LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

Reviews covering publications from February 15, 2019 – September 30, 2019

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ENYGO
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Dear colleagues,

We present LiFE 10! It includes reviews of publications in gynaecological oncology dating from February 15, 2019, through September 30, 2019. LiFE is an initiative of ENYGO supported by ESGO.

This issue was supported by reports from our new authors Annemijn Aarts (the Netherlands), Mara Mantiero (Italy), and Seda Şahin Aker (Turkey). We welcome them to the LiFE team. We would like to thank exiting editor David Lindquist again for his work on past issues of LiFE. Our Swedish colleague Zoia Razumova has replaced David on the LiFE editorial team, and we are looking forward working with her in the editorial team.

As indicated after the last LiFE report, we made some substantial changes to the concept. The discussions between our editorial team and *The International Journal of Gynecological Cancer*, especially with editor-in-chief Prof. Pedro Ramirez, were extremely helpful. We have decreased the number of topics and merged some into one (i.e., the chapter on hereditary cancer). We also strengthened the editorial support of our authors in reviewing the selected papers *a priori* to make sure that papers with the highest scientific value are included in LiFE.

Along the lines of the ENYGO session on scientific writing and reviewing at ESGO Congress in Athens, we aim for the continued education of our authors and the ENYGO community.

We are very 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 10 and find it interesting and informative! A special thanks again to all our global community of LiFE authors for their ongoing effort and cooperation in this project.

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

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Ovarian cancer

Endometrial cancer

Cervical cancer

Vulvar cancer

Miscellaneous

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Surgical treatment of primary ovarian cancer

Ilker Kahramanoglu and Patriciu Achimas-Cadariu

An ongoing, Italian, prospective, multicentre trial (SELLY) studies whether sentinel lymph node detection accurately predicts nodal status in patients with apparent early-stage ovarian carcinoma. Women with an apparent FIGO stage I–II epithelial ovarian carcinoma are eligible. Indocyanine green solution is injected into perivascular connective tissue of the infundibulopelvic ligament, and, if the ovary was removed, into the stump of the utero-ovarian ligament when hysterectomy was not previously performed. After sentinel lymph node mapping, systematic pelvic and paraaortic lymphadenectomy is performed. So far, 31 patients have been included in the study and have undergone laparoscopic or robotic surgery. The overall detection rate was 68%. All cases with nodal involvement (n = 4) were identified by sentinel lymph node. The study is slated to enrol 176 patients. The main challenge with sentinel lymph node mapping was spillage and spread of the tracer. A three-step solution was suggested: 1) laparoscopic injection of indocyanine green dye, 2) aspiration while retracting the needle, 3) close view of the lymphatic drainage of the tracer [1].

The ESMO-ESGO consensus guideline on ovarian cancer continues to recommend peritoneal staging surgery, including peritoneal washing, peritoneal biopsies (pelvic peritoneum, paracolic gutters, diaphragm), and omentectomy for early-stage tumours [2]. These guidelines are discussed in more detail under "Systematic treatment of recurrent ovarian cancer". Hengeveld et al. retrospectively evaluated the importance of a complete staging procedure, including peritoneal washings and -biopsies [3]. They used the Danish Gynaecologic Cancer Database and Dutch data collected from a university hospital database between 2005 and 2017. A total of 1,234 patients with apparent early-stage epithelial ovarian carcinoma were included, but only 3% had undergone complete staging surgery. The right diaphragm was the most frequently missed area for random biopsies. Among patients who had complete staging surgery, 21.6% were upstaged. A total of 393 of 1,234 patients (32%) were upstaged. Among them, nine patients were upstaged due to spread to both ovaries, 71 due to involvement on the surface of the ovary, 105 due to tumour cells in the ascites or peritoneal washing, 38 due to tubal involvement, 12 due to spread to uterine serosa, 19 due to positive anterior or posterior cul-de-sac biopsy, 20 due to nodal involvement, 43 due to spread to the omentum. Serous or endometrioid histology and poor grade of differentiation were associated with a higher risk of being upstaged.

Surgical treatment of recurrent ovarian cancer

Canaz et al. evaluated prognostic factors in 42 patients with recurrent low-grade epithelial ovarian cancer identified in five prospective phase II/III NOGGO trials that included a total of 1,050 patients. A platinum-free interval of six months did not have any prognostic value for recurrent low-grade epithelial cancers that are slow-growing and inherently less chemoresponsive. Median progression-free survival in platinum-sensitive versus platinum-resistant was 8.7 months versus 7.6 months (p = 0.91) and overall survival was 23.9 months versus 41.9 months (p = 0.25). When deemed platinum-resistant, patients with low-grade disease still had longer progression-free survival than those with high grade (7.6 months vs 3.6 months, p = 0.03). Secondary cytoreduction to no-gross residual disease was an independent prognostic factor for improved progression-free survival in recurrent low-grade cancers with a multivariate hazard ratio for patients not undergoing SCRS of 12.64 (95% CI: 2.69–59.38, p = 0.001) compared to no residual disease after completion of surgery. Prospective trials are challenging in this rare disease, so this study is a post hoc analysis of five prospective trials with the exclusion of candidates with severe comorbidities. Further, a central pathological review was not performed, and the findings may not be applicable in chemotherapy-naïve patients in first line. [4]

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Sentinel-node biopsy in early-stage ovarian cancer: preliminary results of a prospective multicentre study (SELLY).	Uccella S et al.	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/31082385
2	ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease	Colombo N et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31046081
3	The value of surgical staging in patients with apparent early stage epithelial ovarian carcinoma.	Hengeveld EM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31230820
4	Survival and prognostic factors in patients with recurrent low-grade epithelial ovarian cancer: An analysis of five prospective phase II/III trials of NOGGO metadata base.	Canaz E et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31230821

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Systemic treatment of primary ovarian cancer

Ilker Selçuk and Muhammad Rizki Yaznil

The mEOC/GOG 0241 was a randomised, controlled phase III trial to evaluate four different treatment regimens: Paclitaxel/carboplatin (Pac-Carbo), oxaliplatin/capecitabine (Oxal-Cape), with or without bevacizumab (Pac-Carbo-Bev and Oxal-Cape-Bev) for advanced-stage mucinous epithelial ovarian cancer [1]. A total of 50 patients were included, who had a histological diagnosis of primary mucinous epithelial ovarian cancer, newly diagnosed FIGO stage II–IV disease or recurrence after stage I disease with no previous chemotherapy. After a median follow-up of 59 months, neither of the two experimental regimens with Oxal-Cape or bevacizumab clearly improved overall survival or progression-free survival (all p values ≥ 0.70). Overall survival was numerically superior for Oxal-Cape compared to Pac-Carbo (median 33.9 vs 27.7 months, HR: 0.77, p = 0.48), and similar results were seen for progression-free survival for patients with any of the two bevacizumab-containing regimen (median 18.1 vs 8.8 months, HR: 0.87, p = 0.70). Progression-free survival and overall survival results for all patients were higher than the previous randomised trials (median 16.4 and 27.8 months, respectively). Adding bevacizumab to any of the regimens did not increase progression-free survival or overall survival when compared to the chemotherapy backbone alone. However, the trial was closed prematurely due to poor accrual and was therefore not powered to detect significant differences. Difficulties in recruitment were attributed to challenges with the local pathology evaluation (since only a minority of tumours was confirmed to be primary advanced mucinous epethielal ovarian cancer), the limited funding options for trials in rare cancers, and also a lack of support from the investigators.

Tewari et al. (GOG-218) analysed the final overall survival results of phase III, international, multicentre, double-blind, placebo-controlled randomised trial of bevacizumab for primary treatment of ovarian cancer [2]. A total of 1,873 women with incompletely resected stage III/IV newly diagnosed ovarian, fallopian tube, or primary peritoneal carcinoma were randomly (1:1:1) assigned to intravenous carboplatin and paclitaxel versus chemotherapy plus concurrent bevacizumab (15 mg/kg, cycles 2 to 6) versus chemotherapy plus concurrent and maintenance bevacizumab (cycles 2–22). The median follow-up was 102.9 months. Compared to the control arm, the bevacizumab-concurrent with maintenance arm showed a reduction in the hazard of progression by approximately 28% (median progression-free survival 14.1 vs 10.3 months, respectively; HR: 0.717, 95% CI: 0.625–0.824, p < 0.001). There was no significant difference in the median disease specific overall survival between the groups. The subset analysis showed a significant benefit for stage IV patients with a median overall survival of 42.8 months (HR:0.75, 95% CI: 0.59–0.95) for the bevacizumab concurrent and maintenance arm, compared to a median overall survival of 32.6 and 34.5 months for the control and bevacizumab concurrent arms, respectively.

The PRIMA study analysed the efficacy of niraparib in newly diagnosed stage III/IV high grade serous or endometrioid ovarian cancer after complete or partial response to first-line platinum-based chemotherapy [3]. This randomised, double-blind, phase III study randomised 733 patients (2:1) to oral niraparib 300 mg or placebo within 12 weeks after completion of first-line platinum-based chemotherapy. The median follow-up time was 13.8 months (<1–28m). The median progression-free survival for patients with homologous-recombination deficiency was 21.9 versus 10.4 months for the niraparib and placebo arms, respectively (HR: 0.43, 95% CI: 0.31–0.59, p < 0.001). In the whole population, the median progression-free survival was 13.8 and 8.2 months, respectively (HR: 0.62, 95% CI: 0.50–0.76, p < 0.001).

Vergote et al. performed a randomised, double-blind, phase III trial to assess whether adding trebananib (a peptibody that inhibits binding of angiopoietin 1 and 2 to Tie2) to standard carboplatin and paclitaxel in newly diagnosed advanced ovarian, peritoneal, or fallopian tube cancer improved progression-free survival [4]. This multicentre, international study randomised 1,015 patients 2:1 to platinum-based chemotherapy with trebananib or placebo after primary debulking or interval debulking surgery and maintenance up to 18 months. The median follow-up was 27.4 months. There was no difference in overall survival (46.6 vs 43.6 months for trebananib and placebo groups, respectively; HR: 0.99, 95% CI: 0.79–1.25) or progression-free survival (15.9 months for trebananib and 15.0 months for placebo; HR: 0.93, 95% CI: 0.79–1.09, p = 0.36). Only 12% of the patients included completed the planned maintenance therapy. Even though sufficient power is assumed for the analysis of the primary endpoint progression-free survival, a limitation of the study is its premature closure.

Coleman et al. analysed the addition of veliparib to first-line chemotherapy and as maintenance in newly diagnosed stage III/IV high grade serous ovarian, peritoneal, or fallopian tube carcinoma [5]. This double-blind, phase III, international study randomised 1,140 patients in a 1:1:1 ratio to receive chemotherapy plus placebo followed by placebo maintenance (control), chemotherapy plus veliparib followed by placebo maintenance or chemotherapy plus veliparib followed by veliparib maintenance (veliparib throughout). After a median follow-up of 28 months, progression-free survival in the veliparib-throughout group was significantly prolonged when compared to the control group: For BRCA-mutated patients in the veliparib throughout and control group, progression-free survival was 34.7 months versus 22.0 months, respectively (HR: 0.44, 95% CI: 0.28–0.68, p < 0.001), and in the homologous deficiency cohort 31.9 versus 20.5 months, respectively (HR: 0.57, 95% CI: 0.43–0.76, p < 0.001). In the intention-to-treat population, progression-free survival was 23.5 versus 17.3 months, respectively (HR: 0.68, 95% CI: 0.56–0.83, p < 0.001). A higher incidence of anaemia and thrombocytopenia was found when adding veliparib to chemotherapy. In the intention-to-treat population, patients in the veliparib-throughout group received 84% of the planned carboplatin doses, compared to 91% in the control group. The median number of cycles were the same across all cohorts. It remains uncertain if the efficacy of veliparib is merely based on maintenance treatment; the study did not include a maintenance-only arm.

Systemic treatment of primary ovarian cancer

Ilker Selçuk and Muhammad Rizki Yaznil

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	An international, phase III randomized trial in patients with mucinous epithelial ovarian cancer (mEOC/GOG 0241) with long-term follow-up: and experience of conducting a clinical trial in a rare gynecological tumor.	Gore M et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31005287
2	Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer.	Tewari KS et al.	J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31216226
3	Niraparib in patients with newly diagnosed advanced ovarian cancer.	Gonzalez-Martin A et al.	N Engl J Med.	https://www.ncbi.nlm.nih.gov/pubmed/31562799
4	Trebananib or placebo plus carboplatin and paclitaxel as first-line treatment for advanced ovarian cancer (TRINOVA-3/ENGOT-ov2/GOG-3001): a randomised, double-blind, phase 3 trial.	Vergote I et al.	Lancet Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31076365
5	Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer.	Coleman RL et al.	N Engl J Med.	https://www.ncbi.nlm.nih.gov/pubmed/31562800

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Systemic treatment of recurrent ovarian cancer

Seda Şahin Aker and Mara Mantiero

The QUADRA study evaluated the anti-tumour activity and safety of niraparib in heavily pre-treated recurrent ovarian cancer, regardless of platinum sensitivity and BRCA status. This multicentre, open-label, single-arm, phase II study included 463 patients with high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with three or more previous chemotherapy regimens. Patients received oral niraparib 300 mg once daily until progression or intolerable toxicity. The primary objective of the study was the proportion of patients achieving a confirmed overall response with homologous recombination deficiency (HRD)-positive tumours. The median follow-up for overall survival was 12.2 months. Forty-eight percent of the patients were HRD+, and 19% had a germline or somatic BRCA mutation. The overall response rate in the 47 platinum-sensitive, HRD+, PARP-naive tumours was 28% (95% CI: 15.6–42.6). The median duration of progression-free survival was 5.5 months (95% CI: 3.5–8.2), and the median duration of response was 9.2 months. Sixty-eight percent of patients achieved disease control (95% CI: 53–81). Response rates were lowest in the group of HRD-negative/unknown and platinum-resistant patients (3%). Patients treated in the fourth line had a progression-free survival ratio greater than 1.3, with a mean increase of 4.1 months compared with the preceding progression-free survival. The exploratory analyses to investigate whether patients had any disease stabilisation on niraparib treatment compared with the previous treatments before enrolment in the study were not sufficiently powered. The study concluded that niraparib had favourable activity among women with ovarian cancer, especially in patients with HRD-positive platinum-sensitive disease, including not only patients with BRCA mutations but also those with BRCA wild-type [1].

The AVANOVA2 study compared niraparib + bevacizumab with niraparib alone in patients with platinum-sensitive, PARP-naive, high-grade serous or endometrioid recurrent ovarian cancer. This open-label, randomised, multicentre, phase II study included 103 patients who received niraparib 300 mg on days 1–21, given either alone or combined with thrice-weekly intravenous bevacizumab 15 mg/kg until disease progression. Median follow-up was 16.9 months (IQR 15.4–20.9). Progression-free survival was significantly longer with the combination therapy, with a median of 11.9 months (95% CI: 8.5–16.7) compared to 5.5 months (3.8–6.3) with niraparib alone ($p < 0.0001$). More adverse events were observed with the combination therapy than single-agent niraparib (65% vs 45%). The limitation of this study was the small sample size, the absence of a blinded independent review of response assessment, and the absence of a standard (chemotherapy-based) control group [2].

Lui et al. evaluated the efficacy of the cediranib/olaparib combination compared with olaparib alone in relapsed platinum-sensitive ovarian cancer. This randomised, open-label, phase II study enrolled 90 patients with platin-sensitive high-grade serous or endometrioid cancer or any other high-grade histology with a known germline BRCA mutation. Patients received a combination of cediranib 30 mg daily and olaparib 200 mg twice daily or olaparib monotherapy with olaparib 400 mg twice daily. Progression-free survival was 16.5 months in the combination arm versus 8.2 months in the olaparib monotherapy arm (HR 0.50, 95% CI: 0.30–0.83, $p = 0.006$) but there was no difference in overall survival in the overall study population. However, in gBRCA wild-type/unknown patients there was a statistically significant improvement in progression-free survival (23.7 vs 5.7 months, $p = 0.002$) and overall survival (37.8 vs 23.0 months, $p = 0.047$) with the combination. The limitation of this study was the small sample size. The most common grade III or higher adverse effects were diarrhoea, fatigue, hypertension and were more common in the combination group. [3]

Matulonis et al. compared the efficacy of cabozantinib, a multityrosine kinase inhibitor, with weekly paclitaxel in patients with recurrent ovarian cancer. This open-label, randomised study enrolled 111 patients with a persistent or recurrent ovarian cancer and one to three prior chemotherapy regimens. Patients received cabozantinib 60 mg orally daily or paclitaxel 80 mg/m^2 weekly. There was no difference in median progression-free survival (5.3 months for cabozantinib vs 5.5 months for weekly paclitaxel; HR 1.11, 0.77–1.61, $p = 0.64$). Event-free survival was worse in the cabozantinib arm (3.5 vs 5.0 months, $p = 0.06$). Response rates were lower in the cabozantinib arm (7% vs 24.1%). In this dosing schedule, cabozantinib will not be further developed [4].

PARAGON, a multicentre phase II basket trial, evaluated the activity of anastrozole in post-menopausal women with hormonal receptor positive (cut-off 10%) recurrent or metastatic gynaecological tumours. The primary endpoint was the clinical benefit rate. One of the cohorts included asymptomatic recurrent ovarian cancer with serum CA-125 progression after response to first-line chemotherapy. The clinical benefit rate at three months was observed in 34.6% of patients, with greater benefit in patients with measurable disease (46.7 vs 29.7%) [5]. In patients with hormonal-receptor-positive low-grade and borderline ovarian cancer, the clinical benefit rate at six months was 61%, with a median duration of clinical benefit of 9.5 months (95% CI: 8.3–25.8) [6]. Both studies confirm tolerance of anastrozole. The rate of clinical benefit did not differ significantly between patients with high, low, or intermediate oestrogen receptor histoscores, underlining the need for better predictive factors [5].

The ESMO-ESGO ovarian cancer consensus conference convened a panel of 40 leading experts who updated guidelines for key topics in ovarian cancer. The topics included pathology and molecular biology, early-stage and borderline tumours, and management of advanced or recurrent disease. The guidelines clarified the role of serous tubal intraepithelial carcinoma as a precursor lesion of high-grade serous carcinoma and gave recommendations for staging. Risk-stratified recommendations for the adjuvant treatment of early-stage disease and borderline tumours were given which suggested observation in distinct subgroups of patients. In the advanced setting, the selection criteria for surgery and adjuvant treatment, including the role of hyperthermic intraperitoneal chemotherapy (HIPEC) were clarified. For now, HIPEC should not be considered as standard therapy and should be limited to well-designed prospective RCTs [6].

For recurrent disease, a revised definition of platinum sensitivity was presented, which goes beyond the calculation of time since last platinum-based therapy. Patients should be considered for further platinum therapy when platinum is not contraindicated or they do not have definite resistance. This group is characterised by progression on the last platinum-based chemotherapy or a symptomatic relapse soon after the end of the last platinum-based chemotherapy.

Results of this consensus conference aim to streamline decision-making and improve the quality of care for patients with ovarian cancer across Europe [7].

Systemic treatment of recurrent ovarian cancer

Seda Sahin Aker and Mara Mantiero

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No	Title	Authors	Journal	Link to abstract
1	Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial.	Moore KN et al.	Lancet Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30948273
2	Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial.	Mirza MR et al.	Lancet Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31474354
3	Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer.	Liu JF et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30753272
4	A randomized phase II study of cabozantinib versus weekly paclitaxel in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study.	Matulonis UA et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30587441
5	PARAGON (ANZGOG-0903): a phase 2 study of anastrozole in asymptomatic patients with estrogen and progesterone receptor-positive recurrent ovarian cancer and CA125 progression.	Kok PS et al.	J Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31328463
6	PARAGON: A Phase II study of anastrozole in patients with estrogen receptor--positive recurrent/metastatic low-grade ovarian cancers and serous borderline ovarian tumors.	Tang M et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31227223
7	ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease.	Colombo N et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31046081

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Early clinical trials in ovarian cancer

Anna-Maria Schütz

Phase I

Konstantinopoulos et al. performed a multicentre, open-label, phase Ib dose-escalation design on olaparib in combination with alpelisib (an α-specific PI3K inhibitor) for patients with epithelial ovarian cancer. Four dose levels were given orally:

- level 0: alpelisib 250 mg + olaparib 2x 100 mg
- level 1: alpelisib 250 mg + olaparib 2x 200 mg
- level 2: alpelisib 300 mg + olaparib 2x 200 mg
- level 3: alpelisib 200 mg + olaparib 2x 200 mg

Thirty-four patients were enrolled. Dose level 3 with alpelisib 200 mg + olaparib 2 x 200 mg was identified as the maximum tolerated dose. Most common treatment-related adverse events were hyperglycaemia (16%), nausea (9%), and increased ALT concentrations (9%). No treatment-related deaths occurred. Dose-limiting toxic effects included hyperglycaemia and febrile neutropenia. In all, 36% of the patients enrolled achieved a partial response, and 50% had stable disease. The response rates of 33% in germline and somatic BRCA wildtype platinum-resistant patients may confirm the synergy between the two drugs, which was the scientific rationale behind the trial. Preclinical work had indicated that alpelisib inhibits homologous recombination repair) and sensitises ovarian cancer models with de novo or acquired HRR proficiency to PARP. The results presented were largely descriptive, and the observed differences in response in subsets of patients will require a larger, adequately powered study [1].

The TOPACIO/KEYNOTE-162 trial was a multicentre, open-label, single-arm phase I and II study evaluating the safety and efficiency of niraparib in combination with pembrolizumab in patients with metastatic triple-negative breast cancer or platinum-resistant ovarian cancer (irrespective of BRCA mutation status). In the dose escalation part, dose level 1 with 200 mg niraparib orally on day one to 21 + 200 mg pembrolizumab intravenously on day one was defined as the recommended phase II dose. Fifty-three patients with ovarian cancer were enrolled in the phase II part. The objective response rate of the pooled (phase I and II) ovarian cancer population was 18% with 5% complete responses, 13% partial responses, and 47% stable disease. Some 33% had progressive disease. The median duration of response was not reached (range, 4.2 to ≥14.5 months). Subgroup analyses showed an objective response rate of 18% and 19% in the tBRCAmut and tBRCAwt population, as well as a rate of 14% and 19% in the HRD+ and HRD- groups, respectively. This trial showed promising activity for recurrent ovarian cancer patients regardless of tBRCA mutations or tissue HRD status [2].

Phase II

The Keynote-100 trial investigated the antitumour activity and safety of pembrolizumab in a multicentre, open label, phase II study in two cohorts of patients with advanced recurrent ovarian cancer. Patients in cohort A (n = 285) were included after one to three prior lines of treatment, while patients in cohort B had received four to six prior lines (n = 91). Both groups had a platinum- or treatment-free interval of at least three months. Intravenous 200mg pembrolizumab was given thrice-weekly until cancer progression, toxicity, or up to two years. Patients in cohort A showed an objective response rate of 7.4% and 9.9% in cohort B, with a median progression-free survival of 2.1 months for both groups. The median overall survival was 17.6 months for cohort B but was not reached in cohort A. In summary, there was modest activity seen with pembrolizumab as a single agent. Combined positive score (CPS) was studied as a potential predictive biomarker. CPS is defined as the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells x 100. A higher level of PD-L1 expression (CPS ≥10, combined positive score) was predictive of a higher overall response rate compared with a CPS ≥ 1 or <1 in both groups and in the total population, i.e., 3.7% with CPS <1, 10.2 with CPS ≥1 and 16.7% with CPD ≥10 in cohort A. These cut-offs were defined in the training set, and the results in the total population (including the training set) need to be interpreted with caution. Responses did not differ by lines of previous treatment or the degree of platinum sensitivity [3].

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No	Title	Authors	Journal	Link to abstract
1	Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial.	Konstantinopoulos PA et al.	Lancet Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30880072
2	Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma.	Konstantinopoulos PA et al.	JAMA Oncol.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6567832/
3	Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase 2 KEYNOTE-100 Study.	Matulonis UA et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31046082

Treatment of ovarian sex cord stromal and germ cell tumours

Anna Dückelmann

Standard guidelines for the treatment of adult ovarian germ cell tumours differ when compared with those for paediatric germ cell tumours. A retrospective multicentre cohort study in four large British cancer centres on 138 patients younger (28%) and older (72%) than 18 with ovarian germ cell tumours aimed to determine whether reduced toxicity treatment could be extended to adult patients [1]. The study showed that chemotherapy reduced future relapse/progression in dysgerminoma, yolk sac tumours, and mixed germ cell tumours but not in immature teratomas. The authors propose that all adult patients with primary immature teratomas may be managed with surgery alone, in line with paediatric practice.

Recent ESMO guidelines consider grade of differentiation in treatment decisions in patients with immature teratoma and conclude that the need for adjuvant chemotherapy in stage IA G2–G3 and IB–IC is still controversial. The same retrospective study [1] found no significant statistical differences in event-free survival in higher stage disease depending on age and suggested carboplatin-based chemotherapy also in adult patients (< 40 years) and JEB (carboplatin, etoposide, and bleomycin) instead of the BEP (bleomycin, etoposide, and cisplatin) regimen. Additionally, findings suggest that platinum-containing chemotherapy can possibly be avoided in all FIGO stage I adult ovarian germ cell tumour patients, which is in line with ESMO guidelines. The ongoing prospective phase III AGCT1531 study (NCT03067181) is looking at active surveillance of low-risk patients with stage I grade 2, 3 ovarian immature teratoma or low-risk stage I malignant germ cell tumours as well as the following treatment regimen in standard risk paediatric and adult patients with germ cell tumours: Bleomycin, etoposide, and carboplatin versus bleomycin, etoposide, and cisplatin in treatment.

A specific entity of uterine neoplasms resembling ovarian sex cord tumour has been described. We have chosen to include two papers on this entity in this chapter. These are rare mesenchymal neoplasm, molecularly distinct from endometrial stromal sarcoma. In a retrospective review, Dickson et al. showed that uterine tumours resembling ovarian sex cord tumours are defined by recurrent fusions involving NCOA2-3 (Nuclear Receptor Coactivator 2), which is amenable to diagnostic evaluation [2]. Another multicentre study by Goebel et al., using fluorescence in-situ hybridisation and targeted RNA sequencing in a larger sample size (n = 26) [3], confirmed the recurrent NCOA gene fusions in uterine tumour resembling ovarian sex cord tumours. Apart from the small numbers, this finding may help to distinguish uterine tumour resembling ovarian sex cord tumours from endometrial stromal tumours, or ovarian sex cord tumours. Additional studies, with larger cohorts or register-bases analyses, are necessary to investigate the relationship between uterine tumour resembling ovarian sex cord tumours and other uterine neoplasms with NCOA gene fusions.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	A multicentre retrospective cohort study of ovarian germ cell tumours: Evidence for chemotherapy de-escalation and alignment of paediatric and adult practice.	Newton C et al.	European Journal of Cancer.	www.ncbi.nlm.nih.gov/pubmed/30954883
2	Uterine tumor resembling ovarian sex cord tumor: a distinct entity characterized by recurrent NCOA2/3 gene fusions.	Dickson BC et al.	Am J Surg Pathol.	www.ncbi.nlm.nih.gov/pubmed/30273195
3	Uterine tumor resembling ovarian sex cord tumor (UTROSCT): a morphologic and molecular study of 26 cases confirms recurrent NCOA1-3 rearrangement.	Goebel EA et al.	Am J Surg Pathol.	www.ncbi.nlm.nih.gov/pubmed/31464709

Borderline ovarian tumours

Anton Ilin

Matsuo et al. presented a retrospective study of 2,130 mucinous-borderline tumours and 581 invasive well-differentiated mucinous ovarian cancers identified in the Surveillance, Epidemiology, and End Results Programme. The primary endpoint was to compare survival between the two entities; the secondary objective was to describe differences in clinico-pathological characteristics. Women with mucinous ovarian cancers had significantly poorer overall survival and cause-specific survival compared to those with mucinous-borderline tumours (10-year OS rates: 76.1% vs 83.6%, net difference 7.5%, p = 0.008; 10-year rates cause-specific survival: 92.7% vs 97.5%, net difference 4.8%, p = 0.003). Women with mucinous ovarian cancers were older, more likely to be stage T1c, and had smaller tumour sizes compared to women with mucinous-borderline tumours. The most common reason for misclassification may be the fact that mucinous ovarian tumours are heterogeneous entities, and benign-appearing, borderline patterns, and invasive tumours often co-exist within a tumour [1]. This is in line with the continuum of progression from mucinous-borderline tumours to mucinous ovarian cancers triggered by mutations such as in the k-ras oncogene. The study is limited by the lack of central pathological review and a standardised specimen sectioning protocol.

The phase II PARAGON study evaluated the aromatase inhibitor anastrozole in patients with recurrent/metastatic low-grade ovarian cancers and serous borderline ovarian tumours. The study is described in the chapter “Systemic treatment of recurrent ovarian cancer”[2].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Mucinous borderline ovarian tumor versus invasive well-differentiated mucinous ovarian cancer: Difference in characteristics and outcomes.	Matsuo K et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30797590
2	PARAGON: A Phase II study of anastrozole in patients with estrogen receptor--positive recurrent/metastatic low-grade ovarian cancers and serous borderline ovarian tumors.	Tang M et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31227223

Surgical treatment of primary uterine cancer

Piotr Lepka

In a prospective cohort study, Persson et al. assessed the diagnostic accuracy of a surgically and anatomically defined indocyanine-green-based sentinel lymph node algorithm for the detection of lymph node metastases located in the pelvis of high-risk endometrial cancer. The study algorithm was designed to detect exclusively pelvic disease. Only high-volume robotic surgeons (n = 5) having experience of > 100 robotic procedures were involved in the study. Two hundred fifty-seven women were injected with indocyanine green into the cervix and reinjected with the tracer in case of non-display of predefined lymphatic pathways. After robotic removal of sentinel lymph nodes, a pelvic and infrarenal para-aortic lymphadenectomy was performed. The overall algorithm applied in the SHREC trial had the sensitivity to identify pelvic lymph node metastases of 100% (95% CI: 92–100) and a negative predictive value of 100% (95% CI: 98–100). Prior to and after reinjection, the bilateral mapping rate was 82% and 95%, respectively. An incomplete lymphatic mapping was more common in women with lymph node metastases (8/54 vs. 6/203, p < 0.001). There were no adverse events related to injection of indocyanine green or the sentinel lymph node procedure. As only two women (1%) had isolated para-aortic metastases, the authors concluded that in the hands of experienced surgeons, this pelvic sentinel lymph node algorithm has the potential to safely replace lymphadenectomy in high-risk endometrial cancer without the need for para-aortic dissection [1].

Backes et al. evaluated the impact of ultrastaging and robotic sentinel lymph node assessment after cervical injection with isosulfane blue and indocyanine green bilaterally in patients with clinically early stage endometrial cancer. After the sentinel lymph node procedure, all 204 patients underwent complete pelvic lymphadenectomy. Adjuvant treatment was based on regular pathologic assessment of the sentinel lymph nodes (similar to non-sentinel lymph nodes). Ultrastaging was completed remote from the surgery and the results remained blinded to the treating physicians and patients. At least unilateral and bilateral mapping was identified in 184 (90.2%) and 138 (68%) of patients, retrospectively. In patients with successful mapping of a hemipelvis, indocyanine green had higher sentinel lymph node detection rates than isosulfane blue (83% vs 64%, p < 0.0001). Increasing body mass index decreased the chance of successful sentinel lymph node mapping. Applying the sentinel lymph node algorithm with the regular pathologic assessment allowed the detection of positive nodes in 21/23 (91.3%) of patients with the negative predictive value 98.9% (95% CI: 96.01–99.71%). There were an additional 11 patients found with positive SLN with micrometastases or ITCs detected on ultrastaging increasing negative predictive value to 99% (95% CI: 95.1–99.7%) and sensitivity to 94% (95% CI: 80.3–99.3%). As there were no recurrences in patients with isolated tumour cells only, the authors concluded that sentinel lymph node mapping is feasible and a safe alternative for complete lymph node dissection and treatment based on routine sectioning of sentinel lymph nodes (without ultrastaging) did not impair outcomes [2].

Compared in a randomised controlled indocyanine green with methylene blue for sentinel lymph node detection in 132 presumably FIGO stage I endometrial cancer patients. All patients underwent robotic or laparoscopic sentinel lymph node mapping after randomisation for the site of the injection; blue dye on one side of the cervix and indocyanine green on the other side. All procedures were performed by the surgeons with the previous experience of at least 200 cases. The use of indocyanine green instead of methylene blue dye resulted in a 26.5% increase of the proportion of hemipelves with successful sentinel lymph node detection rate [(90.9% if mapped with indocyanine green and 64.4% if mapped with blue dye (p <0.0001)]. The proportion of hemipelves with successful sentinel lymph node detection was similar between indocyanine green and methylene blue. The study has a unique design comparing both dyes within the same patient after injecting a different dye on either side of her cervix. This avoided the potential bias present in studies where patients were injected with both dyes bilaterally (i.e., Backes et al.) because the first dye might facilitate easier mapping with the second dye and showed that lymphatic crossover can occur (3%), which had not previously been demonstrated in vivo [3].

Kessous et al. evaluated in a randomised trial whether a mixture of three tracers (patent blue, indocyanine green, and technetium-99 (Tc99)) perform better than two (indocyanine green and Tc99) in 163 patients with stage I endometrial cancer. All patients underwent robotic-assisted total hysterectomy, bilateral salpingo-oophorectomy, and sentinel lymph node dissection; when sentinel lymph node was not detected ipsilaterally a full lymph node dissection was performed. With the unilateral and bilateral sentinel lymph node detection rates of 97.5% and 81.3% for indocyanine green with Tc99 and 93.5% and 80.5% for all three tracers, it was shown that the addition of blue dye did not improve either the detection rate or the accuracy of sentinel lymph node mapping. Further, the addition of blue might interfere with migration of dye as that the metastatic pickup with triple dye was lower than with double dye (six versus 11 patients), although this did not reach statistical significance (p = 0.23). The study is limited by the fact that the sentinel lymph node ultrastaging was performed in 73 patients (45%) of the studied population and the randomisation method by days of surgery does not completely prevent selection bias. Nevertheless, the authors concluded that one can use only indocyanine green and Tc99 can reduce the risk of allergic reactions while maintaining high detection rates [4].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Pelvic sentinel lymph node detection in high-risk endometrial cancer (SHREC--trial)-the final step towards a paradigm shift in surgical staging.	Persson J et al.	Eur J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31181536
2	Prospective clinical trial of robotic sentinel lymph node assessment with isosulfane blue (ISB) and indocyanine green (ICG) in endometrial cancer and the impact of ultrastaging (NCT01818739).	Backes FJ et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31230614
3	Green versus blue: Randomized controlled trial comparing indocyanine green with methylene blue for sentinel lymph node detection in endometrial cancer.	Rozenholc A et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30902369
4	Triple tracer (blue dye, indocyanine green, and Tc99) compared to double tracer (indocyanine green and Tc99) for sentinel lymph node detection in endometrial cancer: a prospective study with random assignment.	Kessous R et al.	Int J Gynecol Cancer.	https://ijgc.bmj.com/content/29/7/1121

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

Zoia Razumova

Loss of DNA mismatch repair leads to the accumulation of numerous mutations across the genome, creating a molecular phenotype known as microsatellite instability (MSI). This contributes to the development of several cancers, including 20–30% of endometrial cancers. Despite the fact that some patients with cancers associated with microsatellite instability are known to respond well to immune checkpoint inhibition, further therapeutic targets are being investigated. In the period covered by LiFE10, four publications discussed the vulnerability of microsatellite instability cancers cells to be knocked out by WRN, a RecQ family DNA helicase that could potentially be targeted with small molecules.

Behan et al. investigated the role of CRISPR-Cas9 screens (targeting ~18,000 genes) in prioritisation of cancer therapeutic targets [1]. Genome scale CRISPR-Cas9 screens in 324 human cancer cell lines from 30 cancer types, including endometrial cancer, were performed. Furthermore, a data-driven framework was developed to identify cancer therapeutics candidates. The authors shared the study results obtained through the project database called Project Score (https://score.depmap.sanger.ac.uk/) to enable others further identification of vulnerabilities in cancer cells that could be targeted therapeutically. They found that most endometrial cancer cell lines with microsatellite instability were dependent on WRNA and identified it as a promising synthetic target. Although further confirmatory studies are necessary to evaluate the priority targets that were identified, three other groups also recently identified this dependency using cancer cell line screens.

Chan et al. analysed data from two independent large-scale cancer dependency datasets, Project Achilles (genome-scale CRISPR/Cas9 library) and Project DRIVE (RNAi library) and have revealed that WRN inactivation promotes cell death and cell cycle arrest preferentially in microsatellite instability cells and indicated WRN as a synthetic lethal vulnerability and promising drug target for microsatellite instability cancers [3]. They also discussed potential side effects and pointed out that while systemic WRN inhibition could induce complications akin to Werner Syndrome, the manifestations of this syndrome require decades to emerge, suggesting that therapeutic benefits would greatly outweigh risks. The results support previously published data in stating that depletion of WRN induces double-stranded DNA breaks and promotes apoptosis and cell cycle arrest selectively in microsatellite instability models.

Kategaya et al. used a candidate gene approach to examine whether WRN were essential in cancer cells with defects in various DNA repair pathways [3]. Knockdown of both WRN and MLH1 (which is part of the mismatch repair pathway) proved to be synergistic in a non-small-cell lung cancer cell line. The authors concluded that MSI-H cells depend on WRN for their survival and that inhibiting WRN helicase activity may represent a unique therapeutic strategy for patients with cancer with MSI-H tumours.

Finally, Lieb et al. demonstrated that WRN inactivation selectively impaired the viability of MSI-H but not microsatellite stable colorectal and endometrial cancer cell lines. In MSI-H cells, WRN loss resulted in severe genome integrity defects. They developed an algorithm to classify WRN-dependent and WRN-independent cell lines, which identified that WRN dependency negatively correlated with MLH1expression.

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No	Title	Authors	Journal	Link to abstract
1	Prioritization of cancer therapeutic targets using CRISPR–Cas9 screens.	Behan FM et al.	Nature.	https://www.ncbi.nlm.nih.gov/pubmed/30971826
2	WRN helicase is a synthetic lethal target in microsatellite unstable cancers.	Chan EM et al.	Nature.	https://www.ncbi.nlm.nih.gov/pubmed/30971823
3	Werner syndrome helicase is required for the survival of cancer cells with microsatellite instability.	Kategaya L et al.	iScience.	https://www.ncbi.nlm.nih.gov/pubmed/30898619
4	Werner syndrome helicase is a selective vulnerability of microsatellite instability-high tumor cells.	Lieb S et al.	Elife	https://pubmed.ncbi.nlm.nih.gov/30910006/

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

Stamatios Petousis

The multicentre, randomised phase III PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy (two cycles of cisplatin 50 mg/m^2 given intravenously during radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 given intravenously) and radiotherapy (48.6 Gy in 1.8 Gy fractions given five days per week) versus pelvic radiotherapy alone for women with high-risk endometrial cancer. Previously reported efficacy results with a median follow-up of 60.2 months showed a significant 7% improvement in failure-free survival for patients treated with chemoradiotherapy compared with those treated with radiotherapy alone (76% vs 69% at five years) without a significant difference in overall survival (82% vs 77% at five years). They reported on the patterns of recurrence and provided updated survival outcomes with a longer median follow-up of 72 months and with 75% of participants having reached five years of follow-up. This post-hoc analysis of survival outcomes showed that absolute improvement at five years was 5% (HR: 0.70; 95% CI: 0.51–0.97) for overall survival and 7% (0.70; 0.52–0.94) for failure-free survival. The greatest absolute benefit was found for women with stage III endometrial cancer (five-year overall survival 78.5% (95% CI: 72.2–85.4) with chemoradiotherapy versus 68.5% (61.2–76.7) with radiotherapy alone (HR: 0.63, 95% CI: 0.41–0.99, p = 0,043) or serous cancers (five-year overall survival was 71.4% (95% CI: 60.1–84.7) with chemoradiotherapy versus 52.8% (40,6–68.6) with radiotherapy alone (HR: 0.48, 95% CI: 0.24–0.96], p = 0.037). In women with a recurrence, the majority had distant metastases with five-year probability 29.1% (95% CI: 24.4–34.3) in the radiotherapy-only group compared with 21.4% (17.3–26.3) in the chemoradiotherapy group (HR: 0.74, 95% CI: 0.55–0.99), p = 0·047. Pelvic control was excellent in both groups. The limitation of this analysis is the fact that the subgroup analyses were not powered, and the survival update was non-prespecified [1].

In their randomised phase III trial with 601 high-intermediate and high-risk early-stage endometrial carcinoma, Randall et al. did not demonstrate superiority of vaginal cuff brachytherapy and chemotherapy (VCB/C) when compared with pelvic radiation therapy with respect to 60-month RFS [0.76 (95% CI: 0.70–0.81) for radiation therapy and 0.76 (95% CI: 0.70–0.81) for VCB/C and overall survival at 0.87 (95% CI: 0.83–0.91) for radiation therapy and 0.85 (95% CI: 0.81–0.90) for VCB/C], nor did they demonstrate equivalence. Study treatment began within 12 weeks of surgery and was randomly assigned between RT (45 to 50.4 Gy over 5 weeks) or VCB followed by intravenous paclitaxel 175 mg/m^2 (3 hours) plus carboplatin (area under the curve, 6) every 21 days for three cycles. Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VCB/C (9% v 4%). After a median follow-up of 53 months, there was no heterogeneity of treatment effect with respect to RFS or overall survival among the clinical or pathologic variables evaluated. The result is consistent with the results of the PORTEC-3 study [2].

Hiroyuki et al. analysed in their multicentre, phase 3 randomised trial whether taxane plus platinum regimens (docetaxel/cisplatin or paclitaxel/carboplatin) are superior to standard doxorubicin plus cisplatin in postoperative adjuvant chemotherapy treatment of patients with high-risk early-stage or optimally debulked advanced-stage endometrial cancer patients. The 788 eligible patients were randomly assigned (1:1:1) to receive six cycles of doxorubicin, 60 mg/m^2, plus cisplatin, 50 mg/m^2, on day one; docetaxel, 70 mg/m^2, plus cisplatin, 60 mg/m^2, on day one; or paclitaxel, 180 mg/m^2, plus carboplatin (AUC 6.0) on day one every three weeks. After a median follow-up period of seven years, there was no statistical difference of progression-free survival (doxorubicin plus cisplatin, 191; docetaxel plus cisplatin, 208; paclitaxel plus carboplatin, 187; p = 0.12) or overall survival (doxorubicin plus cisplatin, 217; docetaxel plus cisplatin, 223; paclitaxel plus carboplatin, 215; p = 0.67) among the three groups. The five-year progression-free survival rate was 73.3% for the doxorubicin plus cisplatin group, 79.0% for the docetaxel plus cisplatin group, and 73.9% for the paclitaxel plus carboplatin group, while the five-year overall survival rates were 82.7%, 88.1%, and 86.1%, respectively. As all the three regimens were comparable in therapeutic effect, the authors concluded that taxane plus platinum regimens can be an alternative to doxorubicin plus cisplatin in adjuvant chemotherapy for patients with endometrial cancer that has risk factors for progression [3].

Mileshkin et al. have published a phase II study of anastrazole given 1 mg/d in 87 patients with recurrent or metastatic endometrial cancer that was oestrogen and/or progesterone and had no prior anti-cancer endocrine treatment. A clinical benefit at three months was reported in 36/82 patients (44%; 95% CI: 34–55%) who also had significant improvements in their global quality of life. A best RECIST response of partial response was observed in six patients (7%; 95% CI: 3–15%). The median progression-free survival for the whole cohort was 3.2 months (95% CI: 2.8–5.4). Progression-free survival was superior in patients with a treatment-free interval prior to registration of >12 months. Treatment was well tolerated in most patients. The main limitation of the study is the fact that testing for oestrogen and progresterone status was based on archival specimens taken at the time of initial diagnosis rather than metastatic sites; therefore, it was not confirmed that expression was still present in metastatic tumours [4].

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No	Title	Authors	Journal	Link to abstract
1	Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial.	de Boer SM et al.	Lancet Oncol.	https://pubmed.ncbi.nlm.nih.gov/31345626/
2	Phase III trial: Adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer.	Randall ME et al.	J Clin Oncol.	https://pubmed.ncbi.nlm.nih.gov/30995174/
3	Doxorubicin plus cisplatin as adjuvant chemotherapy for endometrial cancer at a high risk of progression: A randomized clinical trial.	Hiroyuki N et al.	JAMA Oncol.	https://pubmed.ncbi.nlm.nih.gov/30896757/
4	Phase 2 study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial - ANZGOG 0903.	Mileshkin L et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31130288

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Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Matteo Morotti

Yoshida et al. studied surgery following neoadjuvant concurrent chemoradiation as a potential treatment option for patients with locally advanced cervical cancer, with acceptable adverse events. Fifty patients treated with neoadjuvant concurrent chemoradiation were compared with 74 treated with concurrent chemoradiation only using inverse probability of treatment weighting. Progression-free survival and overall survival Kaplan–Meier curves were significantly longer in the neoadjuvant concurrent chemoradiation group than the concurrent chemoradiation group ($p = 0.027$ and $p = 0.017$, respectively). Patients with squamous cell carcinoma had significantly decreased recurrence in previously irradiated field and recurrence both in and out of irradiated field in the neoadjuvant concurrent chemoradiation group compared with the concurrent-chemoradiation-only group (3.1% and 18.4%, respectively; OR 0.142, $p = 0.001$). There were no grade 4 or 5 adverse events, and 12 patients experienced temporary hydronephrosis grade 3 (23.1%).

Köhler et al. published a different approach of minimally invasive radical hysterectomy for early-stage cervical cancer with similar results as the open radical hysterectomy arm in the LACC trial. They analysed 389 patients treated by laparoscopic-assisted radical vaginal hysterectomy or vaginal-assisted laparoscopic radical hysterectomy without the use of any uterine manipulator, and all patients had the vagina closed by the creation of a vaginal cuff. Median follow-up was 99 months. Three-, 4.5-, and 10-year disease-free survival rates were 96.8%, 95.8%, and 93.1 %; and the three-, 4.5-, and 10-year overall survival rates were 98.5%, 97.8%, and 95.8%, respectively. Additionally, nine of 20 recurrences occurred more than three years after surgery, so they suggest that follow-up for those patients should be redefined.

A study by Tanaka et al. supported the safety of laparoscopic radical hysterectomy. They performed peritoneal cytology before and after total laparoscopic radical hysterectomy with vaginal cuff closure and without the use of a uterine manipulator in 24 patients with early-stage cervical cancer (IA2, IB1, and IIA1). There were no cancer cells before nor tumour spillage after surgery.

Bendifallah et al. developed a classification of cervical cancer recurrence using rTNM classification due to pattern of cancer dissemination: locoregional recurrence (rT), nodal recurrence (rN), or distant organ recurrence (rM). According to the anatomical dissemination pathway, they defined stages of recurrence. A lower three-year survival was observed in women with multiple-site than single-site recurrence ($p = 0.1$). In the rT group, a difference in three-year survival after recurrence was found between patients with the single-site metastasis rT1(recurrence tumour on the vaginal vault only), rT2 (centropelvic recurrence with or without vaginal involvement), and rT3 (abdominal and/or pelvic peritoneal carcinomatosis, ascites) ($p = 0.02$). The three-year survival after recurrence was 69.1%, 49.2%, 37.5%, 34.2%, 23.1%, and 24.4% for rStage I (T1N0M0) II (T0-1,N1,M0), IIIA (T2,N0-1,M0), IIIB(T0-2,N2,M0), IVA(T3,N0-2,M0), and IVB(T0-3,N0-2,M1), respectively ($p = 0.007$).

Bogani et al. evaluated 32 young patients (<40 years) undergoing cervical conisation and laparoscopic pelvic node dissection and sentinel lymph node mapping due to early-stage (IA2, IB1, and IB2 FIGO classification 2018.) cervical cancer. In six (19%) patients, conservative treatment was not conducted, and two of them had definitive surgical or radiotherapy treatment due to recurrent disease. There was no disease recurrence among patients undergoing conservative treatment. Five-year disease-free survival and overall survival were 94% and 97%, respectively. Eleven patients (69%) out of the 16 who attempted to conceive got pregnant. The authors suggest that cervical conisation with pelvic node assessment is a valid fertility-sparing treatment modality for patients with early-stage cervical cancer.

Novackova et al. analysed the short- and long-term of nerve-sparing radical hysterectomy on urinary tract function in 117 patients. Within 14 days after surgery, urination without postvoid residual urine was achieved in all women, including 5 (4.7%) patients who had postvoid residual (volume greater than 100 mL. A urodynamic examination performed one week before and 12 months after surgery (106 patients were available for one-year follow-up) show a slight increase in the average maximum bladder cystometric capacity from 420 to 445 mL ($p = 0.009$) without prolonging the voiding time. Other urodynamic parameters were not significantly different.

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No	Title	Authors	Journal	Link to abstract
1	The role of additional hysterectomy after concurrent chemoradiation for patients with locally advanced cervical cancer.	Yoshida K et al.	Int J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31552530
2	Laparoscopic radical hysterectomy with transvaginal closure of vaginal cuff - a multicenter analysis.	Köhler C et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31155516
3	Intraperitoneal cytology after laparoscopic radical hysterectomy with vaginal closure without the use of a manipulator for cervical cancer: a retrospective observational study.	Tanaka T et al.	Cancer Manag Res.	https://www.ncbi.nlm.nih.gov/pubmed/31440090
4	Cervical cancer recurrence: Proposal for a classification based on anatomical dissemination pathways and prognosis.	Bendifallah S et al.	Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31500783
5	Long-term results of fertility-sparing treatment for early stage cervical cancer.	Bogani G et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/31000470
6	Urinary tract morbidity after nerve-sparing radical hysterectomy in women with cervical cancer.	Novackova M et al.	Int Urogynecol J.	https://www.ncbi.nlm.nih.gov/pubmed/31444536

Systematic treatment of primary and recurrent cervical cancer

Kristina Lindemann

Liu et al. reported on a phase II trial combining trametinib and GSK2141795 in patients with recurrent cervical cancer [1]. In preceding studies, PIK3CA (31.3%) and KRAS (8.8%) mutations have been identified in cervical cancer. There is also evidence for a synergistic activity between PI3K/AKT and MEK inhibitors, which was the rationale for this study. The study was closed early as the company stopped the development of the AKT inhibitor GSK2141795, also due to observed combined toxicity in other tumour groups. Out of 14 enrolled patients, one patient had response (7.1%), and eight patients (57.1%) had stable disease. The overall rate of grades three and four adverse events was 57.1%. The limited number of patients included precluded meaningful translational analyses. However, one patient with long-term stable disease did have a PIK3CA mutation. In conclusion, future use of these drug combinations is challenged by the high toxicity rate and the lack of predictive biomarkers of response.

The MITO-Cerv-2 study randomised 108 patients with recurrent cervical cancer in a phase II trial, prospective, open-label, randomised (1:1), multicentre trial to either carboplatin plus paclitaxel (CT) or carboplatin/paclitaxel/cetuximab (CT/Cetux) [2]. After a median follow-up of 23 months, there was no statistically significant difference in progression-free survival between the arms (median event-free survival of 4.7; 95% CI: 4.1–6.5 for CT vs 6.0; 95% CI: 4.4–7.6 for CT/Cetux) and similar response rates (84.6% and 76.4% standard and experimental arm, respectively). At least one severe (grade ≥ 3) adverse event was reported in 58% of patients in the standard and 80% in the experimental arm, particularly skin toxicity. With the limitations of small numbers, the study supported that PIK3CA mutations could be predictive biomarkers for resistance to cetuximab treatment.

Keynote-158 was an international, open-label, multicohort phase II trial of pembrolizumab monotherapy in multiple advanced solid tumour types [3]. Ninety-eight patients with recurrent cervical were enrolled; 83.7% had PD-L1-positive tumours (CPS ≥1). After a median follow-up duration of 10.2 months, three patients achieved a complete response and nine a partial response, resulting in an overall response rate of 12.2% (95% CI, 6.5% to 20.4%). Disease control rate was higher, with 30.6%. All 12 responses were in patients with PD-L1–positive tumours, corresponding to an overall response rate of 14.6% in PD-L1–positive tumours. Median duration of pembrolizumab treatment was 2.9 months, with a median number of five cycles given. The median progression-free survival was 2.1 months. The median duration of response had not been reached (range, ≥ 3.7 to ≥18.6 months). At six months, 90.9% of the responses were ongoing, 50.0% at data cut-off. Although no responses were observed in patients with PD-L1 negative tumours, the study lacked the power to distinguish response rates according to PD-L1–status reliably. Still, FDA granted accelerated approval of pembrolizumab for the treatment of patients with advanced PD-L1–positive cervical cancer with disease progression during or after chemotherapy based on these study results.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Results from a single arm, single stage phase II trial of trametinib and GSK2141795 in persistent or recurrent cervical cancer.	Liu JF et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31118140
2	The MITO CERV-2 trial: a randomized phase II study of cetuximab plus carboplatin and paclitaxel, in advanced or recurrent cervical cancer.	Pignata S et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30979589
3	Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study.	Chung HC et al.	J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30943124

Early clinical trials in cervical cancer

Novak Zoltan and Marcin Mardas

Tamura et al. reported a multicentre, phase II trial that evaluated the efficacy and safety of nivolumab (monoclonal antibody against PD-1) in patients with advanced/recurrent uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma [1]. The primary endpoint was the objective response rate. Secondary endpoints included overall survival, progression-free survival, and safety. The objective response rate was 25%, 23%, and 0% in patients with cervical cancer (n = 20), uterine corpus cancer (n = 22), and soft tissue sarcoma (n = 21), respectively. Median progression-free survival was 5.6, 3.4, and 1.4 months, and six-month overall survival was 84% for cervical cancer, 73% for uterine corpus cancer, and 86% for soft tissue sarcoma. The objective response rate was higher in patients with cervical cancer with PD-L1-positive (n = 5/15; 33%) versus PD-L1-negative (n = 0/5; 0%) tumours. The authors stated that nivolumab showed acceptable toxicity in all cohorts, with evidence of clinical activity in cervical cancer or uterine corpus cancer. PD-L1 expression in cervical cancer and MSI-high in uterine corpus cancer may predict clinical activity of nivolumab in these cancers.

Harper et al. reported a randomised, double-blind placebo-controlled phase II trial concerning the efficacy of Tipapkinogen Sovacivec vaccine in achieving histologic resolution of CIN2/3 associated with HR HPV types [2]. The primary endpoint was at response month six when the excisional therapy was performed. Cytology and high-risk HPV typing were analysed at months three and six and every six months through month 30. Of the 129 women randomised to vaccine and 63 to placebo, complete response was significantly higher in the vaccine group (24% vs 10%, $p < 0.05$); as well as for only CIN 3 also, regardless of high-risk HPV type (21% vs 0%, $p<0.01$).

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No	Title	Authors	Journal	Link to abstract
1	Efficacy and safety of nivolumab in Japanese patients with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma: Multicenter, open-label phase 2 trial.	Tamura K et al.	Cancer Sci.	https://www.ncbi.nlm.nih.gov/pubmed/31348579
2	The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: Randomized controlled phase II trial with 2.5 years of follow-up.	Harper DM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30955915

Radiotherapy in management of primary cervical cancer

Paweł Bartnik and Erbil Karaman

In a retrospective study, Liu et al. aimed to establish a model for the identification of patients at risk of developing distant cervical cancer metastasis [1]. The study group included 1,193 patients treated with definitive radiotherapy with no previous history of radiotherapy nor other cervical cancer treatment and no distant metastasis. Distant relapse was detected in 13.8% of the cohort. A higher occurrence of distant metastasis was observed in patients with non-squamous cervical cancer, localised to the common iliac lymph node metastasis, and bilateral pelvic iliac lymph node metastases.

A retrospective study by Kroesen et al., the authors examined the impact of thermal dose in 277 primary cervical cancer patients managed with radiotherapy and hyperthermia [2]. Improved local control was associated with higher thermal dose parameters (TRISE and CEM43T90) as well as the use of image-guided brachytherapy.

Wujanto et al. conducted a retrospective study of locally advanced cervical cancer treated with definitive external beam radiation therapy and assessed whether pelvic boost affects recurrence, survival, and toxicities [3]. Patients with positive pelvic lymph nodes (n = 67) either received a nodal boost (n = 36) or not (n = 31). Five-year recurrence-free survival was 48.6% vs. 64.5% (p = 0.169) and five-year overall survival was 74.3% vs. 80.6% (p = 0.143), respectively. The authors concluded that an external beam radiation therapy pelvic lymph node boost does not reduce recurrence nor improve survival in locally advanced cervical cancer with nodal involvement.

Berger et al. described the evolution of external beam radiation therapy from EMBRACE I to the initial phase of the EMBRACE II study [4]. EMBRACE I enrolled 1,426 locally advanced cervical cancer patients treated with chemoradiation including image-guided adaptive brachytherapy while EMBRACE II included 153 patients in an ongoing study, involving a detailed strategy and accreditation procedure for external beam radiation therapy target contouring, treatment planning, and image guidance. External beam radiation therapy planning target volumes (PTVs), treated volumes (V43 Gy), and conformity index (CI; V43 Gy/PTV) were compared. The authors concluded that application of IMRT/VMAT, IGRT, and a 45-Gy dose provides the potential of higher conformality inducing a significant reduction of treated volume.

Kissel et al. investigated the impact of suboptimal tandem implantation on local control and complications in intracavitary brachytherapy for cervical cancer [5]. 172 patients underwent 301 procedures with 95 suboptimal implantations. Risk factors included age, myometrial invasion, and uterine retroversion. Three-year local control and survival rates were 72% and 85%, respectively, with regards to the suboptimal tandem implantation. Failure to perform brachytherapy (n = 47) was associated with poorer local control. By contrast, it was stated that suboptimal implantation did not increase local failure nor toxicity rates in patients undergoing brachytherapy.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Predictors of distant metastasis in patients with cervical cancer treated with definitive radiotherapy.	Liu X et al.	J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31417641
2	Confirmation of thermal dose as a predictor of local control in cervical carcinoma patients treated with state-of-the-art radiation therapy and hyperthermia.	Kroesen M et al.	Radiother Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31302345
3	Does external beam radiation boost to pelvic lymph nodes improve outcomes in patients with locally advanced cervical cancer?	Wujanto C et al.	BMC Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31023261
4	Importance of technique, target selection, contouring, dose prescription, and dose-planning in external beam radiation therapy for cervical cancer: evolution of practice from EMBRACE-I to II.	Berger T et al.	Int J Radiat Oncol Biol Phys.	https://www.ncbi.nlm.nih.gov/pubmed/30904706
5	Impact of suboptimal tandem implantation on local control and complications in intracavitary brachytherapy for cervix cancer.	Kissel M et al.	Brachytherapy.	https://www.ncbi.nlm.nih.gov/pubmed/31495576

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Treatment of primary and recurrent vaginal/vulva cancer

Reyes Oliver and Rubén M. Betoret

As lymph node status is the most important prognostic factor in primary vulvar squamous cell cancer patients, the first large analysis on predictive factors for lymph node metastases conducted by Klapdor et al. might serve as a useful tool in tailoring optimal treatment. Based on the AGO-CaRE-1, a multicentre study cohort of 1,162 patients treated with radical groin dissection was analysed. Lymphovascular space invasion, tumour stage, age, and depth of infiltration are associated with a prevalence of lymph node metastases, whereas tumour stage or tumour diameter are positively associated with the number of lymph node metastases. Due to the multicentre and retrospective design, there are some obvious limitations to this study (selection and reporting bias, missing values, lack of standardisation on the localisation and biology of the tumour). Nevertheless, this is still by far the largest cohort in which multiple factors were analysed [1].

Margin status has been considered a cornerstone when it comes to assessing local recurrence risk and treatment strategies in primary vulvar squamous cell cancer patients. Te Grootenhuis et al. retrospectively analysed 287 patients with a median follow-up of 80 months. The local recurrence rates five and ten years after primary treatment were 28.3% and 42.5%, respectively. Tumour-free margin distance did not influence the risk on local recurrence (HR 1.03, 95% CI: 0.99–1.06), neither does using a cut-off of eight, five or three millimetres. Moreover, only lichen sclerosus and differentiated vulvar intraepithelial neoplasia, when present in the pathologic margin, showed a higher recurrence rate (HR: 2.76; 95% CI: 1.62–4.71), which should raise awareness among physicians and lead to intensified follow-up [2].

Bekos et al. focussed on pre-treatment hypoalbuminemia as independent prognostic biomarker for overall survival in vulvar squamous cell cancer patients (five-year overall survival rate of 17.1% vs 58.6% in the low and normal seric albumin level groups, respectively). Only nine of the women had low albumin in the study. No significant association was found between pre-treatment hypoalbuminemia and risk for postoperative complications ($p = 0.345$) [3].

Surgical resection with free surgical margins is the cornerstone of successful primary treatment of vulvar squamous cell cancer patients, and re-excision should be considered when the minimum peripheral surgical margin is <8 mm microscopically. Kortekaas et al. propose defining a minimum peripheral surgical margin in vulvar squamous cell cancer as the minimum distance from the peripheral edge of the invasive tumour nests toward the inked peripheral surgical margin reported in millimetres and providing guidance to the practicing pathologist in measuring minimum peripheral surgical margin in vulvar squamous cell cancer resection specimens, in order to promote uniformity in measuring and reporting [4].

Recurrent vulvar cancer

Another study published on the basis of data from the dAGO-CaRE-1 multicentre study showed that the localisation of recurrence has a major impact on prognosis. This subgroup analysis included 1,249 patients with surgical groin staging and known lymph-node status (n = 447 N+, n = 802 N-). A total of 28.8% patients developed disease recurrence with nodal involvement and R1 resection as the most relevant prognostic factors for an increased risk of vulvar recurrence. Recurrence site was associated with prognosis: hazard ratios (95% CI) to die for patients with relapse to the vulva only: vulvar only: 5.9 (4.3–8.2); groins only: 6.0 (3.0–10.2); vulvar and groins: 14.1 (7.6–26.4); pelvic/distant: 21.2 (15.3–29.4). Patients with isolated local recurrence had a two- and five-year overall survival of 82.2% and 66.9%, and 30.1% of the patients with local recurrence developed second recurrence with a two-year mortality after any recurrence of 56.3%. The relatively short follow-up of 27.5 months is a major weakness of this study, as well as the limitations of any retrospective setting and the absence of a disease-specific survival [5].

Perrone et al. published preliminary results of the ELECHTRA multicentre study on palliative electrochemotherapy in recurrent vulvar squamous cell cancer. Reversible electroporation, induced by short electric pulses, and the addition of bleomycin, obtained a clinical response rate, based on RECIST criteria, of 83.6% two months after electrochemotherapy in 61 enrolled patients, without serious adverse events reported, and on a favourable cost-effectiveness ratio, thus becoming a treatment option for local disease control in patients unsuitable for standard therapies [6].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Predictive factors for lymph node metastases in vulvar cancer. An analysis of the AGO-CaRE-1 multi center study.	Klapdor R et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31227222
2	Margin status revisited in vulvar squamous cell carcinoma.	Te Grootenhuis NC et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31109660
3	Pre-operative hypoalbuminemia is associated with complication rate and overall survival in patients with vulvar cancer undergoing surgery.	Bekos C et al.	Arch Gynecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/31468203
4	Practical guidance for measuring and reporting surgical margins in vulvar cancer.	Kortekaas KE et al.	Int J Gynecol Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/31460873
5	Predicting the course of disease in recurrent vulvar cancer- A subset analysis of the AGO-CaRE-1 study.	Woelber L et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31324454
6	Palliative electrochemotherapy in vulvar carcinoma: Preliminary results of the ELECHTRA (Electrochemotherapy vulvar cancer) multicenter study.	Perrone AM et al.	Cancers.	https://www.ncbi.nlm.nih.gov/pubmed/31083599

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Hereditary gynaecological cancer

Annemijn Aarts and Sara Giovannoni

Lynch syndrome

The Manchester International Consensus Group has developed the first gynaecology-focussed internationally agreed clinical guideline for the care of women with or at risk of Lynch syndrome [1]. Based on literature and a consensus meeting among experts, including, patient representatives, geneticists, pathologists, gynaecologists, a set of key recommendations have been formulated.

1. The Consensus Group strongly recommends universal screening of endometrial cancer patients for Lynch syndrome. If resources are limited, women ≤60 years should be prioritised.
2. Women with endometrial cancer should be screened for Lynch syndrome. A strategy analysing tumour MMR or MSI status is recommended to identify women for germline MMR testing.
3. Women at risk of Lynch syndrome should be offered risk-reducing total hysterectomy and bilateral salpingo-oophorectomy no earlier than 35–40 years of age following completion of childbearing, in proven MLH1, MSH2, and MSH6 pathogenic variant carriers.
4. Further research is required to establish the value of gynaecological cancer surveillance in Lynch syndrome and to explore other key areas where there is currently deficient evidence to define appropriate standards of care. Screening for Lynch syndrome is only recommended if effective management exists to benefit those who screen positive.

An observational study assessed the preferences for cancer risk-management strategies in 61 women with Lynch syndrome [2]. Women evaluated nine cancer risk-management strategies on a visual analogic scale (from 0 to 100) and with the modified standard gamble method. The standard gamble method is a research tool including a score for a particular health state calculated by subtracting women's stated threshold of lifetime risk (from 0.0 to 1.0). With the standard gamble method, a research interviewer asked each woman how high her risk of colorectal or endometrial cancer would need to be in order to consider a certain management strategy depicted in the health state descriptions. Strategies included chemoprevention with oral contraceptives, cancer screening (including annual and biannual colonoscopy; annual and biannual gynaecological cancer screening with endometrial biopsy, transvaginal ultrasound, and CA125; or annual and biannual combined colorectal and gynaecological cancer screening) and preventive surgery with hysterectomy and bilateral salpingo-oophorectomy. According to the visual analogic scale, annual gynaecologic and colorectal combined screening was preferred by most women, followed by annual screening (colonoscopy alone or gynaecologic cancer annual screening alone) and chemoprevention. By the standard gamble method, women were most willing to endorse oral contraceptives and biannual screening strategies when the estimated lifetime risk was 20% followed by annual screening strategies. Surgical interventions were the least preferred strategies using both visual analogic scale and standard gamble methods, especially among younger women. Women with a family history of gynaecologic or colorectal cancer were less likely to consider prevention or screening options compared to women without a family history. Understanding women's preferences may help physicians in counselling, shared decision making, and adherence to cancer risk-management strategies.

BRCA-associated tumours

ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) has developed variant classification criteria using both quantitative and qualitative methods, including co-segregation, tumour pathology, co-occurrence, and family history. In the analysis by Parsons et al., 1,395 BRCA1/2 variants were analysed [3]. In all, 734 pathogenic variants were identified; 447 of these were likely benign, 94 were likely pathogenic, and 248 were new or considerably altered BRCA1/2 variant classifications based on the ClinVar database. These findings are relevant for variant interpretations when new pathogenic BRCA variants are identified. The generation of 248 new variants may contribute to determining patient eligibility for screening, cascade testing of patients' relatives, and for PARPi treatment.

In an observational study by Gornjec et al., mutation analyses of BRCA1 and BRCA2 genes were performed in three different samples: Blood, cytological samples (ascites, pleural effusion, enlarged lymph nodes), and histological formalin-fixed paraffin-embedded (FFPE) tumour samples, of 44 women with primary or recurrent ovarian, fallopian tube, or primary peritoneal high-grade serous carcinoma [4]. The study compared the concordance of BRCA mutation analysis between cytological-, FFPE-, and blood samples. Eighteen percent of the enrolled women had a positive family history for hereditary breast and ovarian cancer, and 13% had breast cancer. Fifteen germline mutations and two somatic mutations were detected in the cytology samples and FFPE, with 100% concordance. No additional somatic mutations were found in FFPE compared to cytologies. The BRCA germline testing in blood matched with these 15 germline mutations (14 BRCA1 mutations, 1 BRCA2 mutation) detected in cytology and FFPE. BRCA mutation testing in cytological samples could detect germline and somatic mutations with complete concordance independent of sampling site (ascites, pleural effusion or enlarged lymph nodes). Cytological sampling may also allow the study of mechanisms to PARP inhibitor resistance such as BRCA1/2 mutation reversion during cancer progression.

A Dutch nation-wide cohort study included 42 germline BRCA carriers who developed endometrial cancer [5]. Tumour tissue was re-analysed by three expert gynaecologic pathologists. Several analyses were done, such as clinicopathologic characterisation, immunohistochemical staining, analysis of microsatellite instability status, and molecular subgroups according to The Cancer Genome Atlas (TCGA). Nineteen morphologic features were scored to determine the histotype. Endometrial cancers with LOH (loss of heterozygosity) of the germline BRCA-wild-type allele (gBRCA/LOHpos) were defined as "gBRCA-associated", those without LOH (gBRCA/LOHneg) were defined as "sporadic." The cohort comprised 26 endometrioid ECs (61.9%), of which the majority (40.5%) were grade 1, 7.1% were grade 2, 11.9% were grade 3, and 2.4% were mucinous carcinoma. Sixteen ECs were classified as non-endometrioid (38.1%). Germline BRCA1/2 mutation was confirmed in 40 cases. Overall, 60% (24/40) of endometrial cancers were gBRCA/LOHpos. When stratified for gBRCA1 and gBRCA2 mutations, 66.7% and 40% showed LOH, respectively. Non-endometrioid and serous-like histology were significantly more common in gBRCA/LOHpos endometrial cancers than in gBRCA/LOHneg ECs. All but two gBRCA/LOHpos ECs were TP53-mutated, compared with only one of the gBRCA/LOHneg ECs. In conclusion, this study showed that gBRCA-associated ECs are distinctly different from sporadic ECs by histology (high grade) and by molecular subtype (TP53 mutant), both of which are associated with a worse clinical outcome. This could have therapeutic consequences as these patients may benefit from treatment strategies such as PARP inhibitors. Furthermore, these findings suggest that, in contrast to some previous studies, gBRCA-associated endometrial cancer is part of the hereditary breast and ovarian cancer syndrome. gBRCA testing in patients with high-grade endometrial cancer and a previous history of breast cancer or family history with other gBRCA-associated malignancies could be considered. This study did not aim to calculate the risk of development of endometrial cancer in women with gBRCA1/2 mutations; there was no comparison with the general population. Therefore, the study is not suitable for forming conclusions regarding the value of surveillance for EC in gBRCA carriers.

Hereditary gynaecological cancer

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No	Title	Authors	Journal	Link to abstract
1	The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome.	Crosbie EJ et al.	Genet Med.	https://www.ncbi.nlm.nih.gov/pubmed/30918358
2	Women's preferences for cancer risk management strategies in Lynch syndrome.	Sun CC et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30876497
3	Large scale multifactorial likelihood quantitative analysis of BRCA1 and BRCA2 variants: An ENIGMA resource to support clinical variant classification.	Parsons MT et al.	Hum Mutat.	https://www.ncbi.nlm.nih.gov/pubmed/31131967
4	Cytology material is equivalent to tumor tissue in determing mutations of BRCA1/2 genes in patients with tubo-ovarian high grade serous carcinoma.	Gornjec A et al.	BMC Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30940100
5	Germline BRCA-associated endometrial carcinoma is a distinct clinicopathologic entity.	de Jonge MM et al.	Clin Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/31492746

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Screening of gynaecological cancer

Geanina Dragnea

Cervical cancer

A large prospective study by Rebolj et al. compared the outcomes of primary cervical screening with high-risk human papillomavirus (HR-HPV) with and without HPV 16/18 triage at the 12-month early recall for HR-HPV+/ NILM cytology (negative for intraepithelial lesion and malignancy) women. The HPV 16/18 genotyping protocol required 5.9% additional colposcopies and did not lead to a substantial increase in CIN2+ detection (only 1.2%). This only slight increase in CIN 2+ detection may be due to a substantial HPV16/18 infection clearance (a 32% clearance at 12 months recall and a further 26% clearance at 24-month recall) [1]. The results of this comprehensive and rigorous population-based study represent a step forward in the ongoing attempt to find the optimal cost-effective screening strategy for CIN2 + lesions with high attendance while taking into account current data on the natural evolution of HPV infection.

In the second round of HPV-based screening, the proportion of recent HPV infections is higher than in the first round and the risk of CIN 3+ may be different. An analysis of the POBASCAM trial on a subgroup of 336 HPV+ women in the second HPV-based screening round (at five years) evaluated the clinical performance of 16 strategies to detect CIN 3+, including cytology, HPV genotyping, and/ or previous screen HPV result. These strategies aim at a high negative predictive value (NPV) and a low rate of colposcopy referrals. Three strategies proved to be feasible: cytology at baseline and after 6–18 months (NPV 95.8%, colposcopy referral rate of 37.6%), cytology combined with HPV 16/18 genotyping NPV (99.2%, colposcopy referral rate 49.2%) and cytology combined with previous HPV screen status (NPV 96.9%, colposcopy referral rate 38.8%), the last one being also the most cost-effective [2]. Although a small study, this is the first study to evaluate HPV-based screening strategies in the second round at five years.

The Onclarity HPV observational trial on 27,037 enrolled women with NILM cytology, ≥25 years, and evaluated the stratified risk associated with CIN 2+, CIN3+ based on extended genotyping HR-HPV results. The risk for CIN 3+ was the highest for HR-HPV 16 and 31 (8.1% and 7.5%, respectively), these genotypes being the most prevalent in CIN3+ (43.7% and 22.5%, respectively); HPV 16 or 31 positivity exceeded the risk threshold for colposcopy referral. The risk for CIN 3+ was intermediate (risk range: 3.9–5.0%) for HR-HPV 18, 33/58, and 52 and lowest for genotypes 45, 51, 35/39/68, and 56/59/66 (risk range: 1.2–3.6%) [3]. This study is useful for reassessing the existing stratification strategy in the US for NILM and HR-HPV+ women, where colposcopy is performed in case of HPV 16/18 positivity. The results of this study are obtained on the baseline data, and longitudinal results are needed. The HPV genotypes prevalence in this study are representative for the US and may be different for other countries.

The impact of multiple age-cohort vaccination was evaluated in an updated systematic review and meta-analysis including data from 60 million individuals up to eight years of post-vaccination follow-up. Among girls aged 13–19 and women aged 20–24, the prevalence of HPV 16 and 18 decreased significantly (by 83% and 66%, respectively), anogenital wart diagnoses decreased significantly (by 67% and 54%, respectively), and CIN2+ decreased significantly, after 5-9 years of vaccination (by 51%, and 31%, respectively) [4]. Compared to a previous metanalysis performed by the same authors in 2015, this study now has sufficient follow-up to show a significant benefit of multicohort HPV vaccination with a high routine vaccination coverage on CIN2+ lesions.

A retrospective population-based study (138,692 women) in Scotland determined the effect of bivalent HPV vaccine on cervical disease at the age of 20 years. It was observed that vaccinated women showed an 89% reduction in prevalent CIN 3+; younger age at immunisation was associated with an increase in vaccine effectiveness—86% for CIN3+ for women vaccinated at age 12–13 compared with 51% for women vaccinated at age 17 [5]. Longitudinal studies with longer follow-up will elucidate the true protection of vaccination against cancer.

Nine-valent HPV-vaccine (9vHPV) efficacy against preinvasive disease and cervical surgeries (loop electrosurgical excision procedure or conisation) related to all nine vaccine components was assessed compared with a historic placebo population of three international, randomised, double-blind studies. In the 9vHPV vaccine study (NCT00543543), women received 9vHPV or qHPV (quadrivalent HPV vaccine), respectively. In the historic qHPV vaccine studies (FUTURE I and II), women received qHPV vaccine or placebo, respectively. Among women negative for 14 HPV types prior to vaccination, the incidence of CIN2+ and cervical surgery related to the nine HPV types was reduced by 98.2% and 97.8%, respectively. The 9vHPV vaccine did not prevent disease related to vaccine HPV types detected at baseline, but significantly reduced cervical, vulvar, and vaginal diseases related to other vaccine HPV types [6]. Due to ethical concerns, a placebo group was not included in this study.

Endometrial cancer

A retrospective observational study included 25 hysterectomy specimens and 85 endometrial biopsies with a histologically normal endometrium. Targeted sequencing revealed somatic driver-like events in over 50% of normal endometrial samples, including hotspot mutations in KRAS, PIK3CA, and FGFR2 as well as PTEN-loss by IHC. The prevalence of such oncogenic mutations increased with age (OR: 1.05, $p = 0.035$). Caution is needed in the utilisation of mutation-based early detection tools for endometrial or other cancers [7]. The development of screening methods for occult or precancerous disease will need to incorporate a solid understanding of normal age-related somatic mutation accumulation.

Ovarian cancer

A machine learning model incorporated genome-wide fragmentation features for 236 patients with breast, colorectal, lung, ovarian, pancreatic, gastric, or bile duct cancer and 245 healthy individuals. Fragmentation patterns of cell-free DNA across the genome of healthy individuals reflected nucleosomal patterns of white blood cells, whereas patients with cancer had altered fragmentation profiles. This model showed sensitivity in detection ranging from 57% to 99% among the seven cancer types with a specificity of 98%. Fragmentation profiles could be used to identify the tissue of origin of the cancers to a limited number of two sites with an accuracy of 75%. Combining this approach with cell-free DNA (cfDNA) analyses (detection of sequence alterations in cfDNA) detected 91% of patients with cancer [8].

Screening of gynaecological cancer

Geanina Dragnea

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	16/18 genotyping in triage of persistent human papillomavirus infections with negative cytology in the English cervical screening pilot.	Rebolj M et al.	Br J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31409912
2	Management of HPV-positive women in cervical screening using results from two consecutive screening rounds.	Polman NJ et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30565673
3	Stratified risk of high-grade cervical disease using onclarity HPV extended genotyping in women, ≥25 years of age, with NILM cytology.	Stoler MH et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30638767
4	Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis.	Drolet M et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/31255301
5	Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study.	Palmer T et al.	BMJ	https://www.ncbi.nlm.nih.gov/pubmed/30944092
6	Nine-valent HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population.	Giuliano AR et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30982556
7	Oncogenic mutations in histologically normal endometrium: the new normal?	Lac V et al.	J Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/31187483
8	Genome-wide cell-free DNA fragmentation in patients with cancer.	Cristiano S et al.	Nature	https://www.ncbi.nlm.nih.gov/pubmed/31142840

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Prevention and management of surgical complications

Martina Borghese

The impact of robotic surgery on the return of bladder function and genitourinary complications after type C1 (C1-RRH) and C2 (C2-RRH) robotic nerve-sparing radical hysterectomy was investigated in a retrospective analysis of 85 patients. Despite the study limitations (the authors did not perform urodynamic studies and the study had quite a small sample size), the C1-RRH was associated with early bladder function return (days of urinary catheter required one vs. 28, $p < 0.001$) and early discharge (0.7 vs 1.7 days, $p < 0.001$) [1].

Saner et al. conducted a single-centre retrospective study analysing 11 patients undergoing bilateral inguinofemoral lymphadenectomy for vulvar cancer: a fibrin sealant patch (Tachosil®) was located in one groin only and postoperative fluid formation was compared to see if the device could reduce surgical haematomas and lymphoceles. Despite the small number of enrolled patients, significantly larger lymphoceles were detected in the groin with the patch (20 vs 5 mL, $p = 0.002$), and more punctures for symptomatic lymphoceles were required on this side [2].

Kay et al. reviewed 306 ovarian cancer patient charts to investigate if intraperitoneal ports placed concomitantly with bowel resection (IP-BR) was associated with more postoperative complications than ports placed without concurrent bowel resection (IP). The authors reported similar rates of IP port complications between the two groups (19.2% IP-BR vs 23.2% IP, $p = 0.397$). Eleven percent of IP-BR patients vs 2.7% of IP patients had a bowel complication after IP port placing, but the IP-BR group had more patients with stage III disease [3].

Bekos et al. retrospectively analysed 103 vulvar cancer patients, investigating the role of pre-treatment serum albumin for postoperative morbidity. Hypoalbuminemia was found in 8.7% of the patients and, despite a trend towards higher rate of complications (55.6% of patients with hypoalbuminemia and 37.8% with normal albumin), the difference was not statistically significant ($p = 0.345$). Shorter overall survival was detected in patients with hypoalbuminemia ($p = 0.004$) [4].

Meyer-Wilmes et al. retrospectively analysed 25 patients who underwent a transarterial embolisation due to acute bleeding. After a 30-day follow up, the clinical success was 90.5% but rebleeding was identified in 9.5% of the patients. Although the authors could not identify factors that influenced the success of this procedure and despite being a single-centre study, transarterial embolisation proved to be a valid alternative to surgery and radiotherapy in acute bleeding for gynaecological cancers [5].

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No	Title	Authors	Journal	Link to abstract
1	Comparative analysis of genitourinary function after type C1 robotic nerves-paring radical hysterectomy versus type C2 robotic radical hysterectomy.	Paek J et al.	Surgical Oncology.	https://www.ncbi.nlm.nih.gov/pubmed/31500786
2	Fibrin-thrombin sealant does not reduce lymphocele formation in patients with inguinofemoral lymphadenectomy for vulvar cancer.	Saner FA et al.	Cancer Manag Res.	https://www.ncbi.nlm.nih.gov/pubmed/31118780
3	Intraperitoneal ports placed at the time of bowel resection for treatment of ovarian cancer: Complications and surgical outcomes.	Kay AH et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31488245
4	Pre-operative hypoalbuminemia is associated with complication rate and overall survival in patients with vulvar cancer undergoing surgery.	Bekos C et el.	Arch Gynecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/31468203
5	Transarterial embolisation for the treatment of acute gynaecological cancer bleeding.	Meyer-Wilmes P et al.	Arch Gynecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/31576453

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Cancer in pregnancy

Michael J. Halaska

Amant et al. published the third international guidelines of diagnosis, staging, and treatment of gynaecologic cancers in pregnancy [1].

Italian authors published epidemiological data from the Italian district Apulia [2]. Pregnancy-associated cancer was diagnosed in 127.1 per 100,000 pregnancies (cancer diagnosed during pregnancy and within 12 months after delivery). The most common cancers were breast cancer (37.7%), thyroid (22.3%), and cervical cancer (3.8%). Patients aged ≥40 years had elevated risk of cancer diagnosed during pregnancy (OR = 4.29, $p < 0.05$).

Several authors have analysed different types of cancer during pregnancy.

Moro et al. evaluated International Ovarian Tumour Analysis terminology in pregnant women [3]. Most invasive epithelial ovarian cancers were multilocular-solid masses (5/7, 71.4%). All metastatic tumours appeared as solid masses. Most epithelial ovarian carcinomas (4/7, 57.2%) and ovarian metastases (3/5, 60%) had a caesarean section due to disease. Patients with borderline tumours or epithelial ovarian carcinomas had no neonatal complication. Ultrasonographic features in pregnancy were similar to those in non-pregnant patients.

Halaska et al. analysed 132 patients with cervical cancer (INCIP database) compared to matched control non-pregnant patients [4]. Cervical cancer was found at an earlier stage in pregnancy in non-pregnant women. In all, 17.4% of the patients underwent surgery, and 16.7% received neoadjuvant chemotherapy during pregnancy. The unadjusted hazard ratio of pregnancy for progression-free survival was 1.18 (95% CI: 0.74–1.88), showing no difference in survival outcome.

Maggan et al. compared data from 134 pregnant patients with Hodgkin lymphoma diagnosed during pregnancy (INCIP database) matched control non-pregnant patients [5]. Fifty-four percent of patients initiated chemotherapy during pregnancy, with increasing number of patients over time. Four percent of the patients received radiotherapy. Birthweight percentiles were lower in chemotherapy-exposed neonates, and there were more obstetrical complications such as preterm contractions (12%) and preterm rupture of membranes (5%). Survival comparison did not differ between both groups, similar to cervical cancer patients.

Thirteen patients with gastric cancer were analysed from the database [6]. Maggan et al. found that the prognosis of these patients is poor, mainly due to advanced disease at diagnosis. Twelve women were diagnosed with advanced disease and died within two years after pregnancy. Eight out of 10 live births were preterm because of complications such as preeclampsia, maternal deterioration, or therapy planning.

An excretion of cytostatic into breast milk has been evaluated in a breast cancer patient treated with weekly paclitaxel [7]. Paclitaxel levels drop below the minimum quantifiable dose at 72 hours following chemotherapy, with a relative infant dose of 0.091% showing that after 72 hours, it might be safe to allow breastfeeding.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting.	Amant F et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31435648
2	Pregnancy related cancer in Apulia. A population based linkage study.	Murgia F et al.	Eur J Obstet Gynecol Reprod Biol.	https://www.ncbi.nlm.nih.gov/pubmed/31404420
3	Ultrasound features and clinical outcome of patients with malignant ovarian masses diagnosed during pregnancy: experience of a gynecological oncology ultrasound center.	Moro F et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31326950
4	Characteristics of patients with cervical cancer during pregnancy: a multicenter matched cohort study. An initiative from the International Network on Cancer, Infertility and Pregnancy.	Halaska MJ et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30898935
5	Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study.	Maggen C et al.	Lancet Haematol.	https://www.ncbi.nlm.nih.gov/pubmed/31564649
6	Gastric cancer during pregnancy: a report on 13 cases and review of the literature with focus on chemotherapy during pregnancy.	Maggen C et al.	Acta Obstet Gynecol Scand.	https://www.ncbi.nlm.nih.gov/pubmed/31529466
7	Breast milk paclitaxel excretion following intravenous chemotherapy-a case report.	Jackson CGCA et al.	Br J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31363168

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Treatment of elderly patients with gynaecological cancers

Alex Mutombo

A study by Nadraja et al. analysed the transcriptomic profile of primary high-grade serous ovarian carcinoma in 50 patients aged >70. They revealed 81 genes with significantly altered expression in patients experiencing progression after first-line platinum-based treatment within six months versus those who progressed later than 12 months. The expression of ankyrin repeat and PH domain 1 was significantly lower in the group with early- versus late-progression ($p \leq 0.01$), suggesting that this might be an independent prognostic biomarker in older patients receiving platinum-based chemotherapy [1].

In the United States, a retrospective analysis was performed of 2,331 ovarian cancer patients between 2005–2012 regarding hospice enrolment and costs. Sixty-eight percent of patients died within hospice. Black patients were more likely to unenrol from hospice prior to death (OR 2.07; $p = 0.02$) compared to white patients. Lower costs were reported from patients who stayed in hospice till death [2].

Filippova et al. reported on the importance of preoperative/postoperative geriatric and surgical co-management to optimize outcomes in older, frail women who are about to undergo cytoreductive sugery for advanced ovarian cancer. [3]. The prospective study of 42 women demonstarted a optimally debulking rate of 97% (complete gross resection rate of 63%) with no 180 day mortality. The complication rate, including major and minor, was 55% and 8%, respectively, with a median follow-up of 15.7 months (range 3.7–38) and 12-month survival at 93.3%.

Hay et al. prospectively evaluated 80 patients (65% with ovarian and 34% with endometrial cancer) aged 65 or older undergoing neoadjuvant or adjuvant chemotherapy. Eighty-one percent of patients received a chemotherapy regimen consistent with standard-of-care chemotherapy. Age was not associated with receiving standard-of-care chemotherapy or tolerance or completion of chemotherapy [4].

Contradictory findings were reported by a retrospective study from Bun et al. that assessed the rate of receiving standard therapy (debulking surgery or chemotherapy apart from stage IA/B grade I non clear cell cancer who would not receive chemotherapy after surgery), as well as the feasibility and safety of chemotherapy in 36 elderly patients (aged 70 or older) with stage I–IV ovarian cancer compared with 208 younger patients (younger than 70). A significantly lower proportion of elderly patients than younger patients received standard therapy (15.7% vs. 32.5%, $p = 0.026$). The most common deviation from standard treatment was to utilize three weekly regimen instead of platinum/placitaxel insted of dose dense regimen. The rate of debulking surgery of 94.5% was conserably high cmpared to other studies. [5].

In a study to estimate survival in women aged 75 years or older with gynaecological cancer in Japan using data from 21 population-based cancer registries (including 4,089 patients), Inoue et al. reported that the five-year net survival of cervical, endometrial, and ovarian cancer patients was very low in the oldest age group (85–99 years old) compared to the next oldest group (80–84 years old) and the younger age group (75–79 years old). For cervical cancer, it was 54.5% in the younger age group, 40.8% in the older age group, and 28.2% in the oldest age group; for endometrial cancer patients, it was 64.5%, 51.6%, and 39.0%; and for ovarian cancer, 34.7%, 18.8%, and 8.3% % in the younger, older, and oldest age groups, respectively [6].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	ARAP1 is an independent prognostic biomarker in older women with ovarian high-grade serous adenocarcinoma receiving first-line platinum-based antineoplastic therapy.	Nadaraja S et al.	Acta Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31478407
2	How we use hospice: Hospice enrollment patterns and costs in elderly ovarian cancer patients.	Taylor JS et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30876488
3	Geriatric co-management leads to safely performed cytoreductive surgery in older women with advanced stage ovarian cancer treated at a tertiary care cancer center.	Filippova OT et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31078241
4	Chemotherapy in older adult gynecologic oncology patients: Can a phenotypic frailty score predict tolerance?	Hay CM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30503049
5	Feasibility of initial treatment in elderly patients with ovarian cancer in Japan: a retrospective study.	Bun S et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30993482
6	Net survival of elderly patients with gynecological cancer aged over 75 years in 2006–2008.	Inoue S et al.	Asian Pac J Cancer Prev	https://www.ncbi.nlm.nih.gov/pubmed/30803205

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Epidemiology of gynaecological cancers

Kemal Güngördük

Endometrial cancer

A case-control study among postmenopausal women on hormonal replacement therapy showed that circulating oestrogen/oestrogen metabolite levels were not associated with risk of endometrial cancer overall or by dualistic endometrial cancer subtype among women who took combined oestrogen/progestin therapy [1]. In addition, oestrogen/oestrogen metabolite levels were not associated with overall or serous ovarian cancer risk.

Doll et al. reported 1997–2014 data from the SEER databese on the incidence of endometrial cancer. Black women were at greater risk of developing endometrial cancer. Incidence in white women decreased over time from 102 (1997–2001) to 86 (2012–2014) cases per 100,000. However, in black women, there was no decreasing trend found, with 88 (1997–2001), 101 (2002–2006), 100 (2007–2011), and 102 (2012–2014) cases per 100,000 [2].

A large population-based study demonstrated that infertility was associated with a higher incidence rate of both ovarian (HR 1.53, 95% CI: 1.38–1.71) and endometrial cancer (HR 1.25, 95% CI: 1.11–1.40). Moreover, endometriosis was associated with a higher risk of ovarian cancer but not of endometrial cancer [3].

Ovarian cancer

A case-control study by Michels et al. demonstrated that women with metabolic syndrome had reduced ovarian cancer risk compared to women not meeting the diagnostic criteria (OR 0.86, 95 % CI: 0.82–0.89). Having one or two metabolic syndrome components was associated with an increased risk, but having three metabolic syndrome components was not [4].

In a population-based case-control study conducted in Montreal, information was collected on lifetime participation in various recreational physical activities, which was used to estimate moderate-to-vigorous recreational physical activity for each participant. Moderate-to-vigorous recreational physical activity was represented as average energy expenditure over the lifetime and in specific age-periods in units of metabolic equivalents per hour per week. Average recreational moderate-to-vigorous recreational physical activity over the lifetime or over specific life periods was not associated with a reduced ovarian cancer risk. In contrast, it was associated with a higher risk of high-grade serous carcinomas diagnosed before menopause (HR 1.21, 95% CI: 1.00–1.45) but not of cancers diagnosed after menopause (HR 1.04, 95% CI: 0.89–1.21) [5].

A population-based, case-control study demonstrated that breastfeeding was associated with a statistically significant decrease in ovarian cancer risk (OR 0.70, 95% CI: 0.58–0.85) [6]. Akinwunmi et al. showed that women who used statins had a lower risk of ovarian cancer compared to non-users (OR 0.68, 95% CI: 0.54–0.85) [7].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Circulating estrogens and postmenopausal ovarian and endometrial cancer risk among current hormone users in the Women's Health Initiative Observational Study.	Trabert B et al.	Cancer Causes Control.	https://www.ncbi.nlm.nih.gov/pubmed/31542834
2	Assessing endometrial cancer risk among US women: long-term trends using hysterectomy-adjusted analysis.	Doll KM, Winn AN	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/31125544
3	The risk of breast and gynecological cancer in women with a diagnosis of infertility: a nationwide population-based study.	Lundberg FE et al.	Eur J Epidemiol.	https://www.ncbi.nlm.nih.gov/pubmed/30623293
4	Metabolic syndrome and risk of ovarian and fallopian tube cancer in the United States: An analysis of linked SEER-Medicare data.	Michels KA et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31495456
5	Lifetime recreational moderate-to-vigorous physical activity and ovarian cancer risk: A case-control study.	Grundy A et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31199510
6	Breastfeeding factors and risk of epithelial ovarian cancer.	Modugno F et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30686553
7	Statin therapy and association with ovarian cancer risk in the New England Case Control (NEC) study.	Akinwunmi B et al.	Int J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30006925

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Gestational trophoblastic disease

Joanna Kacperczyk-Bartnik

In a phase III randomised controlled trial, Hemida et al. examined the effect of second uterine curettage (n = 43) versus no curettage (n = 43) [1]. Patients with low-risk postmolar gestational trophoblastic neoplasia were enrolled in the study. No reduction in the number of chemotherapy courses nor differences in relapse rate were identified.

A retrospective study by Chan Wah Hak et al. evaluated the outcome of 45 gestational trophoblastic neoplasia patients (41 high-risk and four low-risk with hCG levels exceeding 400 000 IU/L) treated with emergency chemotherapy—an induction two-day regimen with etoposide 100 mg/m^2 and cisplatin 20 mgc available 24/7 [2]. The overall survival during follow-up (at least six months, median follow-up time equal to nine months) was 98%.

Frijstein et al. retrospectively investigated treatment efficacy retrospectively with high-dose chemotherapy (HDC) and peripheral blood stem cell support in 32 patients with drug-resistant choriocarcinomas (n = 14) or poor-prognosis placental site/epithelioid trophoblastic tumours (n = 18) [3]. The overall survival rate after high-dose chemotherapy —administered exclusively or combined with other treatment—was 41%. Severe non-haematological high-dose chemotherapy toxicity affected 23 (72%) patients. Three (9%) patients died of high-dose chemotherapy toxicity due to sepsis and multiorgan failure.

The retrospective cohort study by Mora et al. described the replacement of actinomycin-D in second-line low-risk gestational trophoblastic neoplasia treatment [4]. Methotrexate-resistant patients were treated with actinomycin-D (n = 40), carboplatin (n = 23) or etoposide (n = 7) as a single-agent second-line chemotherapy, achieving remission rates of 80%, 47.8%, and 71.4%, respectively. Toxicity-caused cycle delays occurred in 2.4%, 69.6%, and 17.4% of patients, respectively. These results favoured the protocol with actinomycin-D as second-line treatment in patients resistant to methotrexate.

In a population-based cohort study Balachandran et al. analysed a group of 4,201 patients after low- and high-risk gestational trophoblastic neoplasia treatment to assess surveillance protocol with the emphasis on its duration [5]. As no recurrence beyond seven years post-chemotherapy completion was observed, authors recommend surveillance cessation after 10 years.

A meta-analysis by Tranoulis et al. presented reproductive and obstetric outcomes after gestational trophoblastic neoplasia chemotherapy treatment [6]. Twenty-seven retrospective studies, including 6,752 pregnancies, were analysed. The pooled proportion pregnancy rate after chemotherapy in 3,764 women was 67.42%. The pregnancy rate among women with a desire to conceive (n = 1,329) was 86.7%. The term live-birth rate in 6,752 pregnancies was over 75%. Unfavourable pregnancy outcomes were comparable to the general population. The pre-term birth rate in 5,781 pregnancies was 5.06%. The stillbirth rate in 6,752 pregnancies was 1.32%. The first or second trimester miscarriage rate in 5,439 pregnancies was 14.62%. The malformation rate in 4,682 pregnancies was 1.76%. The gestational trophoblastic neoplasia recurrence rate in 6,384 pregnancies was 1.28%.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Second uterine curettage and the number of chemotherapy courses in postmolar gestational trophoblastic neoplasia: a randomized controlled trial.	Hemida R et al.	Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/30969220
2	Emergency etoposide-cisplatin (Em-EP) for patients with germ cell tumours (GCT) and trophoblastic neoplasia (TN).	Chan Wah Hak C et al.	BMC Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31382912
3	The results of treatment with high-dose chemotherapy and peripheral blood stem cell support for gestational trophoblastic neoplasia.	Frijstein MM et al.	Eur J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30731277
4	Can carboplatin or etoposide replace actinomycin-d for second-line treatment of methotrexate resistant low-risk gestational trophoblastic neoplasia?	Mora PAR et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30857648
5	When to stop human chorionic gonadotrophin (hCG) surveillance after treatment with chemotherapy for gestational trophoblastic neoplasia (GTN): a national analysis on over 4,000 patients.	Balachandran K et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31375268
6	Gestational trophoblastic neoplasia: a meta-analysis evaluating reproductive and obstetrical outcomes after administration of chemotherapy.	Tranoulis A et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31253638

Follow-up after gynaecological malignancies

Jenneke Kasius

Kumarakulasingam et al. evaluated the usefulness of and patients' feedback on a new patient-initiated follow-up scheme [1]. The standard hospital follow-up was replaced by patient-initiated follow-up, without no routine visits in the hospital. Still, patients could contact a nurse specialist whenever they experienced concerns or symptoms. Within 18 months after implementation of the new follow-up, 228 patients with early-stage endometrial cancer were enrolled, of whom 125 were included directly without former hospital follow-up. Patient satisfaction was evaluated by questionnaires at six, 18, and 12 months of follow-up. A total of 19.7% contacted the nurse specialist at least once, mainly in the first six months of follow-up and because of physical symptoms. Only four patients went back to hospital for follow-up due to anxiety and multiple symptoms. The quality of life scores were generally higher than earlier published reference scores. Over 60% of all patients described the patient-initiated follow-up useful and reassuring.

Tamminga et al. randomised 106 cancer patients to an intervention group, receiving hospital-based follow-up enriched with work-related support, or a control group, receiving standard hospital follow-up [2]. Patients between the ages of 18 and 60 who had paid employment and an estimated one-year survival rate of 80% were eligible. Thirty-five percent had gynaecological cancers, 65% breast cancer, and 4% another type of cancer. The intervention group received education and work support by an oncology nurse or medical social worker in four 15-minute-long meetings, a letter from the health care provider to the occupational physician, and a 'return-to-work' plan. The time to return to work, as well as the quality of life (questionnaire at baseline, six, 12, 18, and 24 months of follow-up), physical and mental work ability, and work functioning, were assessed. Suboptimal study characteristics were its small sample size (half of the calculated sample size), significant differences at baseline (more co-morbidities and 'a higher importance of work' in the intervention group), loss to follow-up of around 20%, and actual work support by a nurse in only 88% of the patients in the intervention group. No significant differences were found between the intervention and control groups.

One of the less investigated adverse cancer treatment outcomes is financial toxicity. Bouberhan et al. performed a survey amongst a Massachusetts-based population on financial toxicity after treatment for gynaecologic cancer and its association with other characteristics [3]. The Comprehensive Score for Financial Toxicity tool (COST) was used, a questionnaire including 11 items, leading to a score from 0–44. The lower the score, the higher the financial toxicity. Amongst 240 responders to the median COST score was 29 (range 2–44). Multivariate analysis showed that income, type of insurance, and initial cancer treatment negatively influenced financial toxicity. Avoiding medical care and higher financial toxicity was found to be related.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Acceptability and utilisation of patient-initiated follow-up for endometrial cancer amongst women from diverse ethnic and social backgrounds: a mixed methods study.	Kumarakulasingam P et al.	Eur J Cancer Care.	https://www.ncbi.nlm.nih.gov/pubmed/30748056
2	Two-year follow-up of a multi-centre randomized controlled trial to study effectiveness of a hospital-based work support intervention for cancer patients.	Tamminga SJ et al.	J Occup Rehabil.	https://link.springer.com/article/10.1007/s10926-019-09831-8
3	Financial toxicity in gynecologic oncology.	Bouberhan S et al.	Gynecol Oncol.	https://www.sciencedirect.com/science/article/pii/S0090825819304986

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Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

A retrospective study by Yang et al. assessed the efficacy of diagnostic hysteroscopy and lesion resection combined with progestin therapy in 160 young patients with endometrial atypical hyperplasia and FIGO stage IA endometrial cancer. Patients received constant oral progestins and had a hysteroscopic evaluation every three months until complete response. The authors stated that this is a safe and effective option for patients with endometrial lesions ≤ 2 cm [1]. Wang et al. conducted a retrospective analysis of 41 patients with recurrent endometrial cancer after fertility-sparing treatment. Twenty-three patients presented with an endometrial cancer recurrence, while 18 were diagnosed with atypical hyperplasia after a median disease-free interval of 16 months [2]. Maggiore et al. retrospectively assessed the effectiveness of a levonorgestrel-releasing intra-uterine system in 48 patients with endometrial hyperplasia or cancer. Patients with grade 1 had higher rates of complete response and lower rates of disease progression than patients with grade 2 endometrial cancer, highlighting the efficacy of the levonorgestrel-releasing intra-uterine system in fertility-sparing protocols [3].

Cervical cancer

Malmsten et al. conducted a retrospective analysis of patients with early-stage cervical cancer who underwent a vaginal trachelectomy and pelvic lymphadenectomy. Of the 28 patients who received fertility-sparing treatment, the authors reported two recurrences, 24 pregnancies, and 17 live births. A quality-of-life evaluation revealed low rates of urogynaecological morbidities, but high rates of lymphoedemas. Thus, vaginal trachelectomy with laparoscopic pelvic lymphadenectomy is an acceptable technique with low morbidity [4]. Bogani et al. examined the efficacy and safety of cervical conisation and pelvic node assessment as a fertility-sparing treatment among 32 patients with early-stage cervical cancer. Prospectively collected data revealed no recurrences. Eleven patients managed to achieve pregnancy. Thus, cervical conisation and lymph node assessment is a valid fertility-sparing treatment [5]. Li et al. conducted a retrospective analysis of 333 patients treated with abdominal radical trachelectomy. The results revealed no difference in the recurrence rate among patients with tumours < 2 cm and ≥ 2 cm. The recurrence rate in women with tumours ≥ 2 cm was comparable to that in patients with tumours < 2 cm (5.3 versus 2.0%, respectively, p = NS). However, the recurrence rate was significantly higher in patients with adenosquamous carcinomas, compared to those with adenocarcinomas and squamous cell carcinomas (18.2, 3.9, and 2.6%, respectively, p < 0.05), establishing the histology type as the only independent risk factor for recurrence [6].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrial cancer.	Yang B et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30674421
2	Prolonged conservative treatment in patients with recurrent endometrial cancer after primary fertility-sparing therapy: 15-year experience.	Wang Y et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30746595
3	Efficacy and fertility outcomes of levonorgestrel-releasing intra-uterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: a retrospective study.	Leone Roberti Maggiore U et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31074240
4	Long-term fertility, oncological, and quality-of-life outcomes after trachelectomy in early stage cervical cancer.	Malmsten C et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/30488281
5	Long-term results of fertility-sparing treatment for early-stage cervical cancer.	Bogani G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31000470
6	Oncological results and recurrent risk factors following abdominal radical trachelectomy: an updated series of 333 patients.	Li X et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/30663205

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Palliative care and quality of life in gynaecological cancers

Nadja Taumberger and Engin Çelik

Joly et al. assessed long-term fatigue and quality of life in epithelial ovarian cancer survivors compared to an age-matched healthy control group in a multicentre case-control study in France. They showed that there is a significant difference in quality of life and depression, neurotoxicity, sleep disturbance, as well as long-term fatigue. They suggest that patients should have an evaluation for fatigue after ending treatment and offered specific therapeutic options to prevent long-term fatigue [1].

Palaia et al. retrospectively analysed their data on ovarian cancer patients who died between 2007–2017 and received anti-neoplastic treatment towards end of life. They included 110 adult women whose ovarian cancer had recurred, and they assessed the quality of life using validated questionnaires. More than 75% of patients had received an antineoplastic treatment in the last three months of their life, which was associated with a deterioration in quality of life with a significant worsening of all measured scales. Balancing expected benefit and risks for decereased quality of life is important when considering active cancer treatment vs best supportive care towards end of life [2].

Koole et al. performed a multicentre, open-labelled, randomised phase II trial for patients with stage III ovarian cancer comparing interval cytoreduction surgery with or without intraperitoneal HIPEC according to the health-related quality of life.

They included 245 patients, of which 197 patients completed at least one of the multiple questionnaires, administered at baseline, after surgery, after end of treatment, and every three months thereafter. The results showed no difference in health-related quality of life when adding HIPEC to the interval cytoreduction surgery [3].

Sompratthana et al. investigated end-of-life care in gynaecologic oncology patients at King Chulalongkorn Memorial Hospital (Bangkok, Thailand) in 2011–2016. A total of 159 patients were included in the study, and a majority of patients were diagnosed with tubal-ovarian-peritoneal cancer (87 patients, 54.7%). The most frequent symptoms at hospital admission were poor oral intake (68.6%), and abdominal distension or discomfort (63.5%). Major surgery was done in 36 patients (22.6%) in the last six months of life. According to the study, many patients received aggressive procedures in the end-of- life treatment which causes high discomfort for the patients. The authors suggested that end-of-life care is inadequate in Thailand [4].

Gressel et al. assessed Patient-Reported Outcomes Measurement Information System (PROMIS) electronic patient reported outcomes measures (ePROs) to screen for severe cancer symptomatology in gynaecologic oncology. Three hundred thirty-six patients completed an ePRO survey in the waiting area. The survey was designed to assess physical function, pain interference, fatigue, depression, anxiety, and sexual function. Fifty-nine patients were severely symptomatic at least one in at least of the domains. In the multivariate analysis, ovarian cancer (OR 3.32,95% CI: 1.73–6.39) and active disease (OR 2.22, 95% CI: 1.26–3.93) were significantly associated with severe symptomatology. Thirty-nine were referred to ancillary services, and none of these referrals were made by their treating gynaecologic oncologist during their clinic encounter [5].

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	Long-term fatigue and quality of life among epithelial ovarian cancer survivors: a GINECO case/control VIVROVAIRE I study.	Joly F et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30851097
2	The EOLO (End-of-Life Ovarian Cancer) study: Approach to ovarian cancer patients at the end of life.	Palaia I et al.	Oncology.	https://www.ncbi.nlm.nih.gov/pubmed/31437848
3	Health-related quality of life after interval cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with stage III ovarian cancer.	Koole SN et al.	Eur J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31128948
4	End-of-life symptoms and interventions among women with gynecologic cancers in a tertiary-care hospital in Thailand.	Sompratthana T et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31079059
5	Utilizing the Patient Reported Outcomes Measurement Information System (PROMIS®) to increase referral to ancillary support services for severely symptomatic patients with gynecologic cancer.	Gressel GM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30876496

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Nutrition and perioperative care

Begoña Díaz de la Noval

Lyell et al. reported that a poor preoperative nutritional status (defined as serum albumin levels less than 3.5 g/dL) was associated with worsened long-term survival (HR 1.7; 95% CI: 1.1–2.6) and increased incidence of postoperative complications ($p = 0.03$) in patients that underwent pelvic exenteration [1]. Limitations included the retrospective nature of the study, with a wide variety of malignancies, procedures, surgical teams, previous treatments, and disease history of the cohort, and the postoperative outcome was considered independent of curative or palliative intent, so patients were more likely to have an extensive disease and worse overall survival. The authors suggested including preoperative albumin testing, nutritional consultation, and supplementation before surgery.

A cross-sectional study from Wang et al. reported the development, validation, and application of an MD Anderson Symptom Inventory to evaluate the common symptom burden during perioperative care for gynaecologic cancer or benign tumours in English-speaking patients. The 9 common postoperative symptoms identified in qualitative interviews and were added to the core MDASI items [2]. The study limitations were the absence of a test of sensitivity and low cut-off point between moderate and severe levels for individual symptoms which must be improved.

Recent reports support that perioperative transfusion may result in immunosuppressive effects and has been reported to worsen perioperative and surgical outcomes via a phenomenon called transfusion-related immune modulation. A case-control study performed by Manning-Geist et al. analysed the outcome after perioperative red blood cell transfusion in 270 patients after interval debulking surgery for ovarian cancer [3]. They concluded that transfusion was not independently associated with thrombosis, intra-abdominal infection, wound complication, worse progression-free survival or overall survival. The authors propose that postoperative complications and a decreased outcome seen in previous studies after transfusion may be due to the circumstances under which blood transfusion becomes necessary.

Nelson et al. provided the updated consensus review for the ERAS gynaecologic/oncology guidelines. The updated guidelines contain specific guidence on pre-habilitation programs, bundles to reduce surgical site infection and updated information on ERAS components such as fluid management and nutrition [4].

In their retrospective cohort study (n = 971), Hillman et al. analysed factors associated with the achievement of opioid-free pain control after gynaecologic surgery in an enhanced recovery after surgery (ERAS) program [5]. In the multivariate logistic regression, demographic characteristics such as older age at the time of surgery (OR 1.04, 95% CI: 1.02–1.06), current smoker status (OR 0.42, 95% CI: 0.20–0.81), and white or Caucasian race (OR 0.59, 95% CI: 0.38–0.91) are independently associated with no use of opioids on day prior to discharge; while surgical indication, complexity, and operative time, are not associated. Limitations of the study were its retrospective, single-institution trial design, results that are not applicable out of an ERAS program, and a lack of information on opioid usage after hospital discharge.

Perioperative epidural anaesthesia has become an important aspect of ERAS protocols. In their retrospective cohort study (n = 561) Huepenbecker et al. demonstrated that perioperative epidural use as a part of an ERAS protocol improved postoperative pain control ($p = 0.01$), decreases postoperative opioid use ($p < 0.01$), decreased narcotic pain medications ($p < 0.01$), and improved pain relief in a gynaecologic oncology population .[6]. The study was a retrospective, single-institution trial with no difference by type of tumour or stage, results are not applicable out of an ERAS program, the potential impact of a dedicated anaesthesia service for acute pain or the preoperative use of opioids was not considered, and the results may have confounders as no multivariable analysis was performed.

Relevant articles retrieved February 15, 2019 – September 30, 2019

No	Title	Authors	Journal	Link to abstract
1	The effect of preoperative nutritional status on postoperative complications and overall survival in patients undergoing pelvic exenteration: A multi-disciplinary, multi-institutional cohort study.	Lyell NJ et al.	Am J Surg.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30982571
2	Validation and application of a module of the MD Anderson Symptom Inventory for measuring perioperative symptom burden in patients with gynecologic cancer (the MDASI-PeriOp-GYN).	Wang XS et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30876494
3	Infection, thrombosis, and oncologic outcome after interval debulking surgery: Does perioperative blood transfusion matter?	Manning-Geist BL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30635213
4	Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery after Surgery (ERAS) Society recommendations - 2019 update.	Nelson G et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30877144
5	Patient characteristics and opioid use prior to discharge after open gynecologic surgery in an enhanced recovery after surgery (ERAS) program.	Hillman RT et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30902370
6	Continuous epidural infusion in gynecologic oncology patients undergoing exploratory laparotomy: The new standard for decreased postoperative pain and opioid use.	Huepenbecker SP et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=30798950

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