gungorduk et al. [3] conducted the largest multicentre study on mucinous borderline ovarian tumours (mBOT), including 364 patients from 14 gynaecological oncology department databases from Turkey and Germany. The study confirms the excellent prognosis of these patients. Patients who undergo conservative surgery do not have higher recurrence rates, and fertility-sparing surgery should be considered in the reproductive age group. Twenty-four patients (6.6%) experienced recurrence, thirteen (54.1%) patients had fertility-sparing surgery, and the remaining 11 (45.9%) were in the radical surgery group. No statistically significant difference in recurrence was observed between the two groups. The only predictors of recurrence were the FIGO stage at the first diagnosis (HR = 0.9, 95% CI: 0.7–1.2, p = 0.68) and the presence of invasive implants (HR = 1.4, 95% CI: 1.2–1.6, p = 0.31). The study shows that lymphadenectomy, appendectomy, and omentectomy do not have an impact on survival rates or recurrence.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	What is the impact of stromal microinvasion on oncologic outcomes in borderline ovarian tumours? A multicentre case-control study.	Boyraz G et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28866783
2	Fertility preservation in women with borderline ovarian tumours – how does it impact disease outcome? A cohort study.	Helpman L et al.	Acta Obstet Gynecol Scand	https://www.ncbi.nlm.nih.gov/pubmed/28815550
3	The impact of surgical staging on the prognosis of mucinous borderline tumours of the ovaries: a multicentre study.	Gungorduk K et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28982877

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

Santiago Scasso and Joel Laufer

Results of the PORTEC-3 trial that was initiated to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (chemoradiotherapy) versus pelvic radiotherapy alone for women with high-risk endometrial cancer (HR-EC) were discussed in the chapter on medical (chemo- and radiotherapy) treatment of primary uterine cancer by David Lindquist [1]. In that study, the decision of whether or not to give adjuvant treatment was based on classic clinicopathological risk factors (FIGO 2009 stage 1, endometrioid-type grade 3 with deep myometrial invasion or lymph-vascular space invasion (or both), endometrioid-type stage 2 or 3, or stage 1 to 3 with serous or clear-cell histology). An upfront pathology review was carried out before patient counselling and before randomisation to ensure that the trial only enrolled true HR-EC cases. The role of this process was evaluated for a subset of patients enrolled in the study (48% of the total cohort) by de Boer et al. [2]. In 43% of cases, at least one pathology item changed after review and in 8% of patients this discrepancy led to ineligibility for trial. The changes were most frequently found in histological type (34%), cervical stromal involvement (27%), and histological grade (19%). These lower-risk patients therefore did not risk receiving more intensive and potentially toxic treatment. For 19 patients, the histological type changed to carcinosarcoma and, although they were high risk, they were not eligible for the trial. In order to avoid potential treatment consequences for patients, un upfront pathology review should be incorporated in daily practice, the authors conclude.

Based on The Cancer Genome Atlas, Kommoss et al. previously developed and confirmed a pragmatic molecular classifier for endometrial cancers: ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) [3]. In the current study based on a retrospective cohort of 452 women, they validated it and provided a consistent categorisation of tumours identifying four distinct prognostic molecular subtypes (MMR-D, POLE, p53abn, and p53wt) ready to be tested in future prospective clinical trials. Authors from the same group evaluated five protein biomarkers (L1CAM, PR, ER, stathmin and PTEN) by immunohistochemistry for their prognostic value in the context of these subtypes [4]. They concluded these markers did not provide any additional prognostic value over ProMisE classification alone. The potential value added within molecular subtypes associated with intermediate outcomes may justify further studies on L1CAM and hormone receptor status, specifically in the MMR-D and p53wt subtypes.

Van Gool et al. indicated that a simple combination of tumour type, grade, peritumoural lymphocytes, MLH1, and p53 expression can assist in pre-screening for the detection of POLE-mutant ECs, increasing the probability of a mutation being detected from 7% to 33% [5]. This facilitates the use of this important prognostic biomarker in routine pathology.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial.	de Boer SM et al.	Lancet Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29449189
2	Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high-risk endometrial cancer.	de Boer SM et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29190319
3	Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series.	Kommoss S et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29432521
4	Evaluation of endometrial carcinoma prognostic immunohistochemistry markers in the context of molecular classification.	Karnezis AN et al.	J Pathol Clin Res.	https://www.ncbi.nlm.nih.gov/pubmed/29085668
5	Blinded histopathological characterisation of POLE exonuclease domain-mutant endometrial cancers: sheep in wolf's clothing.	Van Gool IC et al.	Histopathology	https://www.ncbi.nlm.nih.gov/pubmed/28795426

Screening for uterine cancer/Hereditary uterine cancer

María de los Reyes Oliver Pérez

In the period covered by the seventh edition of the LiFE report, three clinical trials [1–3], and three literature reviews have been selected [4–6] for discussion.

Uterine cancer screening

Johnatty et al. have conducted a population-based case-control study (1,353 patients with endometrial cancer and 628 controls) to determine the risk of endometrial cancer (EC) according to the family history of cancer, including evaluation by degree of relationship, type, and age at diagnosis [1]. The authors identified a significant trend in the increased risk associated with a closer relationship and an earlier age at the time of EC diagnosis. Endometrial cancer diagnosed in at least one family member was associated with a three-fold higher risk of EC (OR, 3.38, 95% CI: 2.11–5.42). Although additional studies are required to investigate the underlying genetic explanations of these associations with family history of cancer, the authors suggested increasing screening strategies in these patients.

Universal screening for Lynch Syndrome (LS) in endometrial cancer

Dillon et al. have published retrospective results of universal screening of all newly diagnosed EC on hysterectomy specimens [2]. The screening protocol is based on mismatch repair immunohistochemistry (IHC) with reflex MLH1 promoter hypermethylation analysis for tumours with loss of MLH1/PMS2 expression. Patients with: 1) tumours negative for MLH1 methylation, 2) with a loss of the heterodimer pair MSH2 and MSH6, or 3) isolated loss of either PMS2 or MSH6 were referred to the Familial Cancer Program for genetic counselling and consideration of germline testing. Sixty tumours of 233 screened (27%) had abnormal IHC staining results. LS was confirmed in five patients (2.1%). In addition, three patients with negative germline testing and presumed Lynch-like syndrome were identified and offered additional somatic testing. Takahashi et al. have performed a similar retrospective study based on 348 EC screened patients [3]. Out of the 27 patients who underwent corresponding genetic testing in this study, 10 patients (2.87%) with pathogenic germline abnormality were identified as LS, and another 17 patients who had no pathogenic abnormality in the MMR gene were classified as Lynch-like cases. For both authors, universal screening for LS in EC patients has yielded positive results for identification of patients at risk for this inherited syndrome.

Hereditary uterine cancer

Ring et al. have published an extensive literature review on genetic mutations associated with gynaecologic malignancies, their screening methods, and risk-reduction strategies for high-risk patients [4]. In EC patients, they emphasised the role of universal screening of Lynch Syndrome in all newly diagnosed cases of EC and possible mutations related to Cowden Syndrome. Kaurina et al. reviewed uncommon hereditary gynaecological tumour syndromes including Peutz-Jeghers syndrome, hereditary leiomyoma renal cell carcinoma syndrome, tuberous sclerosis complex, DICER1 syndrome, rhabdoid tumour predisposition syndrome 2, Cowden syndrome, naevoid basal cell carcinoma syndrome, and Von Hippel-Lindau syndrome [5]. Finally, Piszczek et al. published an extensive review about ovarian and uterine cancer risk-reducing strategies in gynaecological surgery [6].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Family history of cancer predicts endometrial cancer risk independently of Lynch Syndrome: Implications for genetic counselling.	Johnatty SE et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=28822557
2	Universal screening for Lynch syndrome in endometrial cancers: frequency of germline mutations and identification of patients with Lynch-like syndrome.	Dillon J et al.	Hum Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=29107668
3	Clinical characteristics of Lynch-like cases collaterally classified by Lynch syndrome identification strategy using universal screening in endometrial cancer.	Takahashi K al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=28847642
4	Current and future role of genetic screening in gynecologic malignancies.	Ring KL et al.	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/28411145
5	Uncommon hereditary gynaecological tumour syndromes: pathological features in tumours that may predict risk for a germline mutation.	Garg K et al.	Pathology	https://www.ncbi.nlm.nih.gov/pubmed/?term=29373116
6	Cancer risk-reducing opportunities in gynecologic surgery.	Piszczek C et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29097232

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

Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up)

Kastriot Dallaku and Elko Gliozheni

Diagnosis, biology, and follow-up for patients with endometrial hyperplasia.

A systematic review by Sasaki et al. estimating hysteroscopically resected endometrial polyps revealed that the frequency of pre-malignant and malignant lesions was 3.4% and factors associated with malignancy were abnormal uterine bleeding, age > 60 years, obesity, diabetes mellitus, systemic arterial hypertension, and tamoxifen usage [1]. Other predictors of malignancy in endometrial polyps were reported to be body mass index and endometrial thickness [2]. Kuribayashi et al. evaluated the frequency of endometrial malignancy after hysteroscopic polypectomy in infertile women [3]. Immunohistochemistry was used to detect DNA fragmentation factors 40, 45, and Bcl-2. The authors concluded that their overexpression may play an important role in the pathogenesis of benign endometrial hyperplasia [4]. Another study in endometrial intraepithelial neoplasia and benign hyperplasia revealed that PAX2 and BCL-2 protein expression changed in early phases of endometrial malignancies [5]. Sahoo et al. provided evidence that VEGF-mTOR signalling drives cell growth leading to endometrial hyperplasia and cancer, whereas Zheng et al. reported that the increased PAX6 expression at insulin-challenged endometrial cells in PCOS patients may contribute to the increased endometrial proliferation [6, 7]. Keizer et al. investigated the accuracy and reliability of imaging techniques in endometrial malignancies according to PALM-COEIN classification and concluded that 3D transvaginal sonography was not more accurate than 2D or 3D saline infusion sonography [8]. According to the results of the study by Berg et al., both immunohistochemistry findings and preoperative imaging, including MRI and PET/CT, yield promising results in the preoperative differentiation between complex atypical hyperplasia and endometrial cancer [9].

Conservative and definitive treatment for patients with endometrial hyperplasia.

Sabbioni et al. presented data supporting the advantage of using levonorgestrel-releasing intrauterine device (LNG-IUD) to reduce the need for radical surgical treatment [10]. Zakhour et al. analysed the response to progestin therapy and reported that women ≤ 55 years of age with atypical endometrial hyperplasia (AEH) had a lower incidence of resolution and a higher incidence of invasive cancer [11]. Cim et al. presented data showing that that LNG-IUD is effective in reducing the amount of menstrual blood loss in women with recurrent heavy menstrual bleeding [12]. LNG-IUD used for the conservative treatment of complex atypical hyperplasia or early grade 1 EC resulted in return to normal histology in 75% of patients at six months [13]. Tamauchi et al. presented data showing that medroxyprogesterone acetate can be an effective treatment in patients with atypical endometrial hyperplasia (AEH) and grade 1 EC without myometrial invasion [14]. Yamagami et al. described effective repeated treatment for recurrence after hormonal therapy for AEH/early G1 EC [15]. An alternative treatment for women with endometrial hyperplasia is metformin, a drug that has been shown in some human studies to reverse endometrial hyperplasia [16]. The risk of incidence of concomitant endometrial carcinoma in patients with AEH is high; lymph node dissection should be recommended to decide about adjuvant treatment [17].Taşkın et al. recommend a different strategy in this group of patients: sentinel lymph node mapping as a staging procedure [18].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Factors associated with malignancy in hysteroscopically resected endometrial polyps: A systematic review and meta-analysis.	Sasaki et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29454147
2	Predictors of malignancy in endometrial polyps: study of 421 women with postmenopausal bleeding.	Ghoubara et al.	Climacteric.	https://www.ncbi.nlm.nih.gov/pubmed/29219004
3	Frequency of endometrial cancer and atypical hyperplasia in infertile women undergoing hysteroscopic polypectomy.	Kuribayashi et al.	J Obstet Gynaecol Res.	https://www.ncbi.nlm.nih.gov/pubmed/28708275
4	Endometrial polyps and benign endometrial hyperplasia present increased prevalence of DNA fragmentation factors 40 and 45 (DFF40 and DFF45) together with the antiapoptotic B-cell lymphoma (Bcl-2) protein compared with normal human endometria.	Banas et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/28914671
5	BCL-2 and PAX2 expressions in EIN which had been previously diagnosed as non-atypical hyperplasia.	Trabzonlu et al.	Pathol Oncol Res.	https://www.ncbi.nlm.nih.gov/pubmed/29270778
6	Adipose-derived VEGF-mTOR signaling promotes endometrial hyperplasia and cancer: Implications for obese women.	Sahoo et al.	Mol Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/29133593
7	Hyperinsulinemia-induced PAX6 expression promotes endometrial epithelial cell proliferation via negatively modulating p27 signaling.	Zheng et al.	Biomed Pharmacother.	https://www.ncbi.nlm.nih.gov/pubmed/29112933
8	Role of 3-dimensional sonography in the assessment of submucous fibroids: A pilot study.	Keizer et al.	J Ultrasound Med.	https://www.ncbi.nlm.nih.gov/pubmed/28777463

Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up)

Kastriot Dallaku and Elko Gliozheni

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
9	Preoperative imaging markers and PDZ-binding kinase tissue expression predict low-risk disease in endometrial hyperplasias and low grade cancers.	Berg et al.	Oncotarget.	https://www.ncbi.nlm.nih.gov/pubmed/28978135
10	Non-contraceptive benefits of intrauterine levonorgestrel administration: Why not?	Sabbioni et al.	Gynecol Endocrinol.	https://www.ncbi.nlm.nih.gov/pubmed/28586290
11	Abnormal mismatch repair and other clinicopathologic predictors of poor response to progestin treatment in young women with endometrial complex atypical hyperplasia and well-differentiated endometrial adenocarcinoma: a consecutive case series.	Zakhour et al.	BJOG.	https://www.ncbi.nlm.nih.gov/pubmed/28128512
12	Two years follow-up of patients with abnormal uterine bleeding after insertion of the levonorgestrel-releasing intrauterine system.	Cim et al.	GynecolObstet Invest.	https://www.ncbi.nlm.nih.gov/pubmed/29223999
13	Treatment of low-risk endometrial cancer and complex atypical hyperplasia with the levonorgestrel-releasing intrauterine device.	Pal et al.	Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29215513
14	Efficacy of medroxyprogesterone acetate treatment and retreatment for atypical endometrial hyperplasia and endometrial cancer.	Tamauchi et al.	J Obstet Gynaecol Res.	https://www.ncbi.nlm.nih.gov/pubmed/29121428
15	Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility?	Yamagami et al.	J Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29400014
16	Metformin for endometrial hyperplasia.	Clement et al.	Cochrane Database Syst Rev.	https://www.ncbi.nlm.nih.gov/pubmed/29077194
17	The utility of sentinel lymph node mapping in the management of endometrial atypical hyperplasia.	Touhami et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29290489
18	Lymph node dissection in atypical endometrial hyperplasia.	Taşkın et al.	J Turk Ger Gynecol Assoc.	https://www.ncbi.nlm.nih.gov/pubmed/28890426

Surgical treatment of primary uterine cancer

Piotr Lepka

Lymphadenectomy in endometrial cancer

Forst et al. released the updated version of the Cochrane Database review evaluating the role of lymphadenectomy (LND) in surgical management of endometrial cancer (EC). Three RCTs were included in the meta-analysis. The results remained unchanged and indicated no differences in overall (OS) and recurrence-free survival (RFS) between women who underwent LND and those who did not as well as no difference in risk of direct surgical morbidity between the groups. Nevertheless, LND was associated with a higher risk of surgery-related systemic morbidity and lymphoedema/lymphocyst formtion.

Previously, two prospective studies suggested that LND does not significantly improve the survival of patients with high-grade endometrial carcinoma (Panici et al. 2008; Barton et al. 2009). However, both trials had substantial limitations (i.e., short follow-up, insuffcient LND, exclusion of paraaortic lymph nodes from LND). Taking these limitations into account, Papathemelis et al. in their population-based, retrospective cohort study evaluated 284 patients with high-grade EC who underwent pelvic (PLD) and paraaortic lymphadenectomy (PALD). An improvement in OS was observed when the number of dissected para-aortic (PALN) and pelvic lymph nodes (PLN) was 25 or more versus patients who did not undergo such intervention ($p < 0.001$) or had fewer lymph nodes removed. The authors concluded that the removal of 25 or more PLN and PALN might reduce the recurrence rate and might be beneficial for the OS and RFS in that group of patients.

Todo et al. retrospectively reviewed 380 patients with EC who underwent PLND and PALND evaluating incidence of PLN and PALN metastasis Overall, 16.8% patients had lymph node metastasis, including 10.3% with para-aortic lymph node metastasis. The most frequent lymphatic spread pattern was PLN+PALN+ (7.9%), followed by PLN+PALN- (6.6%), and PLN-PALN+ (2.4%). Para-aortic lymph node metastasis in patients without PLN metastasis was 2.8% (9/325). The differences in 5-year overall survival rates were as fallows: 96.5% in PLN-PALN-, 77.6% in PLN+PALN-, 63.4% in PLN+PALN+, and 53.6% in PLN-PALN+ patients.

Watari et al. published the protocol of the phase III randomised trial by the the Japan Clinical Oncology Group (SEPAL-P3) aiming to investigate the survival benefit of PLND and PALND to PLND alone. Patients corresponding to possible FIGO Stage 1b, 2, 3a, 3b, and a part of 3c1 will be eligible for the study. The results of the study are expected in 2027.

Ferron et al. described a novel surgical approach (total hysterectomy and complete PLD and PALD through left endoscopic extraperitoneal approach) in 16 consecutive overweight or obese patients (BMI > 25kg/m^2) with high-risk EC and proved that full extraperitoneal approach represents an interesting alternative strategy.

Omentectomy

Based on a cohort of 218 patients, Kaban et al. retrospectively evaluated the need for omentectomy in non-endometrioid EC patients. In 15.1% cases omental metastases were found and 44.1% of these metastases were occult metastases. The sensitivity of the surgeon's visual assessment of an omentum (positive or negative) was 0.55. The authors recommend including omentectomy in the staging procedure.

Treatment related to age

Rousselin et al. retrospectively analysed treatment in patients with high-risk EC according to age. They demonstrated that women > 70 years had lymphadenectomies performed less frequently compared with younger patients (76% vs. 96%) and more frequently recived no adjuvant treatment (17% vs. 8%). As a result, they had 3-year DFS and OS significantly lower than in the younger group and increased risk of recurrence by 57%.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Lymphadenectomy for the management of endometrial cancer.	Frost et al.	Cochrane Database Syst Rev.	https://www.ncbi.nlm.nih.gov/pubmed/28968482
2	Survival benefit of pelvic and paraaortic lymphadenectomy in high-grade endometrial carcinoma: a retrospective population-based cohort analysis.	Papathemelis et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28840384
3	Implications of para-aortic lymph node metastasis in patients with endometrial cancer without pelvic lymph node metastasis.	Todo et al.	J Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28657221
4	Phase III trial to confirm the superiority of pelvic and para-aortic lymphadenectomy to pelvic lymphadenectomy alone for endometrial cancer: Japan Clinical Oncology Group Study 1412 (SEPAL-P3).	Watari et al.	Jpn J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28981739
5	Left lateral endosurgical extraperitoneal total hysterectomy with para-aortic and pelvic lymphadenectomy: A novel approach for the obese patient with endometrial cancer.	Ferron et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29229578
6	Bipolar energy instruments in laparoscopic uterine cancer surgery: A randomized study.	Taskin et al.	J Laparoendosc Adv Surg Tech A.	https://www.ncbi.nlm.nih.gov/pubmed/29323616
7	Is omentectomy necessary for non-endometrioid endometrial cancer.	Kaban et al.	Gynecol Obstet Invest	https://www.ncbi.nlm.nih.gov/pubmed/28848103
8	Patterns of care and the survival of elderly patients with high-risk endometrial cancer: A case-control study from the FRANCOGYN group.	Rousselin et al.	Eur J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28888799

Medical (chemo- and radiotherapy) treatment of primary uterine cancer

David Lindquist

Very recently, the PORTEC-3 study was published [1]. This randomised phase III study included 686 women with high-risk endometrial cancer (EC), and they were randomised to adjuvant radiotherapy with or without chemotherapy (including two cycles of cisplatin during radiotherapy and four cycles of carboplatin and paclitaxel). The results show an increased failure-free survival but no impact on overall survival in the chemoradiotherapy arm. The authors concluded that patients should be individually counselled about combined treatment.

Several studies have focused on adjuvant treatment for FIGO stage 3 EC. Modh et al. included 1,826 women with EC from the National Cancer Database in the US and investigated the prognostic impact on the sequence of the adjuvant therapy given [2]. Sequential treatment (chemotherapy followed by radiotherapy) was superior to concurrent treatment (chemotherapy and radiotherapy within four weeks) in multivariate analysis including other known risk factors. Binder et al. reviewed patient files of 199 women with FIGO stage 3c EC and concluded that chemotherapy combined with radiotherapy was the most beneficial adjuvant treatment irrespective of grade [3]. Another observation was done by Jung et al. where 122 women with stage 2 EC were examined [4]. They were stratified in risk groups, and the high-risk group had worse survival with the most common pattern of recurrence being distant metastasis, suggesting that adjuvant chemotherapy should be considered. In contrast, Lester-Coll et al. identified 6,102 women with FIGO stage 2 EC in the National Cancer Database where the most common adjuvant treatment strategy was either radiotherapy or observation [5], and no benefit on overall survival was observed when adding chemotherapy. Thus, the benefit of adjuvant chemotherapy in FIGO stage 2 EC remains controversial.

Kogan et al. retrospectively compared the use of dose dense carboplatin and paclitaxel to their standard 3-weekly protocol for women with high- or intermediate-high risk EC [6]. In all, 122 women were included, and the dose dense strategy was associated with improved overall survival. One additional study from the National Cancer Database focused on women with endometrial clear cell carcinomas including 4,298 women [7].

The benefit of adjuvant treatment strategies was investigated in all FIGO stages, but no meaningful effect on survival was reported for this aggressive histological type at any stage. One study focused on uterine leiomyosarcoma where 111 women with FIGO stage I disease were studied retrospectively [8]. In total, 33 women received adjuvant chemotherapy with gemcitabine-docetaxel, but there was no effect on disease-free or overall survival. Finally, Gunther et al. retrospectively reviewed 155 women with FIGO stage 1–3 uterine carcinosarcomas at their institution [9]. Different combinations of treatment modalities were used, and in summary, external beam radiation had a higher 5-year pelvic disease control rate and was associated with an improved overall survival in FIGO stage 3 patients. In addition, concurrent chemoradiotherapy was associated with a higher disease-specific survival in multivariate analysis, including other known risk factors.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial.	de Boer SM et al.	Lancet Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29449189
2	What is the optimal adjuvant treatment sequence for node-positive endometrial cancer? Results of a national cancer database analysis.	Modh A et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29240603
3	Benefit of combination chemotherapy and radiation stratified by grade of stage IIIc endometrial cancer.	Binder PS et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28916118
4	Oncologic outcomes after adjuvant radiotherapy for stage II endometrial carcinoma: A Korean radiation oncology group study (KROG 14-10).	Jung J et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28604455
5	Adjuvant therapy use and survival in stage II endometrial cancer.	Lester-Coll NH et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28763364
6	Dose dense carboplatin paclitaxel improves progression free survival in patients with endometrial cancer.	Kogan L et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28735629
7	Adjuvant therapy in patients with clear cell endometrial carcinoma: An analysis of the National Cancer Database.	Nieto K et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29129389
8	Adjuvant gemcitabine-docetaxel chemotherapy for stage I uterine leiomyosarcoma: Trends and survival outcomes.	Littell RD et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28747255
9	Role of radiation therapy in the multidisciplinary management of uterine carcinosarcoma.	Gunther JR et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28930812

Surgical treatment of recurrent endometrial cancer

Arun Kalpdev

The role of surgery in recurrent endometrial cancer (EC) is still a 'feasible option', as a few case reports describe it. The key point is 'precise case selection'.

Gallota et al. has reported the case of a 55-year-old woman who developed isolated vaginal cuff recurrence after 20 months of cytoreduction for early stage (FIGO 1BG2), endometrioid endometrial adenocarcinoma. It was resected with a robotic approach. Postoperatively, the patient received six cycles of carboplatin and paclitaxel. After 17 months, isolated splenic recurrence (~ 3cm intraparenchymal lesion) again developed. was also successfully managed. At the two-month follow up, the patients was disease-free.

Similary, Kato et al. has published an article in which the authors have managed to perform cytoreduction of the para-aortic lymph node recurrence with inferior vena cava involvement. The authors have emphasised that recurrences below the renal vein, even those involving the inferior vena cava, are amenable to resection up to cytoreduction limits.

Mascillini et al. reported there is potential role for intraoperative ultrasound (IOUS) in the detection and localisation of recurrent disease in gynaecologic cancer patients during minimally invasive surgery. Mostly, recurrent lesions may not be evident in the surgical field; due to: either presence of adherences, deep anatomic position, small size, and/or lack of tactile feeling. With the use of intraoperative ultrasound, the lesion can be precisely identified. In the study, the intraoperative ultrasound was able to identify the lesions in all women (who required ultrasound), which helped in achieving complete cytoreduction, with minimal access surgery. In this study, 41% of women had recurrent endometrial cancer. The study implies that single gynaecological cancer recurrence needs IOUS to benefit from MIS for complete secondary cytoreduction.

Though the literature is limited, the role of surgery in recurrent endometrial cancer exists within limited guidelines. The available literature published in the period covered by this LiFE report reveals that 1) precise case selection and 2) precise imaging for evaluating the extent of recurrence (intraoperative ultrasound) are the key factors in achieving complete secondary cytoreduction.

Relevant articles retrieved August 15, 2017 – February 15, 2018

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	Secondary debulking surgery for para-aortic nodal recurrence in endometrial cancer requiring circumferential resection of the inferior vena cava.	Kato K et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29395305
3	Role of intraoperative ultrasound to extend the application of minimally invasive surgery for treatment of recurrent gynecologic cancer.	Mascillini F et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29325966

Medical treatment of recurrent endometrial cancer

Ewa Surynt

The review of the latest literature dedicated to the medical treatment of recurrent endometrial cancer (EC) revealed two articles. Moreira et al. presented results of the retrospective study based on the Brazilian National Cancer Institute database. The authors analysed patients with recurrent or advanced EC treated palliatively with doxorubicin. The objective response rate (CR) was found to be 12.1%. The median progression-free survival (PFS) was 4.4 months, and the median overall survival (OS) was 8.1 months for patients treated with doxorubicin. The most common adverse effect was anaemia, described in 60.6% of patients. Based on these results, the authors suggested that doxorubicin has only limited efficacy in patients with advanced or recurrent EC [1].

Myamoto et al. evaluated the efficacy and toxicity of an irinotecan hydrochloride (CPT) and nedaplatin (N) combination therapy as second- or third-line treatment for recurrent EC, administered based on UGT1A1 genotype. The CPT-N regimen included 40-70mg/m^2 of CPT-11 on days 1, 8, and 15, and 50 mg/m^2 of nedaplatin on day 1, q4 weeks. The number of prior chemotherapeutic regimens ranged from one to two. The response rate (CR) to partial remission (PR) was 14.3%, and clinical benefit rate (CBR) was calculated to be 42.8%. The adverse effects included grade 3 neutropenia, febrile neutropenia, and diarrhoea in 19.0%, 9.5%, and 14.3% of cases, respectively. Patients with a wild-type UGT1A1 genotype status received higher doses of CPT-11 and had similar RR and CBR compared to those with a UGT1A1*6 and *28 status. There were no significant differences in the frequencies of haematological or non-haematological toxicities, regardless of UGT1A1 status. The utilising of UGT1A1 poly- morphism status reduced the incidence of side effects while preserving anti-tumour effects. The authors suggested that the CPT-N regimen is a viable treatment option for recurrent EC. Furthermore, they indicated that the CPT-N regimen needs to be further explored as a potential second-line chemotherapy option for EC [2].

There is no standard of treatment for recurrent endometrial cancer patients who progressed after first-line chemotherapy (carboplatin and paclitaxel). There are some other available drugs of second- and third-line chemotherapy showing a weak response and poor long-term survival. According to the literature above, efficient treatment for patients in second- or third-line therapy of recurrent EC is an unmet need and studies in this setting are urgent.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Efficacy of combination chemotherapy using irinotecan and nedaplatin for patients with recurrent and refractory endometrial carcinomas: preliminary analysis and literature review.	Miyamoto M et al.	Cancer Chemother Pharmacol.	https://www.ncbi.nlm.nih.gov/pubmed/29124328
2	Efficacy of doxorubicin after progression on carboplatin and paclitaxel in advanced or recurrent endometrial cancer: a retrospective analysis of patients treated at the Brazilian National Cancer Institute (INCA).	Moreira E et al.	Med Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29387971

Novel therapies in endometrial cancer (EC)

Ines Vasconcelos

According to our search, there was only one relevant new novel treatment for EC. There were several clinical trials examining different combinations of chemotherapy and radiotherapy, but these do not represent novel treatments per se and were therefore not included in this summary.

This study was a phase II basket trial examining the anti-tumour activity of perifosine by inhibiting AKT phosphorylation. Recurrent or persistent ovarian, endometrial or cervical cancer patients were assigned to PIK3CA wild-type or mutant groups. Each patient received 600mg oral perifosine on day 1 followed by a maintenance dose of 100mg daily. Sixteen and five ovarian, 17 and 7 endometrial, and 18 and 8 cervical cancer patients with PIK3CA wild-type and mutant, respectively, were enrolled. Disease control rates (wild-type/mutant) were 12.5/40.0%, 47.1/14.3%, and 11.1/25.0% in ovarian, endometrial, and cervical cancer, respectively. The most common grade 3/4 toxicities were anaemia (22.5%) and anorexia (11.3%). Perifosine monotherapy showed good tolerability but expected efficacy was not achieved.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Phase II basket trial of perifosine monotherapy for recurrent gynecologic cancer with or without PIK3CA mutations.	Hasegawa K et al.	Invest New Drugs	https://www.ncbi.nlm.nih.gov/pubmed/28864978

Uterine sarcoma

Marcin Bobiński

Treatment and follow-up

The authors of the phase II study aiming to assess the activity of nivolumab (novel PD-1 inhibitor) in treatment of advanced uterine leiomyosarcoma observed no impact on patients' progression-free survival (PFS) [1]. The analysis of 3,165 uterine leiomyosarcoma cases, based on the SEER database, showed that the patients suffering from uterine-limited, completely resected disease do not benefit from any form of adjuvant treatment, no matter if it is radio-, chemo- or hormonotherapy. The authors recommend that these patients should be only observed with periodic surveillance imaging and physical examinations [2]. Kim et al. published a retrospective single-arm analysis assessing the impact of treatment with pazopanib (tyrosine kinase inhibitor) on patients with metastatic soft tissue sarcoma. In the cohort, the majority of tumours were leiomyosarcoma. The authors reported median PFS and overall survival (OS) of 5.8 and 20.0 months, respectively, which was considered a promising result [3]. Retrospective results of the treatment of peritoneal sarcomatosis by hyperthermic intraperitoneal chemotherapy (HIPEC) combined with cytoreductive surgery (CRS) in 36 patients from seven specialised international centres were presented by Sardi et al. [4]. Nineteen patients recurred. CRS/HIPEC OS at 1, 3, and 5 years was 75%, 53%, and 32%, respectively, with median OS of 37 months. PFS in 32 patients with complete cytoreduction at 1, 3, and 5-years was 67%, 32%, and 32%, respectively, with median PFS of 18.9 months. The authors opt to create a global prospective registry of patients to further assess the efficacy of CRS/HIPEC. Wong et al. published a review regarding the risk of minimally invasive approach to uterine mass [5]. A novel therapeutic approach to unresectable uterine sarcoma was presented by Xia et al. The study aimed to evaluate the treatment with gene therapy using rAd-p53 followed by chemotherapy. Results suggest that this strategy could be considered a promising regimen to achieve resectability of primary unresectable disease (4 out of 12 patients underwent a second debulking surgery) [6].

Diagnostic tools

MRI features allowing the differentiation of uterine myomas with endometrial stromal sarcoma and leiomyosarcoma are discussed in the review by Kim et al. [7]. The research by Kusunoki et al. suggests that PET/CT can be beneficial in cases of unclear results of MRI in differentiation between malignant and benign uterine mass by decreasing the false positive rate [8].

Molecular research

Brunetti et al. detected the novel gene fusion GREB1-NCOA2 in uterine leiomyosarcoma cells RNA. It is thought to play a role in carcinogenesis and progression in this disease [9]. Cuppens et al. presented a panel of patient-derived xenograft models of uterine leiomyosarcoma and carcinosarcoma, based on rodents. Experiments based on these models create an opportunity for further development of new therapies [10].

Varia

The problem of providing sufficient information about the risk of malignancy to patients suitable for to minimally invasive treatment of uterine fibroids was discussed by Seagle et al. Furthermore, they present the doubts and potential threats in the process of obtaining informed consent among these patients [11].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: Results of a phase 2 study.	Ben-Ami E et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28440953
2	Options for adjuvant therapy for uterine leiomyosarcoma.	Friedman CF, Hensley ML	Curr Treat Options Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29417238
3	Pazopanib monotherapy in the treatment of pretreated, metastatic uterine sarcoma: A single-center retrospective study.	Kim HJ et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29185261
4	Multi-institutional study of peritoneal sarcomatosis from uterine sarcoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.	Sardi A et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28967566
5	Reducing the spread of occult uterine sarcoma at the time of minimally invasive gynecologic surgery.	Wong M et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/29128980
6	Treatment of uterine sarcoma with rAd-p53 (gendicine) followed by chemotherapy: Clinical study of TP53 gene therapy.	Xia Y et al.	Hum. Gene Ther	https://www.ncbi.nlm.nih.gov/pubmed/29281902
7	What MRI features suspect malignant pure mesenchymal uterine tumors rather than uterine leiomyoma with cystic degeneration?	Kim TH et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29400019
8	Efficacy of PET/CT to exclude leiomyoma in patients with lesions suspicious for uterine sarcoma on MRI.	Kusunoki S et al.	Taiwan J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28805609
9	RNA-sequencing identifies novel GREB1-NCOA2 fusion gene in a uterine sarcoma with the chromosomal translocation t(2;8)(p25;q13).	Brunetti et al.	Genes Chromosomes Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29218853
10	Establishment and characterization of uterine sarcoma and carcinosarcoma patient-derived xenograft models.	Cuppens T et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28625393
11	Discussing sarcoma risks during informed consent for nonhysterectomy management of fibroids: an unmet need.	Seagle BL et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28951264

Cervical pre-invasive disease

Geanina Dragnea

A meta-analysis of 25 articles found that the pooled prevalence of Epstein-Barr virus (EBV) was higher in patients with carcinoma (43.63%) than in healthy patients (19%) or patients with cervical intraepithelial neoplasia 1 (CIN1) (27.34%) or CIN2/3 (34.67%). Cervical carcinoma occurred four times as often among EBV-positive women as in women without EBV infection (OR = 4.01, $p < 0.001$). Further studies are necessary before the link between EBV and cervical carcinoma can be established [1].

Risk stratification

The predictive value of type-specific HPV in detecting cervical cancer and precancers was analysed in a population-based cohort (1,742 women) Hybrid Capture 2-positive (HC2+). HPV+ women for 16, 31, and 58 types had the highest 10-year cumulative risks of CIN2+ (47.5%, 46.3%, and 34.3%, respectively). These results support the risk-based management of HPV+ women using HPV genotyping [2].

The risk stratification potency of HPV 16/18 E6 oncoprotein (E6) as a triage method for HPV positivity was evaluated on a screening cohort of 1,997 women followed for a 15-year period in approximate five-year intervals with HPV DNA testing (HC2), liquid-based cytology (LBC), visual inspection with acetic acid (VIA). E6 was performed on cervical samples collected from this cohort in 2005 and 2014. Among HPV-positive women in 2005, E6 indicated the lowest positive rate (9.9%) compared to LBC (48.4%) and VIA (28.0%). E6-positive women had a higher prevalence rate (10.3%) and 10-year cumulative incidence rate (53.0%) of CIN3+. Meanwhile, only 4.2% and 2.9% of women with abnormal LBC and positive VIA were diagnosed with CIN3+ in 2005, 23.0% and 16.5% developed to CIN3+ after year 10, respectively. Strong associations were found between precedent and subsequent HPV persistence and E6 oncoprotein expression ($OR^{adjusted} = 40.0$ and 21.2, respectively). E6 oncoprotein could serve as a low-cost, highly specific, strongly indicative point-of-care method in the triage and treatment of HPV-positive women [3].

CIN recurrence

A meta-analysis of 97 studies with 44,446 women treated by excision for CIN2+ revealed that the overall risk of residual or recurrent CIN2+ was 6.6% and was increased with positive compared with negative resection margins (RR 4.8). However, high-risk HPV post-treatment predicts treatment failure more accurately than margin status. The pooled sensitivity and specificity to predict residual or recurrent CIN2+ was 55.8% and 84.4%, respectively, for the margin status, and 91.0% and 83.8%, respectively, for high-risk HPV testing. A negative high-risk HPV test post-treatment was associated with a risk of CIN2+ of 0.8%, whereas this risk was 3.7% when margins were free [4].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Association between Epstein-Barr virus (EBV) and cervical carcinoma: A meta-analysis.	de Lima MAP et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29021084
2	Risk prediction of cervical cancer and precancers by type-specific human papillomavirus: Evidence from a population-based cohort study in China.	Dong L et al.	Cancer Prev Res (Phila)	https://www.ncbi.nlm.nih.gov/pubmed/28916509
3	Risk stratification and long-term risk prediction of E6 oncoprotein in a prospective screening cohort in China.	Zhang Q et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28560716
4	Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis.	Arbyn M et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29126708

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

Surgical treatment of primary and recurrent cervical cancer

Aljosa Mandic and Matteo Morotti

Gupta et al. compared the efficacy and toxicity of neoadjuvant chemotherapy followed by radical surgery versus standard cisplatin-based chemoradiation in patients with locally advanced squamous cervical cancer [1].

Nie et al. compared Robotic-Assisted Radical Hysterectomy (RRH) with Traditional Laparoscopic Radical Hysterectomy (TLRH) in one of the largest single-centre studies of surgical outcomes comparing RRH with TLRH [2]. They enrolled 100 patients into the RRH and 833 patients into the TLRH group. The authors concluded that RRH was superior to TLRH with regard to surgical outcome and may pose a safe and feasible alternative to TLRH. The operating time and lymph node yield is acceptable. Note that patients with a larger lesion size were preferably enrolled in the TLRH treatment group.

Canaz et al. investigated the preoperatively assessable clinical and pathological risk factors associated with parametrial involvement (PMI) in surgically treated stage 1B1–2A2 cervical cancer to decrease the multimodality treatment in early-stage cervical cancer [3]. The authors concluded that endophytic clinical presentation and larger clinical tumour size (> 3cm) are independent risk factors for PMI in stage 1B–2Q cervical cancer. Approximately 78% of patients with a tumour size greater than 3cm and endophytic presentation will require adjuvant chemo-radiation for PMI following radical surgery.

Zhou et al. assessed the prognostic role of postoperative clinicopathological factors in patients with stage 1–2b cervical adenocarcinoma (ADC) [4]. The retrospective study examined 312 patients with stage 1–2b cervical ADC who underwent radical hysterectomy, including pelvic lymphadenectomy. The Cox model identified the number of positive pelvic nodes and age at surgery as independent prognostic factors for survival, and number of positive pelvic nodes and postoperative tumour diameter (≥ 4cm) as independent prognostic factors for relapse. The authors concluded a more aggressive therapeutic strategy different from the current practice in cervical cancer is urgently required for cervical ADC. They point to postoperative tumour diameter as a new prognostic factor and suggested it receive special attention in ADC treatment.

Choi et al. presented the effects of body mass index (BMI) on survival in cervical cancer patients who had undergone surgery and radiotherapy (RT) [6]. They concluded that overweight or obese cervical cancer patients showed poorer survival outcomes than normal-weight or underweight patients.

Buda et al. evaluated the added value of the fluorescence dye indocyanine green (ICG) for sentinel lymph node (SLN) mapping in women with cervical cancer who had undergone previous conisation (stage 1a–1b1) by comparing ICG versus Tc99m radiotracer + blue dye (BD) [5]. The authors concluded that in early-stage cervical cancer patients, conisation had no significant impact on the SLN detection rate using both techniques (ICG and radiotracer ± BD). However, a higher bilateral mapping rate was confirmed using the fluorescent dye ICG rather than the standard techniques.

In recurrent cervical cancer, Ida et al. present a study investigating the accuracy of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) in predicting survival for patients with recurrent cervical cancer [7]. Seventy-nine patients with recurrent cervical cancer after undergoing concurrent chemoradiation therapy (CCRT) or radical hysterectomies with or without CCRT were included. In univariate analysis, NLR, PLR, and PNI were significantly associated with 12-month, 24 month, and overall survival (12 months: $p = 0.021$, $p = 0.001$, and $p < 0.001$; 24 months: $p = 0.020$, $p = 0.008$, and $p < 0.001$; overall; $p = 0.032$, $p = 0.032$, and $p < 0.001$, respectively). In multivariate analyses, PNI was an independent prognostic factor for 12-month, 24-month, and overall survival (P=0.001, P=0.001 and P<0.001, respectively). PNI is a useful predictor of survival of recurrent cervical cancer.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: A randomized controlled trial.	Gupta S et al.	J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29432076
2	Robotic-assisted radical hysterectomy results in better surgical outcomes compared with the traditional laparoscopic radical hysterectomy for the treatment of cervical cancer.	Nie JC et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28858908
3	Preoperatively assessable clinical and pathological risk factors for parametrial involvement in surgically treated FIGO stage IB-IIA cervical cancer.	Canaz E et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28617687
4	Postoperative clinicopathological factors affecting cervical adenocarcinoma: Stages I-IIB.	Zhou J et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/29480826
5	Adverse effect of excess body weight on survival in cervical cancer patients after surgery and radiotherapy.	Choi Y et al.	Radiat Oncol J.	https://www.ncbi.nlm.nih.gov/pubmed/27997788
6	Real-time fluorescent sentinel lymph node mapping with indocyanine green in women with previous conization undergoing laparoscopic surgery for early invasive cervical cancer: Comparison with radiotracer ± blue dye.	Buda A et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29032256
7	Prognostic nutritional index as a predictor of survival in patients with recurrent cervical cancer.	Ida N et al.	Mol Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29435286

Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

Primary treatment

Gupta et al. [1] published the results on a single-centre, randomised, phase III trial on neoadjuvant chemotherapy (NACT) followed by surgery compared to chemoradiation in stage 1b2, 2a or 2b cervical cancer with squamous histology. The inferior 5-year DFS in the NACT+surgery group, 69.3% compared with 76.7% in the concomitant chemoradiation group (HR, 1.38; 95% CI: 1.02–1.87; p = .038), was mainly driven by results in stage 2b. The study was not powered to detect any difference in overall survival (75.4% vs. 74.7%, respectively, HR, 1.025; 95% CI: 0.752–1.398; p = .87). At three months, there were more bladder and rectum toxicities related; however, there was no difference at 24 months. It is worth noting that only 72% of the patients were resected in the NACT+surgery arm and about a 23% required adjuvant treatment, meaning they were treated with three modalities.

Treatment of recurrent disease

Immunotherapy in cervical cancer

Lheureux et al. [2] reported the results of a phase I/II study on the cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibiting agent ipilimumab in metastatic cervical cancer (squamous cell carcinoma or adenocarcinoma). Thirty-four of 42 patients were evaluable, with one partial response (2.9%), 10 stable disease, and 23 progressions. Median progression-free survival was 2.5 months (95% CI: 2.1–3.2months). The induction of PD-L1 on peripheral lymphocytes following ipilimumab may have contributed to immune escape. The predefined response rate of 20% was not reached.

The KEYNOTE-028 trial by Frenel et al. [3] studied pembrolizumab in PD-1 positive cohorts of solid tumours. Twenty-four patients with cervical cancer were enrolled. After a median follow-up time of 11.0 months, 17% of the patients had responded. In all, 13% had stable disease. A median OS of 11 months and a 6-month OS rate of 67% indicated the potential of pembrolizumab in the treatment of this disease. For comparison, second-line chemotherapy regimens tested in previous GOG studies have produced response rates of 0–19%.

Review

Gadduci and Guerrieri [4] published a more general overview of the current evidence on immune checkpoint inhibitors in gynaecological malignancies, including cervical cancer.

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No	Title	Authors	Journal	Link to abstract
1	Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: A randomized controlled trial.	Gupta et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29432076
2	Association of ipilimumab with safety and antitumor activity in women with metastatic or recurrent human papillomavirus-related cervical carcinoma.	Lheureux S et al.	JAMA Oncol	https://www.ncbi.nlm.nih.gov/pubmed/ 29145543
3	Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: Results from the phase Ib KEYNOTE-028 trial.	Frenel et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/ 29095678
4	Immune checkpoint inhibitors in gynecological cancers: Update of literature and perspectives of clinical research.	Gaducci and Guerrieri	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/ 29061774

Radiotherapy in the management of primary cervical cancer

Vishal Bahall

Hata et al. reviewed 20 women who received radiation to the pelvis for bone metastases secondary to cervical cancer [1]. All patients received a total dose of 60.2Gy (2Gy per fraction-equivalent dose). They found an overall survival (OS) of 34% in one year and 8% at two years. They concluded that radiation therapy is effective in relieving pelvic symptoms and a curative dose should be used if women are expected to live more than a year.

Cho et al. compared the prognostic potential of haemoglobin, absolute neutrophil count, and absolute lymphocyte count with that of squamous cell carcinoma antigen in 152 women who were treated with concurrent chemoradiotherapy for squamous cell carcinoma [2]. Patients with both anaemia and lymphopenia during concurrent chemoradiotherapy showed poor survival, independent of mid-squamous cell carcinoma antigen.

Kwak et al. reviewed 136 women (68 receiving IMRT (intensity-modulated radiotherapy) and 68 receiving CT (conventional radiotherapy)) [3]. They reported no statistically significant difference in the incidence of chronic GI toxicity, but the conventional RT group had a higher incidence of grade 3 chronic GI toxicity.

Laan et al. reviewed 515 women to evaluate the frequency and risk factors for severe late bowel toxicity after curative radiotherapy in women treated for locally advanced cervical cancer. In all, 59 women developed severe late bowel toxicity [4]. They found that the following factors were significantly associated with severe late bowel toxicity: smoking, severe acute bowel toxicity, previous major abdominal surgery, hypertension, parametrial boost, low socioeconomic status, and low BMI.

Lee et al. reviewed 225 women to assess the association between tumour response in MRI using FIGO classification and clinical outcomes [5]. Of the 225 patients, 112 (49.7%) showed a positive response in post-CRT MRI after a median follow-up time of 36.2 months. These women had a significantly lower rate of para-aortic recurrence (7.5% vs. 12.4%; $p = 0.04$) and distant metastasis (13.2% vs. 27.6%; $p = 0.03$). They concluded that early tumour response evaluation with MRI effectively predicted distant metastases and disease-specific survival.

Yamamoto et al. reviewed 533 women with cervical cancer over a nine-year period to determine the incidence and risk factors for radiation pelvic insufficiency fractures (PIFs) [6]. After a median time of 14 months, 15.8% developed PIF in the irradiated field, with the sacral bone being the most common site. Risk factors for PIF were postmenopausal state, rheumatoid arthritis, and high dose rate intra-cavitary brachytherapy (HDR ICBT).

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Radiation therapy for patients with bone metastasis from uterine cervical cancer: its role and optimal radiation regimen for palliative care.	Hata M et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29374737
2	Prognostic implication of simultaneous anemia and lymphopenia during concurrent chemoradiotherapy in cervical squamous cell carcinoma.	Cho O et al.	Tumour biology	https://www.ncbi.nlm.nih.gov/pubmed/29022484
3	Intensity-modulated radiotherapy reduces gastrointestinal toxicity in pelvic radiation therapy with moderate dose.	Kwak YK et al.	Plos One	https://www.ncbi.nlm.nih.gov/pubmed/28846718
4	Socioeconomic status as an independent risk factor for severe late bowel toxicity after primary radiotherapy for cervical cancer.	Laan JJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29074259
5	Magnetic resonance imaging during definitive chemoradiotherapy can predict tumor recurrence and patient survival in locally advanced cervical cancer: A multi-institutional retrospective analysis of KROG 16-01.	Lee SW et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28935271
6	Pelvic fractures after definitive and postoperative radiotherapy for cervical cancer: A retrospective analysis of risk factors.	Yamamoto K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29055558

Radiotherapy in management of recurrent cervical cancer

Erbil Karaman

Umezawa et al. investigated the efficacy and safety of image-guided high dose-rate (HDR) interstitial brachytherapy (ISBT) for re-irradiation of locally recurrent uterine cervical cancer [1]. They included eighteen patients in the analysis with a median follow-up of 18.1 months. All patients received re-irradiation using HDR-ISBT for local gross recurrence of uterine cervical cancer after definitive or postoperative radiotherapy. A tumour response was obtained in all patients, with radiological and pathological complete remission seen in 12 (66.7%) patients. The 2-year local control, progression-free survival, and overall survival rates for all patients were 51.3%, 20.0%, and 60.8%, respectively. The prognostic factors related with local control were found to be haemoglobin level and maximum tumour diameter. They concluded that image-guided HDR-ISBT for the reirradiation of locally recurrent uterine cervical cancer may play an important role for local tumour control in a subgroup of patients.

An interesting case report published by Feng et al. reported the use of iodine 125 (125I) seed implantation brachytherapy in recurrent cervical cancer [2]. They reported a case of a 47-year-old woman with stage 1b1 cervical cancer treated with radical hysterectomy, left lateral adnexectomy and pelvic lymph node dissection. On follow-up examination, 23 months later, the patient was diagnosed with vaginal invasion and a solitary lump in the cervical stump with a maximum diameter of 38 mm. They applied IMRT and inter-stitial 125I seed implantation combined with six cycles of docetaxel and nedaplatin chemotherapy. The patient's progression-free survival time was 33 months. The response of this patient indicated that 125I seed implantation could be used as a complementary treatment for recurrent cervical cancer.

In a review by Llewelyn et al., re-irradiation of cervical and endometrial cancer was discussed [3]. They stated that re-irradiation historically has been associated with unacceptable toxicity and limited benefit. Recent advances in radiotherapy can change the treatment paradigm to provide new salvage treatments for recurrences of cervical and endometrial cancer. It was reported that stereotactic body radiotherapy (SBRT) now provides the option of radical re-irradiation with local control rates of 50–80% and a low incidence of severe late complications. Also, they stated that image-guided brachytherapy is an effective method for salvaging central pelvic recurrence, although it has resulted in 20–25% severe late toxicity.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Image-guided interstitial high-dose-rate brachytherapy for locally recurrent uterine cervical cancer: A single-institution study.	Umezawa R et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/29275869
2	Intensity-modulated radiotherapy combined with iodine-125 seed implantation in non-central recurrence of cervical cancer: A case report and literature review.	Feng H et al.	Oncol Lett.	https://www.ncbi.nlm.nih.gov/pubmed/28959365
3	Re-irradiation of cervical and endometrial cancer.	Llewelyn M et al.	Curr Opin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28697002

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

Marcin Mardas

Takiguchi et al. studied dasatinib, a Src inhibitor in cervical adenocarcinoma cell lines (HeLa and TCO-2 cells) [1]. The cells were cultured with the addition of anticancer drugs (paclitaxel or oxaliplatin) and dasatinib. Src was activated in the two cell lines, and cell proliferation was significantly suppressed by each anticancer drug in combination with 10 μM dasatinib.

Dan et al. identified the presence of an mTOR inhibitor in an active fraction of the ethyl acetate extract of Streptomyces sp OA293 [2]. The metabolites in the active fraction completely inhibited mTORC1 and thereby suppressed activation of both of its downstream targets, 4E-BP1 and P70S6k, in cervical cancer cells. In addition, it also stalled Akt activation via inhibition of mTORC2. The mechanism of mTOR inhibition overcomes significant drawbacks of well-known mTOR inhibitors such as rapamycin and rapalogs.

Guo et al. presented novel proteasome inhibitor delanzomib (CEP-18770) that exhibited potent pro-apoptotic and cytotoxic effects on a panel of cervical cancer cell lines by blocking proteasomal activity [3]. Delanzomib also significantly sensitised cervical cancer cells to treatment of doxorubicin. Furthermore, proteasome inhibition revealed stabilisation of p53 and p53 transcriptional targets and induction of p38/JNK phosphorylation.

Sato et al. proposed a novel therapeutic approach using an adeno-associated virus (AAV) vector encoding short hairpin RNA (shRNA) against the oncoproteins E6 and E7 (shE6E7) of HPV16, termed AAV-shE6E7 [4]. HPV16-positive cervical cancer cell lines (BOKU, SiHa, and SKG-IIIa cells) and cervical cancer cell-derived tumours in mice were tested for gene transfer efficiency using serotypes of AAV vectors. Following transduction, they observed apoptosis, G1 phase arrest, and cell growth inhibition. The growth of subcutaneously transplanted tumours was markedly inhibited by the single administration of AAV2-shE6E7, and the tumours were almost completely eradicated without any adverse effects.

Jiang et al. evaluated the anticancer activity of fucosterol against a panel of human cancer cell lines and indicated that fucosterol exhibited selective inhibitory activity against HeLa cell line with an IC50 of 40 μM [5]. Fucosterol induced apoptosis and prompted reactive oxygen species mediated alterations in mitochondrial membrane potential. Fucosterol triggered cell cycle arrest of HeLa cells at G2/M and exerted inhibitory effects on cell migration and significantly inhibited the expression levels of key proteins of the PI3K/Akt/mTOR signalling pathway.

Zhang et al. studied anticancer activity of the cucurbitacin 23,24-dihydrocucurbitacin B against a panel of human cervical cancer cell lines [6]. The results indicated that 23,24-dihydrocucurbitacin B inhibited the viability of human cervical cancer cell lines and had an IC50 of 40-60 μM. Additionally, the authors demonstrated that 23,24-dihydrocucurbitacin B induced apoptosis in HeLa cells and caused the cell cycle arrest of HeLa cells at the G2/M. The results indicated that 23,24-dihydrocucurbitacin B significantly decreased the expression of important proteins in the PI3K/Akt/mTOR cascade.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Growth inhibitory effect of the Src inhibitor dasatinib in combination with anticancer agents on uterine cervical adenocarcinoma cells.	Takiguchi E et al.	Exp Ther Med.	https://www.ncbi.nlm.nih.gov/pubmed/29067110
2	Streptomyces sp metabolite(s) promotes Bax mediated intrinsic apoptosis and autophagy involving inhibition of mTOR pathway in cervical cancer cell lines.	Dan VM et al.	Sci Rep.	https://www.ncbi.nlm.nih.gov/pubmed/29434241
3	Novel proteasome inhibitor delanzomib sensitizes cervical cancer cells to doxorubicin-induced apoptosis via stabilizing tumor suppressor proteins in the p53 pathway.	Guo KY et al.	Oncotarget.	https://www.ncbi.nlm.nih.gov/pubmed/29371974
4	Eradication of cervical cancer in vivo by an AAV vector that encodes shRNA targeting human papillomavirus type 16 E6/E7.	Sato N et al.	Int J Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29344635
5	Fucosterol exhibits selective antitumor anticancer activity against HeLa human cervical cell line by inducing mitochondrial mediated apoptosis, cell cycle migration inhibition and downregulation of m-TOR/PI3K/Akt signalling pathway.	Jiang H et al.	Oncol Lett.	https://www.ncbi.nlm.nih.gov/pubmed/29456722
6	Anticancer activity of 23,24-dihydrocucurbitacin B against the HeLa human cervical cell line is due to apoptosis and G2/M cell cycle arrest.	Zhang JX et al.	Exp Ther Med.	https://www.ncbi.nlm.nih.gov/pubmed/29456661

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

Kamil Zalewski

Based on the whole-exome sequencing examination and copy number profiling of 6 HPV (+) and 9 HPV (-) specimens of vulvar squamous cell carcinomas (SCC), Han et al. came to the following conclusions: 1) the overall loads for somatic mutations (total mutations, nonsilent mutations, and driver mutations) are higher in HPV (–) SCCs than in HPV (+) SCCs; 2) the overall loads for copy number alterations (CNAs) (length and number) are not different; and 3) the profiles of driver mutations and CNAs overlap but are not identical. The authors hypothesised that HPV status may not have substantial effects during SCC development [1].

For the first time, Zalewski et al. reported on reference selection for miRNA profiling in plasma of vulvar intraepithelial neoplasia lesions (VIN) and SCC patients. Their analysis of miRNA expression identified hsa-miR-93-5p as the gene that retained the greatest robustness in all the plasma samples analysed (for both VIN and VSCC), hsamiR-93-5p as the most stable reference miRNA for VIN, and hsa-miR-425-5p in plasma samples of patients with VSCC. The authors concluded that a ranking of candidate miRNA stability values for these tumours might serve as a valuable guide for future gene expression studies [2].

Nooij et al. identified not only HPV-related and TP53-related SCCs but also suggested a possible third group of vulvar cancers that are TP53 wild-type and not associated with HPV, based on next-generation sequencing (17 genes), p53 immunohistochemistry, and HPV testing on 36 SCC and 82 VIN samples. A suggested factor for this third pathway may be dysregulation of NOTCH1, a transmembrane receptor involved in many different cell functions: differentiation, proliferation, and apoptosis. In a large cohort of patients with SCC (n = 236) with long-term follow-up, the authors also identified HPV as a significant favourable prognostic factor [3].

Holthoff et al. compared the proteomic profiles of SCCs variants and indicated that a higher expression of collagen subunits and lower expression of STAT1 are associated with a more aggressive SCC variant that is characterised by an infiltrative tumour morphology and a fibromyxoid stromal response. They suggested that a collagen-rich and immune-suppressed microenvironment promotes the aggressiveness of SCC [4].

In a immunohistochemical study on 103 patients, Hecking et al. found that membranous PD-L1 was expressed in a minority (23.3%) of SCC samples, defined by HPV-negativity. Its presence was an independent prognostic factor for poor outcome. The authors suggested that the data supports the notion that vulvar cancer is an immunomodulatory tumour that harnesses the PD-1/PD-L1 pathway to induce tolerance. Immunotherapeutic approaches might have the potential to improve outcome in patients with vulvar cancer and could complement conventional cancer treatment [5].

Based on their retrospective review of a cohort of 58 patients with melanoma originating from gynaecologic sites (MGOS) (vulva, vagina, and cervix), Udager et al. confirmed that MOGS is an aggressive subset of melanoma with an increased rate of local recurrence, metastasis, and death due to disease. In their targeted molecular analysis they identified a subset of MOGS with KIT mutations (particularly exon 11), while BRAF, NRAS, and CTNNB1 mutations were rare or absent [6].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Mutational signatures and chromosome alteration profiles of squamous cell carcinomas of the vulva.	Han MR et al.	Exp Mol Med	https://www.ncbi.nlm.nih.gov/pubmed/29422544
2	Normalizers for microRNA quantification in plasma of patients with vulvar intraepithelial neoplasia lesions and vulvar carcinoma.	Zalewski K et al.	Tumour Biol	https://www.ncbi.nlm.nih.gov/pubmed/29299981
3	Genomic characterization of vulvar (pre)cancers identifies distinct molecular subtypes with prognostic significance.	Nooij LS et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28899974
4	Vulvar squamous cell carcinoma aggressiveness is associated with differential expression of collagen and STAT1.	Holthoff ER et al.	Clin Proteomics	https://www.ncbi.nlm.nih.gov/pubmed/29225558
5	Tumoral PD-L1 expression defines a subgroup of poor-prognosis vulvar carcinomas with non-viral etiology.	Hecking T et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/29190964
6	Gynecologic melanomas: A clinicopathologic and molecular analysis.	Udager AM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28844540

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

Kamil Zalewski

During the period covered by LiFE 7, a number of clinical studies focused on aetiology and the treatment of vulvar intraepithelial neoplasia (VIN) have been published.

Pathology

Goyal et al. systematically examined the expression of tumour suppressor GATA-binding protein 3 (GATA3) in 119 vulvar lesions and neoplasms, including 30 cases of usual-type VIN (uVIN) and 34 cases of differentiated VIN (dVIN) [1]. Moderate to strong GATA3 expression was retained in uVIN whereas partial or complete loss of GATA3 expression in the basal layer with or without loss in the parabasal layer was observed in 88% of dVIN cases. This has also been observed in the majority (87%) of vulvar squamous cell carcinomas (SCC). The authors suggested that downregulation of GATA3 may be an early event during tumourigenesis in dVIN but not in HPV-related uVIN.

Treatment

In their prospective, phase II open, multicentre trial (RT3VIN), Hurt et al. randomised 180 patients to cidofovir (89 total, of whom 41 completely responded to treatment) and to imiquimod (91, of whom 42 completely responded to treatment) [2]. At 18 months, more participants were VIN-free in the cidofovir arm: 94% versus 71.6%. The number of grade 2+ events was similar between treatment arms.

Samuels et al. reported results of the trial testing safety, immunogenicity, and clinical response of a HPV16 E7 DNA vaccine (TTFC-E7SH) in 12 HPV16+ uVIN patients [3]. A low vaccine-induced immune response and no clinical response were observed.

In their systematic review and meta-analysis, Tranoulis et al. reported that patients with vaginal intraepithelial neoplasia (VaIN) treated with 5% imiquimod receive complete response and HPV clearance in 76.5% and 52.5%, respectively, and have relatively low risk for VaIN recurrence [4].

Satmary et al., in their retrospective cohort study of 784 women with a histologic diagnosis of VIN at median follow-up of 89 months, identified 26.3 % of recurrences among treated patients; 25% of them recurred late (up to 16 years) [5]. Independent risk factors for recurrence were: Age > 50 years, immunosuppression, metasynchronous vaginal or intraepithelial neoplasia, positive excision margins, and adjacent lichen sclerosus or human papilloma virus. The authors support the follow up of patients with patients with VIN every 6 months for 5 years, then annually thereafter.

Kim et al. analysed the risk of recurrence and progression to invasive vaginal carcinoma in patients with VaIN [6]. Based on the study where 576 patients with VAIN1-3 were included, they concluded that VaIN is at high risk of recurrence and progression but the progression to vaginal cancer was limited to VaIN3/carcinoma in situ cases (3.2%). The risk factors for recurrence and progression included treatment type (observation and topical management) and high-risk HPV positivity. Both laser ablation and excision therapy demonstrated relatively high regression rates.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Differential expression patterns of GATA3 in usual and differentiated types of vulvar intraepithelial neoplasia: potential diagnostic implications.	Goyal A et al.	Mod Pathol	https://www.ncbi.nlm.nih.gov/pubmed/29434343
2	Recurrence of vulval intraepithelial neoplasia following treatment with cidofovir or imiquimod: results from a multicentre, randomised, phase II trial (RT3VIN).	Hurt CN et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/29336101
3	HPV16 E7 DNA tattooing: safety, immunogenicity, and clinical response in patients with HPV-positive vulvar intraepithelial neoplasia.	Samuels S et al.	Cancer Immunol Immunother	https://www.ncbi.nlm.nih.gov/pubmed/28451790
4	Efficacy of 5% imiquimod for the treatment of vaginal intraepithelial neoplasia-—A systematic review of the literature and a meta-analysis.	Tranoulis A et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/28985547
5	Vulvar intraepithelial neoplasia: Risk factors for recurrence.	Satmary W et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29126556
6	Clinical outcomes and risk of recurrence among patients with vaginal intraepithelial neoplasia: a comprehensive analysis of 576 cases.	Kim M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29185264

Primary vulvar cancer treatment

Rubén M. Betoret

Epidemiology

Butt et al. describe a cohort of patients with vulvar squamous cell cancer (VSCC) in a tertiary referral centre in South Africa, where the mean age at diagnosis is around 10 to 15 years less than in high-income countries (50.4 years in the HPV+ group), with a large proportion presenting as advanced-stage disease. [1] Kang et al. assessed trends in the age-specific incidence of vulvar cancer in 13 high-income countries (Canada, the United States, nine European countries, Australia, and Japan), found that the age-standardised incidence rate of VSCC in women of all ages has increased significantly between 1988–1992 and 2003–2007, which was driven by a significant increase in women < 60 years of age. [2] That suggests a secular change in HPV prevalence. The incidence of vulvar cancer is expected to increase in the future due to population growth and an ageing population, but HPV vaccination is likely to counteract the increase to some extent, particularly at younger ages, depending on vaccination coverage.

Surgical management

Arvas et al. present data on the impact of surgical margins on recurrence showing a higher rate of local recurrences in the subgroup with less than 2mm margin, compared to those of 2–8 and > 8mm. [3] Zhang et al. present data on the lower rate of complications and therapeutic efficacy of video-endoscopic inguinal lymphadenectomy when compared to conventional open inguinal lymphadenectomy [4]. Lahtinen et al. describe a new technique of sentinel lymph node localization with inguinal intradermal contrast-enhanced ultrasound [5].

Adjuvant treatment

Stecklein et al. evaluate the effectiveness of radiotherapy on local disease control in a subset of 33 VSCC patients with gross inguinal lymph node involvement (median long-axis diameter 2.5cm), as well as its low risk for serious long-term toxic effects. [6]

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Vulvar cancer is not a disease of the elderly: Treatment and outcome at a tertiary referral centre in South Africa.	Butt JL et al.	S Afr Med J	https://www.ncbi.nlm.nih.gov/pubmed/29262943
2	Vulvar cancer in high-income countries: Increasing burden of disease.	Kang YJ et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28730615
3	The role of pathological margin distance and prognostic factors after primary surgery in squamous cell carcinoma of the vulva.	Arvas M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29324545
4	A comparative study of video endoscopic inguinal lymphadenectomy and conventional open inguinal lymphadenectomy for treating vulvar cancer.	Zhang M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28885273
5	Preoperative sentinel lymph node localization in vulvar cancer: preliminary experience with inguinal intradermal contrast-enhanced ultrasound.	Lahtinen O et al.	Eur Radiol	https://www.ncbi.nlm.nih.gov/pubmed/29189931
6	Effectiveness of definitive radiotherapy for squamous cell carcinoma of the vulva with gross inguinal lymphadenopathy.	Stecklein SR et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29336837

Treatment of recurrent vulvar cancer

María de los Reyes Oliver Pérez

Squamous cell carcinoma of the vulva (VSCC)

In the period covered by the seventh edition of the LiFE report, two literature reviews on VSCC were selected. Grootenhuis et al. published the first systematic review on prognostic factors for local recurrences in VSSC [1]. Studies reporting prognostic factors specific for local recurrences of VSSC were included. Eligible study designs for inclusion were: randomised controlled trials, controlled clinical trials, case-control studies, cross-sectional studies, and cohort studies. Finally, 22 studies were included with an estimated annual local recurrence rate of 4%. The review shows that for all variables analysed the prognostic relevance for local recurrence of VSSC remains questionable, including these commonly considered as a risk factor of recurrence: tumour-free pathologic margin distance, presence of vulvar lichen sclerosus, groin lymph node metastases, and a variety of primary tumour characteristics. The authors concluded that the current quality of data on prognostic factors for local recurrences does not allow evidence-based clinical decision-making and they suggest further research on prognostic factors to identify high-risk patients and to develop alternative primary and secondary prevention strategies.

Sciacero et al. have performed an extensive review of the role of radiation therapy in VSSC, emphasising the use of intensity- modulated radiotherapy (IMRT) in disease management [2].

Japan Society of Gynaecologic Oncology guidelines

The Japan Society of Gynaecologic Oncology guidelines for the treatment of vulvar and vaginal cancer were also published in this period [3]. It consists of five chapters and five algorithms for the treatment of vulvar and vaginal cancer. Each chapter is divided into parts: clinical questions, recommendations, background, objectives, explanations, and references. Recommendations for recurrent disease are as follows:

- Re-excision should be considered for postoperative localised recurrence
- Radiotherapy should be considered for local unresectable recurrences or recurrences infiltrating adjacent organs (if unirradiated)
- Systemic chemotherapy should be considered for recurrences in the pelvis, with distant metastasis or with multiple lesions
- Best supportive care should be considered if no other effective treatments exists.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: A systematic review.	Grootenhuis NC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29137809
2	The role of radiation therapy in vulvar cancer: review of the current literature.	Sciacero P et al.	Tumori	https://www.ncbi.nlm.nih.gov/pubmed/27443892
3	Japan Society of Gynecologic Oncology guidelines 2015 for the treatment of vulvar cancer and vaginal cancer.	Saito T et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=29159773

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

Anna Dückelmann

In the seventh such case published so far, Abu Jamea et al. describe primary vaginal endometrial stromal sarcoma without association with endometriosis. The patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy, lymph node dissection and received hormone therapy with a good result [1]. Jahanseir et al. examined the clinical, morphologic, immunohistochemical, and molecular cytogenetic features of 11 cases of vulvar dermatofibrosarcoma protuberans (DFSP) [2].

Campaner et al. report two cases of patients presenting with late diagnosed vulvar melanoma. Surgery (wide local excision) remains the best option, albeit without the need for radical procedures. The main prognostic factors include patient's age and tumour site, depth of invasion, presence of ulceration, tumour stage, and occurrence of lymph node metastases [3]. In a series of 13 cases of malignant melanomas of the vulva, PD-L1 expression was detected in 69% [4]. Targeting PD-L1 by selective antibodies may therefore be of benefit in the treatment of these uncommon tumours. A review of women with primary melanoma of the vagina (PMV) summarises the management and prognosis [5]. Surgical excision either by local wide excision or radical surgery with colpectomy with/without exenteration is the mainstay of treatment for women with PMV. Many adjuvant treatment options have been described, including radiotherapy, immunotherapy (mostly interferon-alpha), and chemotherapy (mostly dacarbazine). No data on the clinical value of immune checkpoint inhibitors in PMV have been published so far. The authors recommend molecular characterisation of PMV (PD-1 surface expression, BRAF mutation) for therapeutic options and diagnosis.

In their large report of Bartholin gland cancer, Di Donato et al. analyse clinical and histopathological features and evaluate outcome and prognostic factors. Of 275 reported cases, 30.7% of were squamous cell carcinoma, 29.6% adenoid cystic carcinoma, and 25% adenocarcinomas. Adenocarcinoma histotype and positive lymph node were statistically correlated with worse prognosis. The authors recommend an international reporting system or registries to facilitate the investigation of this rare cancer [6].

It is well known that diethylstilbestrol (DES), the first orally-active non-steroidal synthetic oestrogen, used to prevent miscarriage and other pregnancy complications from 1948 to the early 1970s, is strongly associated with the development of clear-cell adenocarcinoma of the vagina and cervix (CCA) in exposed daughters. Huo et al. provide an update of incidence rates and risks after a 40-year follow-up. The rate of DES-related CCA peaked at age 19; there was a second peak at age 42. DES-related CCA has occurred in those as old as 55 years. CCA risk across birth cohorts was closely correlated with DES prescription over time. The cumulative risk of CCA up to the age of 50 is one per 750 exposed. There is evidence that many of the cases with negative histories were exposed [7].

Torky et al. present a rare case of an infiltrating mammary duct adenocarcinoma in the right labia majora along the nipple line. The most common form is a painless, solitary nodule, originating from the labia majora occurring at the age of 60 or older; this case presented as an ulcer and was treated by wide local excision followed by bilateral inguinofemoral lymphadenectomy and hormonal therapy [8].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Primary low-grade endometrial stromal sarcoma arising in the vagina: report of an unusual case and literature review.	Abu Jamea GA et al.	J Surg Case Rep	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5710654/
2	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
3	Vulvar melanoma: relevant aspects in therapeutic management.	Campaner AB et al.	An Bras Dermatol	https://www.ncbi.nlm.nih.gov/pubmed/29186258
4	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
5	Melanoma of the vagina: Case report and systematic review of the literature.	Rapi V et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29187473
6	Bartholin gland cancer.	Di Donato V et al.	Crit Rev Oncol Hematol	https://www.ncbi.nlm.nih.gov/pubmed/28807231
7	Incidence rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix: Update after 40-year follow-up.	Huo D et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28689666
8	Infiltrating mammary duct adenocarcinoma in the right labia majora along the milk-line.	Torky HA et al.	Z Geburtshilfe Neonatol	https://www.ncbi.nlm.nih.gov/pubmed/28915525

Treatment of primary vaginal cancer

Elis Ismail

The prognosis of women with primary vaginal melanoma (PVM) is poor and there is no standardised therapy for this type of malignancy. Rapi et al. presented a case of a 72-year-old woman with PVM (cT2, pN0, M0) and systematic literature review on this topic where they identified 805 cases of PVM [1]. This paper is described in the chapter by Anna Dückelmann on vulvovaginal adenocarcinoma/melanoma/sarcoma.

Fedus et al. presented a case report of the patient with a primary squamous cell carcinoma (SCC) in prolapsed vagina with bladder involvement. The authors underlined that primary vaginal SCC in a prolapsed vagina may be misinterpreted as decubitus and it may delay proper diagnosis and treatment. In the article by Babrovic et al., a case of primary vaginal carcinosarcomas (VCS) associated with differentiated squamous intraepithelial neoplasia in a postmenopausal patient with complete uterine prolapse was presented [3]. Here, the authors also emphasise the diagnostic problems that can be encountered and point to the need for systemic presentation of the case to help pathologists to provide proper diagnosis.

Another group presented a case of patient with vaginal sarcoma (VS) treated with radiation therapy aiming to control the symptoms and to cause tumour reduction prior to posterior pelvic exenteration with intraoperative radiotherapy [4]. The authors also discussed the strategies of managing advanced VS. One of the groups described the case of robot-assisted anterior pelvic exenteration in vulvovaginal malignant melanoma (bilateral inguinal and pelvic lymphadenectomy, en bloc resection of the bladder, uterus, vagina, and vulva through abdominal and perineal approaches) [5]. Diao et al. presented a study aiming to assess the feasibility and efficacy of irinotecan and cisplatin in the neoadjuvant management of patients with vaginal SCC. The authors described three patients for whom such treatment decreased the size of the tumour, induced tumour regression, or even achieved pathologically-confirmed complete tumour eradication [6].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Melanoma of the vagina: Case report and systematic review of the literature.	Rapi V et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29187473
2	Primary vaginal squamous cell carcinoma with bladder involvement in uterine prolapsed patient: Case report.	Fedus T et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/29390294
3	Primary carcinosarcoma of the vagina associated with differentiated squamous intraepithelial neoplasia in a patient with complete uterine prolapse: Case report and review of the literature.	Babarović E et al.	Int J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/29207889
4	When an unexpected diagnosis occurs: A vaginal premenopausal sarcoma.	Marcos-Figueiredo P et al.	Rev Bras Ginecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/29341035
5	Robot-assisted anterior pelvic exenteration in vulvovaginal malignant melanoma.	Kim SI et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29276058
6	Effects of neoadjuvant chemotherapy on patients with primary vaginal squamous cell carcinoma.	Diao Y et al.	Mol Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28894577

Sentinel node mapping in gynaecological malignancies

Anton Ilin

Vulvar cancer

When both Tc-99 and blue dye are used for sentinel lymph node (SLN) assessment, scintigraphy is used to identify suspicious lymph nodes (LN) before surgery. PET-CT may help to select node-negative patients to SN procedure, who would otherwise not be suitable for the procedure due to tumour size, etc. Garganese et al. reported the result of the GroSNa-PET study. Forty-seven patients entered the study for a total of 73 groins, with a negative predictive value of 93%. The authors concluded that PET/CT allows a reliable assessment of LN status and may be an effective support for the selection of patients who are safe candidates for SNL biopsy [1].

Endometrial cancer

Buda et al. evaluated the survival outcomes of two different strategies in apparent uterine-confined disease by comparing sentinel lymph node (SLN) mapping and selective lymphadenectomy (LD). In all, 802 women (LD = 392, SLN = 410) who underwent surgical staging for preoperative stage 1 endometrial cancer were reviewed. Disease-free survival curves did not show a statistically significant difference between centres and strategies adopted (SLN mapping, LD, SLN + LD), with an HR of 0.87 (95% CI: 0.63–2.16; p = 0.475). Applying an SLN algorithm does not impair the prognosis of endometrial cancer patients [2].

Persson et al. described a reproducible, anatomically based surgical algorithm for the detection of pelvic sentinel lymph nodes in endometrial cancer patients. The bilateral detection rate, including tracer reinjection, was 96% [3]. Another novel algorithm proposed by Tanner et al. allows the decrease of unnecessary side-specific and overall pelvic lymphadenectomy rates comparing to NCCN guidelines in low-grade endometrial cancer patients. Similar to the NCCN algorithm, in patients who underwent successful identification of bilateral SLNs, no further resection of normal-appearing lymph nodes was performed. In patients who failed to map bilaterally, intraoperative frozen-section analysis of the uterus was performed (i.e., "Mayo criteria"). Ipsilateral completion pelvic lymphadenectomy was performed only if high-risk features were present in the uterine specimen (defined as grade 3 tumour, outer half myometrial invasion, or tumour > 2cm in diameter). The study included 113 patients. Using Tanner's technique, side-specific and overall PLND rates were 5.3% and 7.1%, respectively. If all patients with failed mapping had undergone PLND according to the NCCN algorithm, side-specific and overall PLND rates would have been higher, 12.4% and 18.6%, respectively (p = 0.01) [4].

Baiocchi et al. determined the impact of sentinel lymph node (SLN)-mapping on the staging of high-risk endometrial cancer (endometrioid grade 3, serous, clear cell, carcinosarcoma, deep myometrial invasion, or angiolymphatic invasion). Overall sensitivity of 90%, a negative predictive value of 95.7%, and a false-negative predictive value of 4.3% was achieved. Only five patients (3.5%) in the N-SLN group had isolated para-aortic node metastases [5].

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No	Title	Authors	Journal	Link to abstract
1	Groin sentinel node biopsy and18F-FDG PET/CT-supported preoperative lymph node assessment in cN0 patients with vulvar cancer currently unfit for minimally invasive inguinal surgery: The GroSNaPET study.	Garganese G et al.	European Journal of Surgical Oncology	https://www.ncbi.nlm.nih.gov/pubmed/28751058
2	The impact on survival of two different staging strategies in apparent early stage endometrial cancer comparing sentinel lymph nodes mapping algorithm and selective lymphadenectomy: An Italian retrospective analysis of two reference centres.	Buda A et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29032824
3	Description of a reproducible anatomically based surgical algorithm for detection of pelvic sentinel lymph nodes in endometrial cancer.	Persson J et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/28751118
4	Use of a novel sentinel lymph node mapping algorithm reduces the need for pelvic lymphadenectomy in low-grade endometrial cancer.	Tanner E et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29056441
5	The impact of sentinel node-mapping in staging high-risk endometrial cancer.	Baiocchi G et al.	Annals of Surgical Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29058141

Prevention and management of complications in surgical treatment of gynaecological malignancies (i.e., lymphocele, urological, wound, etc.)

Elisa Piovano

Surgical site infections (SSI) and colon surgery in gynae-cancer treatment

Schiavone et al. retrospectively evaluated the frequency of SSI in 233 gynaecologic cancer patients undergoing colon surgery before and after implementation of an "SSI reduction bundle": 1) preoperative oral antibiotics with optional mechanical bowel preparation, 2) skin preparation with an antibacterial solution, 3) the use of a separate surgical closing tray. The initiative provided over three-fold reduction in SSI at 30 days post-surgery compared to the pre-implementation group (12% vs. 37%; $p < 0.001$) and wound dehiscence was decreased from 26% to 2% ($p < 0.001$). The intervention remained effective in patients undergoing longer operations and in those with increased blood loss [1].

Another "five-point SSI prevention bundle" was tested by Lippitt et al. in 219 women undergoing surgery for ovarian cancer: 1) preoperative and intraoperative skin preparation with 4% chlorhexidine and intraoperative vaginal preparation with 4% chlorhexidine, 2) preoperative use of oral antibiotics + mechanical bowel preparation, 3) appropriate timing of intraoperative antibiotics, 4) adoption of enhanced sterile surgical techniques for colon procedures and incisional closure, 5) perioperative incision management. Overall, the initiative provided over six-fold reduction in the SSI rate (20% pre-bundle vs. 3 % post-bundle ($p < 0.001$)). Patients who underwent a colon resection pre-bundle had an infection rate of 33% compared with 7% in the post-bundle group ($p < 0.001$). Rates of SSI-related readmission dropped from 13% to 3% ($p = 0.005$) [2].

Avila et al. retrospectively evaluated pelvic infection rates and genitourinary infection rate in 88 women submitted to robotic radical hysterectomy before and after the introduction of a solitary dose of vaginal metronidazole the night before surgery. The pelvic infection rate was significantly higher in nonusers compared with users (13% vs. 0% $p \leq 0.05$). The genitourinary infection rate was also significantly higher in nonusers (20%) as compared with users (2.2%) ($p = 0.02$) [3].

Tozzi et al. retrospectively investigated the morbidity of diverting loop ileostomy (DLI) performed during 47 visceral peritoneal debulkings for stage 3c–4 ovarian cancer with sigmoid-rectum resection (SRR) followed by DLI. They reported the rate, timing, and morbidity of DLI reversal. Stoma-related complications occurred in 46.8%. In all, only 68.1% had their stoma reversed. The primary cause of non-reversal was tumour recurrence/progression (46.7%). Patient's age, length of hospitalisation, complications after VPD, were associated with non-reversal of DLI. The mean time from DLI formation to stoma reversal was six months (± 1.7). Post-reversal related complications occurred in 37.1% of patients. The authors suggest a careful preoperative counselling about these aspects with patients at high risk of bowel resection [4].

Grimm et al. retrospectively investigated risk factors for anastomotic leakage (AL) in patients undergoing primary advanced ovarian cancer surgery and evaluated the prognostic implication of AL on overall survival. AL occurred in 36/518 (6.9%) patients undergoing bowel resection during debulking surgery. One out of three patients had multiple bowel resections. In these patients, AL rate per patient was only slightly higher (9%) than in patients with rectosigmoid resection only (6.9%), despite the higher number of anastomoses. No independent predictive factors for AL were identified. AL was independently associated with shortened overall survival (HR 1.9 [1.2–3.4], $p = 0.01$).

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Surgical site infection reduction bundle in patients with gynecologic cancer undergoing colon surgery.	Schiavone MB et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28734498
2	Outcomes associated with a five-point surgical site infection prevention bundle in women undergoing surgery for ovarian cancer.	Lippitt MH et al.	Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/28885412
3	Preoperative vaginal metronidazole decreases the risk of pelvic infections after radical robotic hysterectomy.	Avila M et al.	Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28763367
4	Morbidity and reversal rate of ileostomy after bowel resection during Visceral -Peritoneal Debulking (VPD) in patients with stage IIIC-IV ovarian cancer.	Tozzi R et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29169615
5	The impact of type and number of bowel resections on anastomotic leakage risk in advanced ovarian cancer surgery.	Grimm C et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28610745

Technical aspects/tricks of surgery in the management of gynaecological malignancies

Elisa Piovano

During the period covered by this edition of the LiFE report, two interesting papers dealing with technical aspects in gynae-onc surgery were published.

Khatib et al. describe the "Çukurova technique" in a case report, a CO_2-assisted technique of stripping the peritoneal surfaces as a part of open cytoreductive surgery for advanced ovarian cancer. With the assistance of an injector needle connected to the insufflator tube (as in laparoscopic surgery), carbon dioxide gas is blown into the right retroperitoneal area and, subsequently, the peritoneum is rapidly stripped up to the right diaphragm. The same procedure can be applied to the diaphragm and meso of the bowels (a surgical video is provided). Gas insufflation causes convenient detachment of the peritoneal surfaces along their anatomical line, facilitating the stripping procedures of all involved peritoneal surfaces, without bleeding, toward the R0 goal. Complications of the CO_2 gas used may not differ from those used in transperitoneal or retroperitoneal laparoscopic procedures. In this report, no perioperative complications were noted; however, it remains unclear if other patients have been treated with this technique. Long-term outcomes have yet to be investigated [1].

Grimm et al. evaluated the efficacy of a collagen-fibrin patch for the prevention of symptomatic and asymptomatic lymphoceles after pelvic lymphadenectomy in women with gynaecologic malignancies in a multicentre, randomised, clinical trial. In it, 164 women were allocated either to bilateral pelvic application of two collagen-fibrin patches or no intervention. Symptomatic lymphoceles were observed in 7.4% women in the intervention group and 3.5% women in the control group ($p = 0.47$). Asymptomatic lymphoceles were observed in 23.5% in the intervention group compared to 21.2% in the control group ($p = 0.85$). In a multivariate logistic regression model, no independent risk factor for the development of a symptomatic lymphocele was identified. The collagen-fibrin patch did not prevent lymphoceles after pelvic lymphadenectomy [2].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	A novel technique: Carbon dioxide gas-assisted total peritonectomy, diaphragm and intestinal meso stripping in open surgery for advanced ovarian cancer (Çukurova technique).	Khatib G et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28720378
2	A collagen-fibrin patch for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malignancies: A randomized clinical trial.	Grimm C et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29395308

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Minimal invasive surgery in gynaecological cancer

Mir Fuad Hasanov

Cervical cancer

Early or same-day discharge (SDD) after benign total laparoscopic hysterectomy is not unusual. A single-institution retrospective cohort study evaluated the safety and feasibility of SDD after laparoscopic radical hysterectomy for cervical cancer. A total of 119 patients were included. Of these, 75 (63%) were SDD patients (mean stay 156.7 ± 50.2min) and 44 (37%) were admitted patients (mean stay 1.2 ± 0.6days).

Ten (13%) SDD patients versus nine (20%) admitted patients sought medical attention within 30 days post-operatively (p = 0.17). Reasons included pain (n = 1), wound concerns (n = 2), vaginal bleeding (n = 2), DVT/VTE (n = 1), fever (n = 2), and fistula (n = 2). Four SDD patients were readmitted within 30 days of surgery (p = 0.25); two required re-operation (p = 0.16).

The investigators conclude that, in general, SDD after laparoscopic radical hysterectomy for cervical cancer is safe, with a low risk of post-operative morbidity and hospital readmission [1].

There are various publications regarding laparoscopic and/or robotic surgery in gynaecological cancers. Colleagues from Korea analysed data of 142 patients with stage 1a1 to 2b cervical cancers who underwent robotic radical hysterectomy (RRH). Patients were divided into two groups (three robotic arms vs. four robotic arms). The three-arm approach showed favourable outcomes over the four-arm approach in terms of postoperative pain at six and 24 hours (3.8 ± 1.8 vs. 4.5 ± 1.7 and 2.8 ± 1.7 vs. 3.4 ± 1.6, respectively; p = .033 and .049) and postoperative haemoglobin difference (1.8 ± 0.9 vs. 2.6 ± 1.3 and 1.9 ± 1.1 vs. 2.4 ± 0.9 on days 1 and 3, respectively; p = .002 and .004). The median length of postoperative hospital stay, total operative time, docking time, lymph node yield, and intraoperative and postoperative complication rates were comparable between the two cohorts. Unfortunately, no cost-benefit analysis was performed [2].

Konstantinidis et al. summarised in a video-illustrated article a stepwise approach to robotic total pelvic exenteration (TPE) in a 70-year-old female Jehovah's Witness with a history of cervical cancer post-chemoradiation and radical hysterectomy who experienced local recurrence at the vaginal cuff involving the rectum and bladder [3].

Endometrial cancer

At the moment, minimally-invasive surgery is the gold standard of the treatment of endometrial cancer. In some cases, operating time is relatively long, especially in obese patients. A group of physicians from MetroHealth Medical Center in Cleveland, USA, analysed the impact of (prolonged) operating time on the occurrence of post-operative complications in patients undergoing minimally-invasive surgery for endometrial cancer. A total of 9,145 patients from the ACS-NSQIP database were included. Operating time ≥ 240 min was associated with increased overall complication rate (11.7% vs. 6%, p < 0.001), medical complication rate (9.3% vs. 4.2%, p < 0.001), and surgical complication rate (3.9% vs. 2.4%, p = 0.001). Notably, lymphadenectomy alone was not associated with increased operative time or increase in complications [4].

A retrospective cohort study by Galotta et al. also shows that the robotic approach is feasible, safe, and has good short-term outcomes, especially in elderly and very elderly gynaecological cancer patients [5].

Ovarian cancer

Near-infrared-guided surgery using ICG (indocyanine green) is rapidly gaining popularity and is already widely used in patients with endometrial and cervical cancer. Buda et al. published a video article with a step-by-step description of the laparoscopic technique in a 31-year-old woman with occult ovarian cancer after simple left ovarian cystectomy. ICG was injected in two separate injections in the proper ovarian ligament and the infundibulopelvic ligament, just below the peritoneum, at a concentration of 1.25mg/mL. Two sentinel lymph nodes (SLN) were identified in the left inframesenteric para-aortic and superficial left common areas and were negative. The authors concluded that the minimally invasive approach in combination with the ICG near-infrared fluorescence system should be prospectively studied in ovarian cancer [6].

An interesting economic analysis was provided by colleagues from the Netherlands together with a randomised controlled trial to evaluate the cost-effectiveness of a diagnostic laparoscopy prior to primary cytoreductive surgery to prevent futile primary cytoreductive surgery (residual tumour > 1cm). Of 201 patients with advanced-stage ovarian cancer in total 102 patients were randomised to laparoscopy and 99 to primary cytoreductive surgery. No significant difference in quality-adjusted life-years (utility = 0.01; 95% CI: 0.006–0.02) was observed. Diagnostic laparoscopy reduced the number of futile laparotomies from 39% to 10%. Costs per laparoscopic intervention were €1,400, making the overall costs of both strategies comparable (difference € – 80 per patient (95% CI: – 470–300)), demonstrating that diagnostic laparoscopy reduced the number of futile laparotomies without increasing total direct medical health care costs, or adversely affecting complications or quality of life [7].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Feasibility and safety of same-day discharge after laparoscopic radical hysterectomy for cervix cancer.	Philp L et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28965697
2	Perioperative outcomes of 3-arm versus 4-arm robotic radical hysterectomy in patients with cervical cancer.	Yim GW et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29287717
3	Robotic total pelvic exenteration: video-illustrated technique.	Konstantinidis I et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28808931
4	Longer operative time is associated with increased post-operative complications in patients undergoing minimally-invasive surgery for endometrial cancer.	Singh S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28982521
5	Robotic surgery in elderly and very elderly gynecologic cancer patients.	Galotta V et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29339300
6	Laparoscopic minimally invasive approach to sentinel lymph node mapping of the ovary using the near-infrared fluorescent S1 HD pinpoint system with indocyanine green dye.	Buda A et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28760628
7	Cost-effectiveness of laparoscopy as diagnostic tool before primary cytoreductive surgery in ovarian cancer.	van de Vrie R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28645428

Cancer in pregnancy

Michael J. Halaska

Out of seven articles, three relevant articles were chosen to be discussed in this report.

Sekine et al. have collected patients diagnosed with malignancy during pregnancy from 760 Japanese institutions between Jan 2008–Dec 2008. Out of 227 analysed patients, the most common cancer types were cervical-, ovarian-, breast-, and haematological cancers: 71.4%, 7%, 6.6%, and 3.1%, respectively. Further several cases of colon, gastric, thyroid, brain, and endometrial cancer were identified. Gynaecological cancers accounted for 79.3 % of all cancer types. Cervical and ovarian malignancies were diagnosed at an early stage, underscoring the importance of regular prenatal visits.

de Haan et al. evaluated the delay in diagnosis in 26 pregnant patients. Ten specialists assessed the medical records of the patients. Delay in the diagnosis or treatment occurred in 65% of cases, mainly caused by health care providers. Afterwards, 65% of pregnancies ended preterm, mostly by induction of delivery (85%). The increase of knowledge of health care providers about the risk of occurrence of cancer during pregnancy is necessary both in terms of early diagnosis and also in treatment options.

Siegler et al. focused on precancerous and invasive cervical lesions. In all, 93 patients diagnosed with high grade lesion during pregnancy were retrospectively analysed. Fifty patients underwent follow-up during pregnancy and surgical procedure after delivery, while 43 patients underwent LOOP excision in the first 15 weeks of gestation. Final histopathology revealed an invasive carcinoma in as many as 5.4% of patients with CIN2/3. Six per cent in the follow-up group were diagnosed with cervical cancer postpartum , and 4.6% in the intervention group. No complications of LOOP excision during pregnancy were observed.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Malignancy during pregnancy in Japan: An exceptional opportunity for early diagnosis.	Sekine M et al.	BMC Pregnancy Childbirth	https://www.ncbi.nlm.nih.gov/pubmed/29422016
2	Cancer related maternal mortality and delay in diagnosis and treatment: A case series on 26 cases.	de Haan J et al.	BMC Pregnancy Childbirth	https://www.ncbi.nlm.nih.gov/pubmed/29301502
3	Should the risk of invasive cancer in pregnancy and the safety of loop electrosurgical excision procedure during the first 15 weeks change our practice?	Siegler E et al.	J Low Genit Tract Dis	https://www.ncbi.nlm.nih.gov/pubmed/28953123

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Immunotherapy in gynaecological cancers

Zoltan Novak

A phase II study compared epacadostat with tamoxifen in biochemical recurrent epithelial ovarian cancer patients. Epacadostat is an indoleamine 2,3-dioxygenase-1 enzyme inhibitor; the latter is a key regulator of immune tolerance in ovarian cancer. The study was terminated because of lack of efficacy. CA125 response was observed in 5% and 16% of epacadostat- and tamoxifen-treated patients, respectively [1]. A case report presented the case of a recurrent ovarian cancer patient treated 14 years ago with one cycle of intraperitoneal chemotherapy and interleukin-2 immunotherapy. The patient showed a complete response and is still in complete remission, showing that combined immunotherapy and chemotherapy might produce a durable clinical response [2]. Another case report presented an endometrial cancer patient who developed pelvic and liver metastases following primary treatment with surgery, chemotherapy, and radiotherapy. Chemotherapy with paclitaxel and cytokine-induced killer cell therapy was initiated. After four cycles of combined therapy, the patient was in complete response with an overall survival of 13.6 months [3].

Immune checkpoint inhibitors

A clinical study evaluated the safety and antitumour activity of ipilimumab in recurrent or metastatic cervical cancer patients and is discussed in the chapter on medical treatment of primary and recurrent cervical cancer by Kristina Lindemann. [4]. Yamashita et al. investigated if endometrial adenocarcinomas with microsatellite-instability (MSI) had an enhanced immune microenvironment and whether MSI could be a predictor of the therapeutic effect of PD-1/PD-L1 immunotherapy. In patients where loss of mismatch repair proteins was found (MSI group), the presence of tumour-infiltrating lymphocytes (CD8+) and PD-L1/PD-1 expression were significantly higher compared to the microsatellite-stable group. The authors confirm that the presence of MSI may be a biomarker for good response to checkpoint inhibitor immunotherapy in endometrial cancer [5]. The following papers reported the association of different molecular markers with immune checkpoint inhibitor treatment efficacy. Lin et al. found that the absence of host PD-L1, PD-L1 blockade remains ineffective in mice-bearing tumour cells with enforced PD-L1 expression; however, PD-L1+/+ antigen presenting cell (APC) transfer enables the therapeutic effect of anti–PD-L1 immunotherapy in mice. The expression of programmed death-ligand 1 (PD-L1) on dendritic cells and macrophages in ovarian cancer and melanoma patients correlated with the efficacy of treatment with either anti-PD-1 alone or in combination with anti-CTLA-4. The authors concluded that PD-L1-expressing dendritic cells and macrophages may mechanistically shape and therapeutically predict the clinical efficacy of PD-L1/PD-1 blockade [6].

Miscellaneous

Abagovomab—an anti-idiotypic mAb that mimics the CA125 protein—failed to demonstrate efficacy in the phase III ovarian cancer trial MIMOSA. The investigators reanalysed the results with special emphasis on the immune status of 111 participants. A robust immune system did not confer a survival advantage per se, but the results showed that a strong immune system was crucial in producing a significant clinical response. The subgroup with a stronger CD8+ T cell activation following enterotoxin B stimulation receiving abagovomab had a better relapse-free survival than both the abagovomab-treated subgroup with less immune activation or the placebo group [7].
An interesting paper reports a patient with relapsed ovarian cancer who exhibited regression of some metastatic lesions with concomitant progression of other lesions during a treatment-free period. They clearly showed that progressing metastases were characterised by immune cell exclusion, whereas regressing and stable metastases were infiltrated by activated T cells. These results suggest that within a single patient multiple distinct tumour immune microenvironments could co-exist, explaining in part the heterogenous response of different metastatic lesions [8]. The following paper used a novel ex vivo expansion technique to generate large amounts of cytotoxic, expanded NK cells from the ascites of ovarian cancer patients. These ascites-derived NK cells are highly cytotoxic against ovarian cancer cells derived from the same patients. The authors propose clinical studies to evaluate the clinical benefit of this immunotherapy [9].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer.	Kristeleit R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28698009
2	Prolonged survival after intraperitoneal interleukin-2 immunotherapy for recurrent ovarian cancer.	Minor DR et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/29034306
3	Clinical effects of autologous cytokine-induced killer cell-based immunotherapy in the treatment of endometrial cancer: a case report and literature review.	Zhang Y et al.	Onco Targets Ther	https://www.ncbi.nlm.nih.gov/pubmed/29026316
4	Association of ipilimumab with safety and antitumor activity in women with metastatic or recurrent human papillomavirus-related cervical carcinoma.	Lheureux S et al.	JAMA Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29145543
5	Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer.	Yamashita H et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/29464025
6	Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression.	Lin H et al.	J Clin Invest	https://www.ncbi.nlm.nih.gov/pubmed/29337305

Immunotherapy in gynaecological cancers

Zoltan Novak

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
7	A robust immune system conditions the response to abagovomab (anti-idiotypic monoclonal antibody mimicking the CA125 protein) vaccination in ovarian cancer patients.	Battaglia A et al.	Immunol Lett	https://www.ncbi.nlm.nih.gov/pubmed/28919454
8	Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient.	Jiménez-Sánchez A et al.	Cell	https://www.ncbi.nlm.nih.gov/pubmed/28841418
9	Ex vivo-expanded NK cells from blood and ascites of ovarian cancer patients are cytotoxic against autologous primary ovarian cancer cells.	Nham T et al.	Cancer Immunol Immunother	https://www.ncbi.nlm.nih.gov/pubmed/29299659
10	Immunotherapy in ovarian cancer.	Odunsi K et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29232467

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Imaging in gynaecologic malignancies

Tanja Nikolova and Natasha Nikolova

Endometrial cancer

Lavaud et al. investigated whether magnetic resonance imaging (MRI) findings could contribute to the prediction of histologic type, tumour grade and lymphovascular space invasion (LVSI) to improve preoperative assessment of endometrial cancer (EC) using the ESMO, ESTRO, and ESGO classification. In 9.1% women, the accuracy of the ESMO-ESGO-ESTRO classification with the inclusion of the MRI short-axis criterion was higher than that of the conventional ESMO classification to predict high-risk recurrence endometrial cancer ($p = 0.02$) [1].

Lee et al. evaluated in a prospective study of 529 patients the role of preoperative MRI in EC patients in identifying a group having a low risk of lymph node metastasis. Preoperative assessment based on MRI and histological analysis can identify low-risk patients, who may be candidates for omitting lymphadenectomy [2].

Gee et al.prospectively assessed the accuracy of PET/CT staging in the detection of distant metastasis in patients with local-regionally advanced cervical cancer (CC), and high-risk EC and compared central and institutional reader performance. Blinded central review of imaging provided improved specificity and PPV for the detection of metastases and should be considered for future oncologic imaging clinical trials [3].

Alcazar et al. compared the diagnostic accuracy of transvaginal ultrasound (TVS) and MRI for detection of myometrial infiltration (MI) in EC. MRI showed a better sensitivity than TVS for detection of deep MI in women with EC. However, the difference observed was not statistically significant [4].

Using the International Endometrial Tumour Analysis (IETA) terminology, Epstein et al., prospectively studied of 1,714 women with EC undergoing a standardised transvaginal grayscale and Doppler ultrasound examination. The obtained features were associated with grade and stage and differ between high- and low-risk EC [5].

Cervical cancer

Morkel et al. analysed patients diagnosed with FIGO stage 3b CC. A whole-body FDG PET/CT was performed before initiation of treatment. PET/CT affected the management of 40% of patients, with 19% requiring a change in the radiation field due to identification of para-aortic nodal involvement and 21% of patients were upstaged [6].

Ovarian Cancer

Lee et al. retrospectively reviewed the medical records of 134 patients with ovarian cancer (OC) who underwent secondary cytoreduction after imaging with either ^{18}F-FDG-PET/CT or contrast-enhanced computed tomography (CECT). ^{18}F-FDG-PET/CT shows higher sensitivity in lesion-based analysis and better accuracy of patient selection for secondary cytoreduction [7].

Merti et al. investigated patients undergoing primary debulking surgery for stage 3c/4 OC with residual disease (RD) ≤ 1.0cm and a preoperative abdominopelvic CT scan. Prognostic significance of abnormal cardiophrenic lymph nodes (CPLNs) and overall survival (OS) was evaluated. Abnormal CPLNs are an important predictor of survival in advanced stage OC [8].

Pascual et al. assessed the natural history of 408 ultrasonographically diagnosed benign ovarian teratomas in asymptomatic women. During follow-up, 31.8% women underwent surgery and histologic diagnosis of tumours removed surgically revealed a benign ovarian teratoma in 79.2% of the women [9]. No case of malignant disease was detected.

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No	Title	Authors	Journal	Link to abstract
1	Preoperative MR imaging for ESMO-ESGO-ESTRO classification of endometrial cancer.	Lavaud P et al.	Diagn Interv Imaging	https://www.ncbi.nlm.nih.gov/pubmed/29472031
2	Role of preoperative magnetic resonance imaging and histological assessment in identifying patients with a low risk of endometrial cancer: a Korean Gynecologic Oncology Group ancillary study.	Lee JY et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/29285310
3	Identification of distant metastatic disease in uterine cervical and endometrial cancers with FDG PET/CT: Analysis from the ACRIN 6671/GOG 0233 multicenter trial.	Gee MS et al.	Radiology	https://www.ncbi.nlm.nih.gov/pubmed/29185901
4	Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: a systematic review and meta-analysis.	Alcázar JL et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29027404
5	Ultrasound characteristics of endometrial cancer as defined by the International Endometrial Tumor Analysis (IETA) consensus nomenclature - A prospective multicenter study.	Epstein E et al.	Ultrasound Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28944985
6	Evaluating the role of F-18 fluorodeoxyglucose positron emission tomography/computed tomography scanning in the staging of patients with stage IIIB cervical carcinoma and the impact on treatment decisions.	Morkel M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29324535
7	Diagnostic value of integrated ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography in recurrent epithelial ovarian cancer: accuracy of patient selection for secondary cytoreduction in 134 patients.	Lee YJ et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29400023
8	Clinical significance of enlarged cardiophrenic lymph nodes in advanced ovarian cancer: Implications for survival.	Mert I et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29129390
9	Long-term results for expectant management of ultrasonographically diagnosed benign ovarian teratomas.	Pascual MA, et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29112653

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Treatment of elderly patients with gynaecological cancers

Alex Mutombo

Ovarian cancer is the most common cause of death from gynaecological cancers in developed countries and a common disease of older women. Thanks to advances in new treatments, mortality from ovarian cancer has declined in developed countries in the last decade [1].

The incidence of endometrial cancer (EC) is increasing, due in part to an aging world population and rise in rates of obesity. Patients with obesity and advancing age are vulnerable populations, as they are both often subject to physician bias regarding surgical choices and assumptions regarding long-term outcomes. Elderly women with EC are at increased risk of local recurrence and cancer-specific death compared to younger women [2]. Therefore, in their review, Hagemann et al. suggest the establishment of standard of care surgery and treatment for the management of obese and elderly patients with EC [3].

In a retrospective analysis of early-stage uterine cancer patients randomised to laparotomy versus laparoscopy, Bishop et al. concluded that laparoscopic staging was associated with decreased postoperative morbidity in patients aged 60 years and above [4]. The FRANCOGYN group conducted a case control study on patterns of care and the survival of elderly patients with high-risk EC. Compared to younger patients, elderly patients had shorter disease-free survival and were less likely treated with lymphadenectomy and chemotherapy [5]. Eggemann et al. reported a retrospective study of 1,550 patients with EC. Elderly women were more likely undertreated because the therapy was not recommended by the physicians based on performance status and medical diseases rather than patient refusal [6]. Older EC patients are less likely to receive adjuvant radiotherapy, and this negatively impacts their survival [2].

Ferrero et al. stated that also elderly epithelial ovarian cancer (EOC) patients can receive adequate treatment, but patients who are older than 75 years are at risk for undertreatment, if not adequately selected. They suggested a pretreatment assessment of frailty with a modified frailty index in the surgical and medical management [7]. Tortorella et al. also reported that older women were underrepresented in EOC clinical trials and frequently received less chemotherapy and are less likely to receive standard of care treatment. This may be mainly due to the lack of evidence and physician's confidence in the management of elderly women with EOC [1]. Some observational studies suggest that statin therapy for cardio-protection is associated with improved survival in cancer patients; a SEER-Medicare analysis demonstrated improvement in overall survival with lipophilic statin use after surgery in elderly patients with EOC [8].

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No	Title	Authors	Journal	Link to abstract
1	Ovarian cancer management in the oldest old: Improving outcomes and tailoring treatments.	Tortorella L et al.	Aging Dis	https://www.ncbi.nlm.nih.gov/pubmed/28966809
2	Disparities in care for elderly women with endometrial cancer adversely effects survival.	Torgeson A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28802765
3	Defining and mitigating the challenges of an older and obese population in minimally invasive gynecologic cancer surgery.	Hagemann AR et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29329881
4	Surgical outcomes among elderly women with endometrial cancer treated by laparoscopic hysterectomy: a NRG/Gynecologic Oncology Group study.	Bishop EA et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29037481
5	Patterns of care and the survival of elderly patients with high-risk endometrial cancer: A case-control study from the FRANCOGYN group.	Rousselin A et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28888799
6	Management of elderly women with endometrial cancer.	Eggemann H et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28666541
7	Ovarian cancer in elderly patients: Patterns of care and treatment outcomes according to age and modified frailty index.	Ferrero A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28763363
8	Statin treatment is associated with survival in a nationally representative population of elderly women with epithelial ovarian cancer.	Vogel TJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28596017

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Nutritional support/status in gynaecological cancer

Fernanda Santos

Malnutrition has been defined as a condition that results from the activation of systemic inflammation by an underlying condition which causes anorexia and tissue breakdown, leading to a significant loss of body weight, alterations in body composition, and declining physical function. Cachexia is a multifactorial wasting syndrome characterised by involuntary weight loss with ongoing loss of skeletal muscle mass with or without loss of fat mass; such wasting cannot be reversed by conventional nutrition care and may lead to functional impairment [1]. Cachexia associated with cancer produces: deterioration of body image, functional status, and quality of life, with a higher risk of toxicity from cancer treatments; loss of muscle mass with risk of heart and respiratory failure and decubitus ulcers; delay in healing that favours fistulas and dehiscences; deterioration of the immune system, which favours infections and the decrease of digestive enzymes with risk of malabsorption. In addition, cachexia and malnutrition have a negative prognostic impact and are associated with up to 30% of cancer deaths [2].

Although evidence of an adequate nutritional assessment and intervention and an improved survival in patients with gynaecologic cancer exists, many health professionals are unaware of it. In the NutriCancer2012 study, the interviewed physicians overestimated the prevalence of malnutrition but underestimated the impact of malnutrition on patients' "quality of life'' [3].

In spite of a lack of sensitivity by some professionals, others argued that there is a lack of human resources and knowledge on nutrition which leads to a series of doubts regarding the nutritional management of cancer patients in the clinical practice [2].

In order to help professionals, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the Academy of Nutrition and Dietetics (AND) developed guidelines on nutritional management for patients with cancer. They recommend screening each patient's nutritional status early in the course of cancer treatment; identifying signs or symptoms of anorexia, cachexia, and sarcopenia as early as possible; measuring body cell or muscle mass precisely by sensitive imaging technologies (computed tomography and others) for early detection of malnutrition/sarcopenia; using specific biomarkers to assess severity of cancer-related systemic inflammation, e.g., C-reactive protein (CRP) and albumin; using indirect calorimetry to estimate resting energy expenditure (REE) in order to personalise energy and protein needs; using nutrition and metabolic support as a vital part of cancer care (some new strategies show promise for reducing inflammation and restoring lean body mass); using nutritional intervention with individualised plans, including care focussed on increasing nutritional intake, decreasing inflammation and hypermetabolic stress, and assessing physical function routinely to monitor and guide physical rehabilitation [1].

A multidisciplinary group of experts in Medical Oncology, Pharmacy, and Nutrition recently reported an expert consensus where they argued that the choice for different nutrition support (nutritional recommendations and hygienic-dietary advice or artificial nutrition, as supplementation with oral enteral nutrition (ONS), enteral nutrition by tube or parenteral nutrition-PN) depends on the patient's diagnosis, treatment, prognosis, nutritional status, nutritional requirements, and duration of nutritional support. The panel stated that PN is indicated mainly when it is not possible to use the digestive tract and/or oral feeding, and/or enteral nutrition is not sufficient or possible. The panel also considers that the nutritional monitoring of the cancer patient should be multidisciplinary and adapted to the characteristics of each centre [2].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	ESPEN expert group recommendations for action against cancer-related malnutrition.	Arends J et al.	Clinical Nutrition	https://www.sciencedirect.com/science/article/pii/S0261561417302285
2	Nutritional support and parenteral nutrition in cancer patients: an expert consensus report.	Virizuela JA et al.	Clinical and Translational Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29043569
3	Malnutrition in patients with cancer: comparison of perceptions by patients, relatives, and physicians-Results of the NutriCancer2012 study.	Gyan E et al.	JPEN J Parenter Enteral Nutr.	https://www.ncbi.nlm.nih.gov/pubmed/29505137

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Epidemiology of gynaecological cancers

Kemal Güngördük

Endometrial cancer

In a large population-based study of 47,555 black women (Black Women's Health Study) there were lower rate ratios (IRR) for endometrial cancer (EC) after ≥ 10 years' duration of oral contraceptive (OC) use compared with never-OC use (multivariable IRR 0.45, 95% CI: 0.27, 0.74), but risk was higher among current users of oestrogen-only pills (IRR 3.72; 95% CI: 1.67, 8.30) and oestrogen + progestin HRT preparations (IRR 1.55, 95% CI: 0.77, 3.10). Risk was not increased among former users of oestrogen-only or oestrogen + progestin female menopausal hormones [1].

A Swedish population-based cohort study including 5,704,154 women reported that tubal ligation was associated with a significantly reduced risk of EC (HR 0.73, 95% CI: 0.65–0.83). Furthermore, when the effect of exposure time was considered, tubal ligation was associated with a significantly reduced risk of EC 10 years or more after the procedure (HR 0.74, 95% CI: 0.65–0.84) [2].

Hartman et al. reported that energy density, glycaemic load, and glycaemic index were not associated with a risk for EC in postmenopausal women [3].

A case-control study carried out in Italy that included 297 cases and 307 controls reported that high vegetable intake (OR 0.34; 95% CI: 0.17–0.68), adherence to the Mediterranean diet (OR 0.34; 95% CI: 0.17–0.68), and a low dietary inflammatory index (OR 3.28; 95% CI: 1.30-8.26) are related to lower endometrial cancer risk [4].

A recent meta-analysis by Lafranconi et al. included 12 case-control and cohort studies. The authors reported that increased coffee consumption is associated with a decreased risk of endometrial cancer (RR 0.79; 95% CI: 0.73–0.87), especially in postmenopausal, obese women. (RR 0.75; 95% CI: 0.63–0.88) [5].

Ovarian Cancer

A large population-based prospective cohort study of 104,318 women demonstrated a strongly reduced risk of ovarian cancer (OC) (OR 0.53; 95% CI: 0.32–0.88) and endometrial cancer (OR 0.22; 95% CI: 0.13–0.40) in those who used or had used levonorgestrel-releasing intrauterine system (LNG-IUS) compared to never-users of LNG-IUS [6].

In the NIH-AARP Diet and Health Study, a population-based case control study, oral contraceptive use was inversely associated with ovarian (HR 0.74; CI: 0.65, 0.84) and endometrial cancer (HR 0.78; CI: 0.70, 0.86) [7]. Long-term exposure pronounced this risk reduction in both cancers [8].

In contrast to some earlier publications, a prospective analysis of the Nurses' Health Study and Nurses' Health Study-II, reported no association between a proinflammatory diet and the risk of OC [9].

In the Million Women Study, nulliparous women had a 24% greater OC risk than women with one child, with significant heterogeneity by histotype. There was no significant increase in serous tumours, a modest increase in mucinous tumours, but a substantial increase in endometrioid (RR 1.49; 95% CI: 1.18–1.89) and clear-cell tumours (RR 1.68; 95% CI: 1.29–2.20). The incremental increase with each additional birth also varied by histotype, with the largest reduction in risk for clear-cell tumours (RR per birth 0.75; 0.65–0.85). There was about a 10% risk reduction per 12-months breastfeeding (RR 0.89; 95% CI: 0.84–0.94), with no significant heterogeneity by histotype, but statistical power was limited [10].

Rice et al. evaluated the association between migraine and OC in the prospective Nurses' Health Study II (NHSII) and the Women's Health Study (WHS). There was no statistically significant association between migraine and OC risk. Only in women < 45 years of age, there was a statistically significant positive association between migraine and OC risk (HR 1.76; 95% CI: 1.01–3.07) [11].

A case-control study including 302 cases and 336 controls and showed anti-Müllerian hormone concentration was not associated with overall OC risk in premenopausal women (OR 0.99; 95% CI: 0.59–1.67) [12].

A population-based case (n = 597) control (n = 742) study of African-American women reported a significant inverse association with OC risk among women who had a tubal ligation at age 35 years or older (OR 0.64; 95% CI: 0.41–0.98), but not among those who had a tubal ligation before age 35 (OR 0.98; 95% CI: 0.74–1.29) [13]. These findings are in line with reports from primarily white populations.

A meta-analysis of 27 studies, including a total of 14,311 women, showed perineal talc use was associated with increased risk of OC (OR 1.31; 95% CI: 1.24–1.39). More than 3,600 lifetime applications (OR 1.42; 95% CI: 1.25–1.61) were slightly more associated with ovarian cancer than < 3,600 (OR 1.32; 95% CI: 1.15–1.50) [14].

The Ovarian Cancer Association Consortium (Babic et al.) showed that severe menstrual pain is associated with a modest, but statistically significant, increase in ovarian cancer risk. Furthermore, among women with severe menstrual pain, ovarian cancer risk increased with higher frequency (RR 1.17; 95% CI: 1.00–1.38) and longer duration of menstrual pain. (RR 1.18; 95% CI: 0.99–1.40) [18]. A potential bias by recall bias or co-existing endometriosis cannot be excluded [15].

The Ovarian Cancer Association Consortium also studied menstrual cycle length and irregularities and OC risk. A case-control study including 16,594 women with invasive ovarian cancer (n = 13,719) or borderline ovarian disease (n = 2,875) and 17,718 controls reported that women with menstrual cycle length > 35 days had a decreased risk of OC compared with women with cycle length ≤ 35 days (OR 0.70; 95% CI: 0.58–0.84). In addition, there is a decreased risk of OC among women with irregular menstrual cycles compared with women with regular cycles (OR 0.83; 95% CI: 0.76–0.89). No significant association was reported between self-reported PCOS and OC risk (OR 0.87; 95% CI: 0.65–1.15). There was a decreased risk of all invasive histotypes for women with menstrual cycle length > 35 days, but no association with serous borderline tumours [26].

Epidemiology of gynaecological cancers

Kemal Güngördük

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Exogenous hormone use and endometrial cancer in U.S. black women.	Sponholtz RT et al.	Cancer Epidemiol Biomarkers Prev.	https://www.ncbi.nlm.nih.gov/pubmed/29475971
2	Association between tubal ligation and endometrial cancer risk: A Swedish population-based cohort study.	Falconer H et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29388208
3	Dietary energy density, glycemic load, glycemic index, and risk for endometrial cancer in the CPS-II nutrition cohort.	Hartman TJ et al	Cancer Epidemiol Biomarkers Prev.	https://www.ncbi.nlm.nih.gov/pubmed/29284671
4	Diet and endometrial cancer: a focus on the role of fruit and vegetable intake, Mediterranean diet and dietary inflammatory index in the endometrial cancer risk.	Ricceri F et al.	BMC Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29132343
5	Coffee decreases the risk of endometrial cancer: A dose-response meta-analysis of prospective cohort studies.	Lafranconi et al.	Nutrients	https://www.ncbi.nlm.nih.gov/pubmed/29120352
6	Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study.	Jareid M et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29482839
7	Oral contraceptive use and risks of cancer in the NIH-AARP diet and health study.	Michels KA et al.	Am J Epidemiol.	https://www.ncbi.nlm.nih.gov/pubmed/29394309
8	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
9	The inflammatory potential of diet and ovarian cancer risk: results from two prospective cohort studies.	Tabung FK et al.	Br J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28772285
10	Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study.	Gaitskell K et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28929490
11	Migraine and invasive epithelial ovarian cancer risk in the Nurses' Health Study II and the Women's Health Study.	Rice MS et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28929486
12	Anti-Müllerian hormone and risk of ovarian cancer in nine cohorts.	Jung S et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28921520
13	Tubal ligation and ovarian cancer risk in African American women.	McNamara C et al.	Cancer Causes Control.	https://www.ncbi.nlm.nih.gov/pubmed/28871344
14	Perineal talc use and ovarian cancer: A systematic review and meta-analysis.	Penninkilampi R et al.	Epidemiology	https://www.ncbi.nlm.nih.gov/pubmed/28863045
15	Menstrual pain and risk of epithelial ovarian cancer: Results from the Ovarian Cancer Association Consortium.	Babic A et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28833087
16	Polycystic ovary syndrome, oligomenorrhea, and risk of ovarian cancer histotypes: Evidence from the Ovarian Cancer Association Consortium.	Harris HR et al.	Cancer Epidemiol Biomarkers Prev.	https://www.ncbi.nlm.nih.gov/pubmed/29141849

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Gestational trophoblastic disease management (pathology, diagnosis, follow-up, pregnancies)

Joanna Kacperczyk-Bartnik

In this brief summary of available literature covering the topic of gestational trophoblastic disease, the results of six retrospective studies, one CRT, one prospective cohort study, and one systematic review are presented.

Treatment

A retrospective study by Zhao et al. aimed to identify which prophylactic management – expectant, prophylactic chemotherapy (P-Chem) or total hysterectomy – is most effective in preventing post-molar gestational trophoblastic neoplasia (GTN) in women older than 40 years. Women after prophylactic total hysterectomy had the lowest incidence of GTN [1].

Another retrospective cohort study by Maestá et al. compared the effectiveness and adverse outcomes of first-line 8-day methotrexate/folinic acid (n = 151) versus one-day methotrexate infusion and folinic acid (n = 174) therapy in patients with low-risk postmolar gestational trophoblastic neoplasia (GTN) [2]. More promising results in terms of efficacy were obtained in the case of the 8-day MTX/FA regimen, however, also with greater toxicity.

A pilot randomised controlled trial by Ayatollahi et al. investigated the need for chemotherapy treatment defined as the number of courses in patients with nonmetastatic GTN in association with different management strategies: repeat uterine curettage (n = 31) and standard care (n = 31) [3]. More promising results with decreased need for chemotherapy were observed in patients who underwent repeat uterine curettage.

A Cochrane systematic review by Wang et al. assessed the effectiveness and safety of P-Chem in prevention of GTN among women with HM, concluding that P-Chem may reduce the risk of progression to GTN in women with complete HMs [4]. At the same time, taking into consideration the possibility of increase in drug resistance, delayed GTN treatment, and toxic side effects, P-Chem cannot routinely be recommended in this population.

A multicentre retrospective cohort study by Braga et al. analysed the outcome of expectant management (n = 47) versus immediate chemotherapy treatment (n = 152) in patients with nonmetastatic gestational choriocarcinoma (GCC), presenting similar results in both groups [5]. The authors concluded that a careful analysis of patients with pathological diagnosis of nonmetastatic GCC is vital in order to avoid exposure to unnecessary chemotherapy.

Wang et al. published retrospective data on the use of selective arterial embolisation in the treatment of haemorrhage accompanying GTN in 41 patients, stating that it was an effective method in bleeding control [6].

Follow-up

Evaluation of the association between hCG levels and indications for chemotherapy in patients after uterine evacuation for complete HM was the aim of the retrospective analysis from Braga et al. [7]. The authors reached the conclusion that hCG ≥20,000 IU/L four weeks following uterine evacuation for complete HM was very predictive of development of post-molar GTN. However, a delay in treatment until hCG plateau or increase did not affect outcomes.

Fertility

A prospective cohort study by Bi et al. aimed to assess the ovarian reserve of 34 patients treated with chemotherapy due to GTN, showing that this treatment affects Anti-Müllerian hormone levels, especially with regimens including etoposide or vincristine [8].

Conversely, Cioffi R et al. concluded in their retrospective study that both single-agent (n = 42) and multiagent (n = 33) chemotherapy can be safely administered to patients with GTN and a desire for childbearing [9].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Comparison of different therapeutic strategies for complete hydatidiform mole in women at least 40 years old: a retrospective cohort study.	Zhao P et al.	BMC Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29121880
2	Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: The New England Trophoblastic Disease Center experience.	Maestá I et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29092742
3	A pilot randomized controlled clinical trial of second uterine curettage versus usual care to determine the effect of re-curettage on patients' need for chemotherapy among women with low risk, nonmetastatic gestational trophoblastic neoplasm in Urmia, Iran.	Ayatollahi H et al.	Int J Womens Health.	https://www.ncbi.nlm.nih.gov/pubmed/29033610
4	Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia.	Wang Q et al.	Cochrane Database Syst Rev.	https://www.ncbi.nlm.nih.gov/pubmed/28892119
5	Is chemotherapy always necessary for patients with nonmetastatic gestational trophoblastic neoplasia with histopathological diagnosis of choriocarcinoma?	Braga A et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29248195
6	Bleeding from gestational trophoblastic neoplasia: embolotherapy efficacy and tumour response to chemotherapy.	Wang Z et al.	Clin Radiol.	https://www.ncbi.nlm.nih.gov/pubmed/28673447
7	Does a human chorionic gonadotropin level of over 20,000 IU/L four weeks after uterine evacuation for complete hydatidiform mole constitute an indication for chemotherapy for gestational trophoblastic neoplasia?	Braga A et al.	Eur J Obstet Gynecol Reprod Biol.	https://www.ncbi.nlm.nih.gov/pubmed/29477553
	Anti-Müllerian hormone levels in patients with gestational trophoblastic neoplasia treated with different chemotherapy regimens: a prospective cohort study.	Bi X et al.	Oncotarget.	https://www.ncbi.nlm.nih.gov/pubmed/29371957
8	Reproductive outcomes after gestational trophoblastic neoplasia. A comparison between single-agent and multiagent chemotherapy: Retrospective analysis from the MITO-9 group.	Cioffi R et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29324534

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Follow-up after gynaecological malignancies

Jenneke Kasius

To determine the significance of different follow-up tests to detect cervical cancer recurrence, Hillesheim et al. performed a retrospective case-control study [1]. Data on the follow-up test results were retrieved from patients' records. A total of 359 patients were included, of whom 34 had symptomatic, and 30 had asymptomatic recurrences. There were abnormal findings on physical examination, cytology, colposcopy, chest X-ray, abdominal ultrasound, abdominal CT scan, or bone scintigraphy in 57.8%, 3.1%, 1.6%, 1.6%, 1.6%, 14.1%, and 6.3%, respectively. The authors conclude that physical examination was the preeminent method and that none of the other tests were sufficient in detecting recurrences in both symptomatic and asymptomatic patients.

A similar study was published by Alexander et al. in patients who underwent follow-up after ovarian cancer treatment [2]. The records of 112 patients were retrospectively reviewed. A recurrence was detected by presenting symptoms, physical examination, Ca125 or imaging in 32.1%, 6.3%, 24.1%, and 34.8%, respectively. The median overall survival time was not significantly different between the detection methods (6.6, 20.7, 26.8, and 17.8 months). Ten different follow-up regimens were compared for their cost-effectiveness. The most cost-effective strategy was thought to be biannual visits, including Ca125 combined with annual imaging.

A survivorship care plan (SCP) is formal document provided at discharge from cancer treatment that contains the individual treatment summary and a tailored follow-up plan. The 2-year-follow-up data of the Registration system Oncological Gynecology (ROGY) care trial were recently published [3]. Included patients were randomly allocated to receive an SCP following cancer treatment or standard care. Health care use was assessed using questionnaires. One hundred twenty-eight patients completed all questionnaires for 24 months. In the first year after diagnosis, the SCP group visited their GP more often than in the standard care group ($\beta = 0.7$, 95% CI: 0.2, 1.2). This difference was not present at two years of follow-up. Particularly, women with anxiety symptoms and women who received radiotherapy had a higher use of GP when receiving an SCP. Also, additional health care was also more often used by the SCP group in the first six months of follow-up (24 vs. 11%, $p = 0.04$). No differences were found in cancer-related specialist care. These findings suggest that the SCP enables women in need of supportive care to seek help from health care providers at an early stage after treatment.

In a systematic review, the role of HE4 in diagnosis, prognosis, and follow-up of ovarian cancer was evaluated [4]. Of the 75 included studies, six studies on HE4 in the follow-up of ovarian cancer were identified, involving 136 patients. No randomised controlled trials were found, and only one was a prospective, controlled study. HE4 was demonstrated to detect a recurrence earlier than Ca125. The lead time was 5–8 months. Moreover, the sensitivity and specificity of HE4 alone or in combination with other markers were higher than the sensitivity and specificity of Ca125 alone. The final conclusion based on the limited available evidence was that HE4 seems to be a better predictor of recurrence in comparison to Ca125.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Cervical cancer posttreatment follow-up: Critical analysis.	Hillesheim I et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28937445
2	Outcomes and cost analysis of surveillance strategies after initial treatment for women with recurrent ovarian cancer.	Alexander VM et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28692633
3	The impact of the survivorship care plan on health care use: 2-year follow-up results of the ROGY care trial.	Jeppesen MM et al.	J Cancer Surviv	https://www.ncbi.nlm.nih.gov/pubmed/28875470
4	The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: a systematic review.	Scaletta G et al.	Expert Rev Anticancer Ther	https://www.ncbi.nlm.nih.gov/pubmed/28756722

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Sexual function in gynaecologic cancer patients and survivors

Stamatios Petousis

Endometrial cancer

Shisler et al. have performed a systematic review examining quality-of-life parameters in patients after an endometrial cancer diagnosis. They included 27 studies, concluding that sexual function is dependent on age, time from diagnosis, and consultation with a physician before engaging in sexual activities. Furthermore, they observed that physical activity intervention resulted in improved sexual interest, but not sexual function. Finally, as a laparoscopic approach was associated with a higher quality-of-life index, this also implies the potential correlation between laparoscopic approach and improved sexual function [1].

Another interesting study was published by Segal et al., even though the study had a retrospective character. The authors studied a retrospective cohort of 149 patients, concluding that those not having received radiation presented with improved sexual function. Furthermore, age, BMI, and radiation exposure were independent predictors of decreased sexual function score [2].

Ovarian cancer

Bober et al. reported on the effects of sexual therapy and rehabilitation after treatment for ovarian cancer. They reported that brief behavioural intervention led to significant improvements in overall sexual functioning and psychological distress [3].

Cervical cancer

Rahman et al. performed a prospective study evaluating quality of life and, therefore, sexual dysfunction before and after treatment for cervical cancer. A total of 90 patients were included. Despite the fact that a significant improvement was found in physical, emotional function, pain, fatigue, and vaginal symptoms, sexual function worsened significantly according to authors [4].

An interesting meta-analysis was also published by Bogani et al. [5]. The authors examined the outcomes of patients undergoing minimally invasive radical hysterectomy with nerve-sparing approach. They observed that these patients have improved sexual dysfunction score. Furthermore, nerve-sparing approach may be oncologically equivalent to radical hysterectomy and may be superior in reducing pelvic floor dysfunction rates. However, they also concluded that the low level of evidence of the included studies warrants randomised trials.

Hofsjö et al. [6] performed a case-control study in patients receiving radiotherapy for cervical cancer and concluded that cervical cancer treatment including radiotherapy is associated with vaginal epithelial atrophy and sexual dysfunction. Therefore, they suggest to start early local oestrogen after therapy to hamper the atrophic process affecting the sexual function.

Finally, Bakker et al. [7] published a multicentre cross-sectional study enrolling 194 patients. They concluded that higher levels of sexual distress were shown to be associated with higher levels of vaginal sexual symptoms, sexual pain worry, relationship dissatisfaction, and body image concerns. Thus, appropriate rehabilitation programs should be developed for cervical cancer survivors to prevent and not only reduce vaginal sexual symptoms.

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Life after endometrial cancer: A systematic review of patient-reported outcomes.	Shisler R et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29150143
2	Urinary incontinence and other pelvic floor disorders after radiation therapy in endometrial cancer survivors.	Segal S et al.	Maturitas.	https://www.ncbi.nlm.nih.gov/pubmed/28396018
3	Improvement in sexual function after ovarian cancer: Effects of sexual therapy and rehabilitation after treatment for ovarian cancer.	Bober SL et al.	Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/28881456
4	Assessment of quality of life in treated patients of cancer cervix.	Rahman Z et al.	J Midlife Health.	https://www.ncbi.nlm.nih.gov/pubmed/29307981
5	Nerve-sparing approach improves outcomes of patients undergoing minimally invasive radical hysterectomy: A systematic review and meta-analysis.	Bogani G et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29191471
6	Radiotherapy for cervical cancer - impact on the vaginal epithelium and sexual function.	Hofsjö A1 et al.	Acta Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29140150
7	Sexual distress and associated factors among cervical cancer survivors: A cross-sectional multicenter observational study.	Bakker RM et al.	Psychooncology.	https://www.ncbi.nlm.nih.gov/pubmed/27862635

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Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis and Dimitris Papatheodorou

Endometrial cancer

In a retrospective study, Fukui et al., reviewed 35 patients with endometrial cancer, treated with 600mg MPA orally on a daily basis for 26 weeks. The association of recurrence-free survival (RFS) was analysed in relation to clinical factors such as age, BMI, and polycystic ovarian morphology (PCOM). Notably, none of the 10 cases with PCOM experienced recurrence under maintenance with oral contraceptives, suggesting that PCOM might be a good prognostic factor in patients achieving CR after MPA therapy for EC [1]. Kawahara et al. conducted a study in a xenograft mouse model to assess the effect of aromatase inhibitors (AI) on endometrial cancer growth or recurrence during ovarian stimulation. Forty mice were allocated to four groups: 1) no ovarian stimulation (control), 2) ovarian stimulation, 3) AI administration + ovarian stimulation, and 4) ovariectomy and ovarian stimulation. Compared to ovarian stimulation alone, significant suppressions of tumour growth were observed in the other three groups ($p < 0.05$) and correlated with oestrogen levels [2]. In a retrospective study by Yamagami et al., the authors assessed repeated MPA therapy in cases of intrauterine recurrence after fertility-preserving therapy of atypical endometrial hyperplasia and grade 1 endometrial carcinoma. Patients were divided into initial treatment and repeated treatment groups (162 and 82 patients, respectively) and oral MPA administration (400–600mg/day) was continued until complete tumour regression. Complete response rates were similar in the two groups, but the size and design of the study do not allow final conclusions regarding the oncological saftey of repeated treatment [3].

Ovarian cancer

In a case series presented by Gouy et al., six patients treated for stage 1 mucinous infiltrative cancer underwent bilateral salpingo-oophorectomy with uterine preservation. Of them, two patients succeeded in getting pregnant, while two presented with recurrence. The authors stated that the results of this short series question the safety of this uterine-preserving strategy [4].

Cervical cancer

In a retrospective study by Sonoda et al., the value of an intraoperative SLN diagnosis in 201 patients during trachelectomy for early-stage cervical cervical cancer was assessed.. The diagnostic sensitivity was higher in 2mm slices along the short axis than on bisection along the longitudinal axis. Imprint cytology correctly diagnosed two patients who had false-negative results on frozen section. The authors stated that the accuracy of intraoperative SLN diagnosis requires improvement, especially in cases where small metastatic foci are present [5].

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No	Title	Authors	Journal	Link to abstract
1	Polycystic ovarian morphology may be a positive prognostic factor in patients with endometrial cancer who achieved complete remission after fertility-sparing therapy with progestin.	Fukui Y et al.	Asian Pac J Cancer Prev	https://www.ncbi.nlm.nih.gov/pubmed/29172287
2	Aromatase inhibitor use during ovarian stimulation suppresses growth of uterine endometrial cancer in xenograft mouse model.	Kawahara T et al.	Hum Reprod	https://www.ncbi.nlm.nih.gov/pubmed/29300901
3	Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility?	Yamagami W et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29400014
4	Is uterine preservation combined with bilateral salpingo-oophorectomy to promote subsequent fertility safe in infiltrative mucinous ovarian cancer?	Gouy S et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/29022007
5	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

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Quality of life in gynaecological cancers/Palliative care

Nadja Taumberger and Engin Celik

Quality of life in the AGO-OVAR 16 trial

The AGO-OVAR 16 trial compared pazopanib versus placebo administration in 940 patients with advanced epithelial ovarian cancer (EOC) after first-line chemotherapy. A secondary end point was the health-related quality of life (HRQoL) to explore if the statistically significant prolongation of progression-free survival with pazopanib is beneficial in terms of HRQoL. They suggested that prolonging progression-free survival may be considered worthwhile, but further studies are required [1].

Physical activity in cancer survivorship

The review from Pennington et al. focused on the role of physical activity in breast and gynaecological cancer survivors in relation to cancer-related symptoms and quality of life (QoL). All reviewed studies suggested that the implementation of regular physical activity improves QoL and cancer-related symptoms during and after treatment [2].

Integrated palliative care for patients with metastatic breast cancer

Rabow et al. compared standalone palliative care (PC) with an outpatient PC program integrated in breast oncology for patients with metastatic breast cancer (MBC). They showed that this interdisciplinary and embedded PC program resulted in earlier PC consultation and high-quality end-of-life care [3].

Palliative care in gynaecologic oncology

The review by Karlin et al. showed that early implementation of palliative care (PC) is associated with less aggressive care at the end of life, increased hospice enrolment, and lower rates of psychological symptoms [4].

Nipp et al. investigated the relationship between patients' physical symptoms with the Edmonton Symptom Assessment System (ESAS) and psychological symptoms with Patient Health Questionnaire 4 (PHQ-4) and health care utilisation. Advanced cancer patients who had unplanned hospital admission (1,036 patients) at Massachusetts General Hospital between 2.9.2014 and 6.5.2016 were included. Physical symptoms (ESAS unstandardised coefficient (B) 0.06 $p < 0.001$), psychological distress (PHQ-4 total: B, 0.11; $p = 0.40$) and depression symptoms (PHQ-4 total : B, 0.22; $p = .014$) were associated with a longer hospital stay. Physical (ESAS hazard ratio 1.01; $p < 0.001$), and anxiety symptoms (PHQ-4 anxiety, hazard ratio 1.06; $p = 0.45$) were associated with a higher risk for readmission [5].

Hui et al. investigated the effect of lorazepam in addition to haloperidol on agitated delirium patients with advanced cancer receiving palliative care. A double-blinded randomised clinical trial conducted at MD Anderson enrolled 93 patients. Lorazepam (3mg iv) was given to 47 patients or placebo to 43 patients in addition to haloperidol (2mg iv), upon onset of an agitation episode. Lorazepam + haloperidol resulted in a higher reduction of Richmond Agitation Sedation Scale score (-4.1 points) than placebo (-2.3 points) (mean difference: -1.9 points (95 % CI: -2.8 to -0.9); $p < 0.001$) [6].

Copenhauer et al. reviewed opioids prescribed to patients with cancer and terminal illness. The authors emphasised that the current WHO, EAPC, NCCN guidelines do not provide support and guidance for prescribing opioids. Current evidence suggests that patients with cancer are at relatively similar risk of misuse, abuse, and addiction as the general population [7].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters—patient-centered end points in trials of maintenance therapy.	Friedlander M et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29267856
2	The role of physical activity in breast and gynecologic cancer survivorship.	Pennington KP et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29395306
3	The value of embedding: integrated palliative care for patients with metastatic breast cancer.	Rabow M et al.	Breast Cancer Res Treat	https://www.ncbi.nlm.nih.gov/pubmed/29086230
4	Palliative care in gynecologic oncology.	Karlin D et al.	Curr Opin Obstet Gynecol	https://journals.lww.com/co-obgyn/Citation/2018/02000/Palliative_care_in_gynecologic_oncology.6.aspx
5	Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: A randomized clinical trial.	Hui D et al.	JAMA	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5661867/
6	Risk management for opioid prescribing in the treatment of patients with pain from cancer or terminal illness: Inadvertent oversight or taboo?	Copenhaver DJ, Karvelas NB, Fishman SM	Anesth Analg	https://www.ncbi.nlm.nih.gov/pubmed/29049111
7	The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer.	Nipp RD et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29057450

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