LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

Reviews covering publications from September 30, 2019 – March 31, 2020

Kristina Lindemann
Kamil Zalewski
Michael J. Halaska
Zoia Razumova

Supported by ESGO

Issue No. 1 (11) May 2020

ENYGO
ESGO European Network of Young Gynae Oncologists
www.esgo.org
The European Voice of Gynaecological Oncology

Dear colleagues,

We present LiFE 11! It includes summaries of publications in gynaecological oncology dating from September 15, 2019, through March 30, 2020. LiFE is an initiative of ENYGO supported by ESGO.

We are proud to be able to share LiFE with you despite the difficult times. Some of you may be enjoying the careful opening up of societies while some of you may still be caught in the middle of the COVID-19 pandemic lockdowns. We have been through a period of cancelled or postponed international meetings, and we hope that LiFE will therefore be of additional value to all of you.

This issue was supported by reports from our new authors Natalia Rodriguez Gómez-Hidalgo and Ariel Glickman (Spain), Nicolas Samartzis and Dimitrios Rafail Kalaitzopoulos (Switzerland), Chrysoula Margioula-Siarkou (Greece), and Khayal Gasimli (Germany). We are proud of the ongoing effort of our author team and the enthusiasm of our new authors.

Following the ESGO workshop on scientific reviewing and writing, we held two webinars this spring. In one, we presented the highlights of the LiFE 10 report; the second was held in collaboration with Prof. Pedro Ramirez and was dedicated to the professional development of LiFE authors.

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 11 and find it interesting and informative! A special thanks again to our global community of LiFE authors for their ongoing effort and cooperation in this project. Stay safe!

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

Stay up to date!

Yours,

The LiFE team

Kristina Lindemann
Kamil Zalewski
Michael J. Halaska
Zoia Razumova

Creative Commons licence
LiFE reports are freely available to read, download and share from the time of publication. Reports are published under the terms of the Creative Commons Licence Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this licence visit: http://creativecommons.org/licenses/by-nc-nd/4.0/

CONTENTS

Ovarian cancer

Endometrial cancer

Cervical cancer

Vulvar cancer

Miscellaneous

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

Surgical treatment of primary and recurrent ovarian cancer

Ilker Kahramanoglu and Patriciu Achimas-Cadariu

Primary surgery or neoadjuvant chemotherapy in advanced ovarian cancer

In a multicentre, randomised, open-label phase III trial conducted in 34 Japanese centres, Onda et al. analysed whether neoadjuvant chemotherapy is non-inferior to primary debulking surgery in terms of overall and progression-free survival in patients with stage III/IV ovarian, tubal, and peritoneal cancers. The trial enrolled 301 patients; 149 in the primary debulking surgery group and 152 in neoadjuvant chemotherapy group. Patients in the primary debulking surgery arm received eight cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 6) every three weeks. The neoadjuvant chemotherapy arm patients received four cycles of preoperative and four cycles of postoperative chemotherapy. Complete macroscopic resection was achieved in 11.6% of those who underwent primary debulking surgery. The median overall survival was 49 and 44.3 months in the primary debulking surgery and neoadjuvant chemotherapy arms, respectively. The median progression-free survival was 15.1 and 16.4 months in the primary debulking surgery and neoadjuvant chemotherapy arms, respectively. Hazard ratios for death and progression with neoadjuvant chemotherapy compared to primary debulking surgery were 1.052 (90.8% CI: 0.835–1.326, p = 0.24) and 0.96 (95% CI: 0.75–1.23), respectively. The small sample size and the low complete cytoreduction rate in the primary debulking surgery arm limit the conclusions of the study. The results of the AGO TRUST study with stringent requirements for the quality of the participating centre as well as for surgical technique are awaited. [1]

Surgical technique

In a single-centre retrospective study performed at Charité Medical University Berlin, Muallem et al. reported on their novel technique for primary debulking surgery in advanced ovarian cancer and compared complete resection rates with a conventional surgical approach. The 'Total retroperitoneal en bloc resection of multivisceral-peritoneal packet (TROMP)' allows removal of the parietal peritoneum with no-touch isolation (A descriptive video is available at https://www.youtube.com/watch?v=UkXjSQ7p1SY). The study did not report if the technique was applied by a single surgeon or by several members of the team. Complete macroscopic resection rates were 88% and 61.3% in the TROMP group (n = 58) and in the conventional surgery group (n = 150), respectively (p = 0.001). Blood loss, duration of surgery, and postoperative complications were similar between groups. [2]

Surgical treatment of recurrent ovarian cancer

The GOG 213 study, a randomised, multinational, phase III clinical trial of secondary surgical cytoreduction in women with resectable, platinum-sensitive, recurrent ovarian cancer randomised patients to secondary cytoreduction before chemotherapy (n = 240) and chemotherapy alone (n = 245). Adding secondary surgical cytoreduction before chemotherapy did not result in longer overall survival than chemotherapy alone (median 50.6 months vs 64.7 months, HR 1.29, 95% CI: 0.97–1.72, p = 0.08). The median progression-free survival was longer in the secondary surgical cytoreduction group than in the chemotherapy group; however, hazard ratios for disease progression or death did not indicate a statistically significant benefit (median 18.9 months vs 16.2 months, HR 0.82, 95% CI: 0.66–1.01). When restricting the analysis to patients who had complete gross resection (67% of patients undergoing surgery), there was no benefit of secondary surgical cytoreduction on overall survival compared to the chemotherapy group (HR 1.03, 95% CI: 0.74–1.46), although there was a benefit in progression-free survival (HR 0.62, 95% CI: 0.48–0.80). [3]

In contrast with GOG 213, the previously published DESKTOP III trial reported that patients with a positive AGO score and a first platinum-sensitive relapse who underwent secondary surgical cytoreduction had a significantly longer progression-free survival than patients in the chemotherapy-only group; however, in a cross-trial comparison, the difference occurred from a shorter progression-free survival in the control group of the DESKTOP III trial (14.0 months) compared to the GOG 213 control group (16.2 months), while the progression-free survival in the surgical arms of both trials was similar (19.6 months in the DESKTOP III trial and 18.9 months in the GOG 213 trial). Another difference between the two studies was the more frequent use of bevacizumab in the GOG 213 trial (84%) compared to the DESKTOP III trial (approximately 20%), which may have masked an incremental benefit from surgery together with the introduction of PARP inhibitors in routine clinical practice. Overall survival data from DESKTOP III were recently published at the ASCO annual meeting. Median overall survival in the intent-to-treat population was 53.7 months and 46.0 months for those treated with and without surgery, respectively (HR 0.75, 95% CI: 0.58–0.96, p = 0.02). Notably, median overall survival for the subgroup of patients in the surgery arm who achieved complete resection versus an incomplete resection was 61.9 months and 28.8 months, respectively (HR 0.40, 95% CI: 0.28–0.59, p <0.001). In addition, median overall survival in the subgroup achieving a complete resection with surgery was 61.9 months compared 46.0 months for those patients in the no-surgery arm (HR 0.57, 95% CI: 0.43–0.76, p < 0.001). [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial	Onda T et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/32179446/
2	Total retroperitoneal en bloc resection of multivisceral-peritoneal packet (TROMP operation): a novel surgical technique for advanced ovarian cancer	Muallem MZ et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32221020/
3	Secondary surgical cytoreduction for recurrent ovarian cancer	Coleman RL et al.	N Engl J Med	https://pubmed.ncbi.nlm.nih.gov/31722153/
4	Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: Final analysis of AGO DESKTOP III/ENGOT-ov20	Du Bois A et al.	J Clin Oncol	https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.6000

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

Medical treatment of primary ovarian cancer

Ilker Selçuk and Muhammad Rizky Yaznil

Coquard et al. analysed the role of olaparib plus bevacizumab in patients with a newly diagnosed ovarian cancer regardless of BRCA mutation status as a maintenance treatment with a randomised, double-blind, international, phase III study (PAOLA-1). After complete or partial response to platinum-based chemotherapy in combination with bevacizumab, patients were randomised 2:1 to receive olaparib (300 mg twice daily) or a placebo up to 24 months or disease progression. Bevacizumab was given for 15 months. Progression-free survival (PFS) was significantly longer in the olaparib group (537 patients) than in the placebo group (269 patients), (median, 22.1 months vs 16.6 months; HR 0.59; 95% CI: 0.49–0.72; $p < 0.001$). In patients with a somatic BRCA mutation, PFS was 37.2m versus 21.7m in the olaparib and placebo arms, respectively (HR 0.31, 95% CI: 0.20–0.47). In homologous-recombination-deficiency-positive tumours, including those with a somatic BRCA mutation, the median progression-free survival was 37.2 vs. 17.7 months (HR 0.43, 95% CI: 0.28–0.66). However, in patients without a tumour BRCA mutation, the PFS was 18.9m versus 16.0m in the olaparib and placebo arms, respectively (HR 0.71, 95% CI: 0.58-0.88). The mean global quality of life score at baseline was also higher in the olaparib group than the control (68.6 vs 67.1). There was not any statistically significant change in global health-related quality of life between the groups. Grade 3 or higher adverse effects of anaemia and lymphopenia were more common for the olaparib group, but hypertension was more common in the placebo group. The study could conclude regarding a potential synergistic effect of olaparib and bevacizumab in the homologous recombination deficiency positive group due to the lack of a comparator arm with olaparib alone. Further, multiple testing adjustments were not performed for the pre-planned subgroup analysis of homologous recombination deficiency positive patients. [1]

Coquard et al. finalised the AGO-OVAR 12 trial of adding the oral triple angiokinase inhibitor nintedanib to standard front-line chemotherapy. Primary debulked, stage IIB-IV newly diagnosed advanced ovarian cancer patients were randomised 2:1, to nintedanib (200 mg, twice daily, 911 patients) or placebo (455 patients), given concomitantly and for up to 12 months. The median duration of follow-up was 60.9m (IQR: 60.5–61.3m). There was no significant difference in overall survival with a median 62.0m with nintedanib and 62.8m with placebo (HR 0.99, 95% CI: 0.83–1.17, $p = 0.86$). In an updated PFS analysis, the previously reported benefit in patients with non-high-risk disease (stage III with residual disease $\leq$ 1 cm, or any stage II) persisted (27.7m vs 21.7m, respectively; HR 0.77; 95% CI: 0.64–0.93) but did not translate into any overall survival benefit. Nintedanib was associated with an increased incidence of gastrointestinal adverse effects, particularly diarrhoea; moreover, gastrointestinal perforation as a fatal complication was more common. [2]

ICON-8 was a randomised, phase III three-arm trial of weekly dose-dense chemotherapy as first-line treatment in a total of 1,566 patients with epithelial ovarian, primary peritoneal, or fallopian tube carcinoma patients of European ethnicity. Group 1 received three-weekly carboplatin AUC5/6 and three-weekly paclitaxel 175 mg/m^2; group 2 three-weekly carboplatin and weekly paclitaxel 80 mg/m^2; and group 3 weekly carboplatin AUC2 and weekly paclitaxel 80 mg/m^2. The median follow-up period was 36.8m. The median PFS was 17.7, 20.8, and 21.0m for groups 1, 2, and 3, respectively; there was no statistically significant difference of PFS for any group. The subgroup analyses according to primary debulking surgery and interval debulking surgery showed that the restricted mean survival time in the primary debulking cohort was 32.6, 33.0, and 33.3m, respectively; however, in the interval debulking surgery arm, the restricted mean survival time was 18.6, 19.1, and 19.6m, respectively. Differences in the distribution of FIGO stage in the primary debulking arm and neoadjuvant chemotherapy arm may explain the longer progression-free survival on the primary debulking cohort. The toxicity profiles were similar in all three groups, including those of grade 2 or higher sensory neurotoxicity (group 1 had 27%; group 2, 24%; and group 3, 22%). A cross-sectional analysis of quality of life nine months after randomisation was also similar. In conclusion, dose-dense chemotherapy did not lead to an improved PFS in the European population. Despite the survival advantage in the Japanese population with a dose-dense chemotherapy protocol (JCOG 3016), the MITO-7 trial in Europe did not show a prolonged PFS. Nevertheless, the toxicity profile was better in the European study, with less haematological toxicity and neuropathy. The effect of gene polymorphisms on drug metabolism may in part explain the differences in toxicity and efficacy. [3]

Final overall survival data were presented for the AGO-OVAR 16 study of daily 800 mg pazopanib compared to placebo in newly diagnosed epithelial ovarian cancer patients after first-line chemotherapy for up to 24m or disease progression. In the updated analysis, median progression-free survival was longer in the pazopanib arm with 17.9m versus 12.3m for the pazopanib and placebo arms, respectively (HR 0.766, 95% CI: 0.643–0.911, $p = 0.0021$). However, there was no difference in median overall survival between the groups: 59.1m (95% CI: 53.5–71.6m) versus 64.0m (95% CI: 56.0–75.7m) in the pazopanib and placebo arms, respectively (HR 0.960, 95% CI: 0.805–1.145, log rank $p = 0.6431$). The confounding factors of multiple agents after recurrence may mask the potential effect of initial treatment strategies. [4]

Medical treatment of primary ovarian cancer

Ilker Selçuk and Muhammad Rizky Yaznil

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Olaparib plus bevacizumab as first-line maintenance in ovarian cancer	Ray-Coquard I et al.	N Eng J Med	https://www.ncbi.nlm.nih.gov/pubmed/31851799
2	Final results from GCIG/ENGOT/AGO-OVAR 12, a randomised placebo-controlled phase III trial of nintedanib combined with chemotherapy for newly diagnosed advanced ovarian cancer	Ray-Coquard I et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31381147
3	Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial	Clamp AR et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/31791688
4	Overall survival results of AGO-OVAR16: A phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer	Vergote I et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31519320

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

Medical treatment of recurrent ovarian cancer

Seda Şahin Aker and Mara Mantiero

ENGOT-OV16/NOVA was a multicentre, double-blind, randomised, phase III study of 553 patients with recurrent ovarian cancer receiving niraparib/placebo (300 mg daily) as maintenance therapy after response to last platinum-based chemotherapy. The authors have now published the efficacy data according to response to last chemotherapy (partial vs complete response). In the gBRCA cohort, 99 had a partial response, and 104 had a complete response to their last platinum-based therapy; in the non-BRCA cohort, 173 had a partial, and 177 had a complete response. In both cohorts, patients had significantly longer progression-free survival (PFS) independent of their response status (gBRCAmut cohort: HR for partial response 0.24, 95% CI: 0.131–0.441 vs HR for complete response 0.30, 95% CI: 0.160–0.546, $p < 0.0001$. non–gBRCAmut cohort: HR for partial response 0.35, 95% CI: 0.230–0.532, $p < 0.0001$ vs HR for complete response 0.58, 95% CI: 0.383–0.868, $p = 0.0082$). At least 5% of patients had a grade 3 or greater adverse event. The most common adverse events were thrombocytopenia (25.6% vs 31.0%), anaemia (26.1% vs 23.5%), neutropenia (10.0% vs 12.3%), hypertension (9.4% vs 7.0%), and fatigue (2.8% vs 8.6%). [1]

Pfisterer et al. performed a multicentre, open-label, randomised, phase III superiority trial. The aim of the study was to analyse a standard bevacizumab-containing regimen versus carboplatin–pegylated liposomal doxorubicin combined with bevacizumab in recurrent epithelial ovarian cancer. In all, 337 patients were assigned to the standard therapy group (carboplatin–gemcitabine–bevacizumab) and 345 to the experimental group (carboplatin–pegylated liposomal doxorubicin–bevacizumab). The median PFS was 13.3 months in the experimental group versus 11.6 months in the standard group (HR 0.81, 95% CI: 0.68–0.96, $p = 0.012$). Grade 3 or worse adverse events were more common with standard therapy (81% vs 71%). The most common grade 3–4 adverse events were hypertension (27% in the experimental group vs 20% in the standard group) and neutropenia (12% vs 22%). The study is limited by the absence of a PARP inhibitor in maintenance in either treatment group and the lack of information on BRCA mutation status. [2]

SOLO3 was a randomised, controlled, open-label, phase III trial. In all, 266 patients with gBRCA mut platinum-sensitive relapsed ovarian cancer treated with at least two prior lines of platinum-based chemotherapy were enrolled. Patients were randomly (2:1) assigned to olaparib ($n = 178$; 300 mg twice a day) or a non-platinum single-agent chemotherapy group (PLD, paclitaxel, gemcitabine, or topotecan) ($n = 78$). The primary endpoint was the objective response rate (ORR). The BICR-assessed ORR rate was significantly higher in the olaparib group than in the chemotherapy group (72.2% vs 51.4%, OR 2.53, 95% CI: 1.40–4.58, $p = 0.002$). BICR-assessed PFS was also significantly higher in the olaparib vs chemotherapy group (HR 0.62, 95% CI: 0.43–0.91]; $p = 0.013$; median, 13.4 vs 9.2 months). In the subgroup that received two prior lines of treatment, the ORR was 84.6% with olaparib and 61.5% with chemotherapy (OR 3.44, 95% CI: 1.42–8.54). The most common grade 3 adverse events were anaemia in the olaparib group and palmar-plantar erythrodysesthesia and neutropenia in the chemotherapy group. Fatal adverse events occurred in four patients (2.2%) in the olaparib group (i.e., MDS/AML) versus one patient (1.3%) in the chemotherapy group (mesenteric vein thrombosis). The study was limited by its open-label design and the lack of a control arm with platinum-based chemotherapy arm. [3]

Cecere et al. performed a non-interventional, retrospective study conducted in 13 MITO centres to describe the effectiveness and safety of olaparib on post-progression treatment and response. In the 234 BRCA mutated patients, median PFS was 14.7 months. Patients receiving olaparib after second-line platinum-based chemotherapy had longer PFS compared to those treated in the third and later lines, with a median PFS of 16.6, 15.5, and 8.2 months, respectively. Sixty-six patients received further treatment after progression on olaparib and were evaluable for response; the ORR was 22.2%, 11.1%, and 9.5% in patients with a platinum-free interval of >12 months, 6–12 months and <6 months, respectively. The most common grade 3–4 adverse event was anaemia (6%), and dose reduction was recorded in 20.9% of patients. This study showed lower response rates than expected according to the platinum-free interval in patients treated with chemotherapy after olaparib progression. This may be explained by cross resistance between PARPIs and chemotherapy and warrants further investigation. [4]

Colombo et al. published a multicentre, randomised, open-label, two-stage design, non-comparative phase II trial aimed assessing the efficacy and safety of the combination bevacizumab-trabectedin with or without carboplatin in 71 women with partially platinum-sensitive recurrent ovarian cancer. Primary endpoints were PFS and severe toxicity rate at six months (PFS6, ST6). Efficacy and safety at six months for the non-platinum-based doublet (combination bevacizumab-trabectedin) was six-month progression-free survival over 35% and a severe toxicity rate below 30%; combination bevacizumab-trabectedin compared favourably with other platinum- and non-platinum based regimens. The cohort with triplet combination bevacizumab-trabectedin-carboplatin was not expanded to the second stage due to toxicities that exceeded the pre-defined threshold of 30%. Information on BRCA status was not available in the study. [5]

Arend et al. published a phase II double-blind trial comparing the combination of primasertib (MEK inhibitor; 60 mg daily) with SAR245409 (PI3K inhibitor; 70 mg daily) versus primasertib alone in 65 patients with previously treated unresectable borderline and low-grade ovarian cancer. There were no significant differences in the objective response rate (12.1% vs 9.4%); however, the trial was not completed, mainly due to the high rate of discontinuation (about 25%) due to toxicity. [6]

Gorringe et al. published a large cohort ($n = 202$) of mucinous ovarian cancer patients. They analysed gene copy number and DNA sequencing data to evaluate mismatch repair and homologous recombination deficiency. About 26% of patients have an amplification of ERBB2, 66% have a KRAS/NRAS mutation, and 9% a BRAF mutation. However, only 1/184 patients had a mismatch repair deficiency, and 1/191 had a high homologous recombination deficiency score. Patients with mucinous ovarian cancer may be candidates for targeted treatment, but biomarker-driven prospective trials are difficult to conduct in these rare cancers. [7]

Medical treatment of recurrent ovarian cancer

Seda Şahin Aker and Mara Mantiero

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the ENGOT--OV16/NOVA trial	Del Campo JM et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31173551
2	Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, open-label, phase 3 trial	Pfisterer J et al.	Lanset oncol	https://pubmed.ncbi.nlm.nih.gov/32305099/
3	Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): A randomized phase III trial	Penson RT et al.	.J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/32073956
4	Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome	Cecere SC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31699415
5	Multicenter, randomised, open-label, non-comparative phase 2 trial on the efficacy and safety of the combination of bevacizumab and trabectedin with or without carboplatin in women with partially platinum-sensitive recurrent ovarian cancer	Colombo N et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31537908
6	EMR 20006-012: A phase II randomized double-blind placebo controlled trial comparing the combination of pimasertib (MEK inhibitor) with SAR245409 (PI3K inhibitor) to pimasertib alone in patients with previously treated unresectable borderline or low grade ovarian cancer	Arend RC et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31870556
7	Therapeutic options for mucinous ovarian carcinoma	Gorringe KL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31902686

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

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

Anna-Maria Schütz

Phase I

Gerber et al. performed a phase I, multicentre, open-label, dose-escalation study on the safety, tolerability, and preliminary antitumour activity of lifastuzumab vedotin, an antibody-drug conjugate of anti-NaPi2b mAb, in patients with non-small cell lung cancer and platinum-resistant ovarian cancer. A total of 87 patients, of those 30 with platinum-resistant ovarian cancer after a median four prior lines, were enrolled. Doses between 0.2 and 2.8 mg/kg lifastuzumab vedotin were administered intravenously every three weeks, following a 3+3 dose-escalation design. The median number of cycles was four and the median number of days on treatment was 63 in both groups. Maximum tolerated dose (MTD) was not reached. One dose limiting toxicity (DLT) (dyspnea) was reported in a patient with non-small cell lung cancer at a dose of 1.8 mg/kg. The recommended phase II dose was defined as 2.4 mg/kg i.v. every three weeks. The most common adverse events related to lifastuzumab vedotin included fatigue (52%), nausea (38%), decreased appetite (33%), vomiting (24%), and peripheral sensory neuropathy (29%). The most common treatment-related grade ≥3 adverse events at 2.4 mg/kg were neutropenia (10%), anaemia (3%), and pneumonia (3%). Treatment on a dose level of 2.4 mg/kg had to be discontinued in 16% due to adverse events. Partial responses per RECIST criteria were observed in one of four (25%) patients with non-small cell lung cancer and in one of two (50%) patients with platinum-resistant ovarian cancer at a dose of 1.8 mg/kg, and in three of 45 (7%) and seven of 18 (39%) in non-small cell lung cancer and platinum-resistant ovarian cancer patients, respectively, at a dose of 2.4 mg/kg. All RECIST responses were seen in patients with a high expression of NaPi2b. Overall, lifastuzumab vedotin showed promising activity for platinum-resistant ovarian cancer at a recommended phase II dose of 2.4 mg/kg. [1]

O'Malley et al. investigated the safety and clinical activity of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate, in combination with bevacizumab in 66 patients with platinum-resistant FRα positive ovarian cancer in a phase IB study. The patients had progressed or relapsed epithelial ovarian cancer within six months after last platinum-based treatment; all had received one to three prior lines of treatment. Prior bevacizumab therapy was permitted. Treatment was performed until disease progression, intolerable toxicity, or adverse events. Clinical activity was assessed by RECIST 1.1 criteria. The most common adverse events were diarrhoea (52%), blurred vision (50%), nausea (45%), and fatigue (41%). Most common serious adverse events included small intestinal obstruction (6%), diarrhoea and gastrointestinal haemorrhage (5%). The most common toxicity responsible for study discontinuation was thrombocytopenia (8%), gastrointestinal haemorrhage (5%), pneumonia (5%), and peripheral neuropathy (3%). Overall, the objective response rate was 39%, with five complete and 21 partial responses. The median duration of response was 8.6 months. This drug combination was particularly active in the bevacizumab-naïve group, which had had only one or two prior treatments (objective response rate 56%, duration of response 12 months). The ongoing FORWARD II trial (phase IB study of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, or pegylated liposomal doxorubicin in FRα-positive ovarian and endometrial cancer patients) will further evaluate the role of the combination of mirvetuximab soravtansine + bevacizumab. [2]

Morgan et al. evaluated the safety and efficacy of pazopanib and fosbretabulin in patients with recurrent ovarian cancer (PAZOFOS) in a phase IB (12 patients) and a randomised phase II trial (21 patients, randomised 1:1). Patients with recurrent epithelial ovarian cancer with a platinum-free interval (PFI) of three to 12 months were included. Pazopanib was given orally every 28 days. Fosbretabulin was administered intravenously on days one, eight, 15, and every 28 days for a maximum of six cycles. In phase II, patients were randomised to the recommended phase II dose vs pazopanib 800 mg once daily every 28 days until disease progression or unacceptable toxicity. The primary endpoints of the phase IB trial were MTD and DLTs, whereas the primary endpoint for phase II was progression-free survival. Secondary endpoints were defined as objective response rate, overall survival, and safety. Dose level 1 (pazopanib 600 mg once daily and fosbretabulin 54 mg/m^2) was defined as the recommended phase II dose. Two patients developed treatment-related cardiac adverse events in phase IB. It was not considered a DLTs as it occurred after the first cycle. Importantly, two more patients developed treatment-related grade 3 cardiac adverse events, which resulted in the early termination of the trial. Fortunately, the reported adverse events (troponin elevations and left ventricular dysfunction) appeared to be reversible. Outcome data at the time of trial closure was: Median progression-free survival of 7.6 months in the experimental versus 3.7 months in the control group. Median overall survival was not reached in the experimental arm (two events) and was 8.4 months in the control arm. The objective response rate was 18% versus. 22% for the experimental and the control groups, respectively. The efficacy data demonstrated that this drug combination may have potentially improved survival outcomes compared to pazopanib alone. However, further evaluation of the origin of the observed cardiotoxicity needs to be performed. Future trials might consider lower doses of fosbretabulin. [3]

Phase II

Liu et al. performed a single-arm phase II study to evaluate the activity of nivolumab, a PD-L1 inhibitor, in combination with bevacizumab in 38 women with relapsed ovarian cancer. Participants had one to three prior lines of platinum-based therapy and relapsed within 12 months after last treatment. Every two weeks, 240 mg nivolumab p.o. and 10 mg/kg bevacizumab i.v. were given. The primary endpoint was objective response rate by RECIST 1.1 criteria; secondary endpoints were defined as objective response rate by platinum sensitivity, progression-free survival, safety data, and association of tumour PD-L1 with response to therapy. Eleven patients experienced a confirmed response (objective response rate of 28.9%), eight (objective response rate 40%) confirmed responses were in patients with platinum-sensitive disease, and three were (objective response rate 16.7%) in the platinum-resistant group. Twenty-seven patients (71.1%) experienced some degree of tumour decrease. Median progression-free survival was 9.4 months, with 12.1 months in the platinum-sensitive versus 7.7 months in the platinum-resistant group. Referring to safety, 34 patients (89.5%) had at least one treatment-related

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

Anna-Maria Schütz

adverse event, nine of them (23.7%) reported grade ≥ 3 treatment-related adverse events. PD-L1 testing could be performed in 36 samples, 22 (61.1%) of which had a PD-L1 tumoral percentage of <1 and 14 (38.9%) of ≥ 1. Ten responses occurred in the first group and two in the second. This is in contrast to prior studies that reported a better response rate in the PD-L1 positive group (KEYNOTE-100) or showed no correlation between PD-L1 expression and response rate (JAVELIN). Currently, a phase III trial (AGO-OVAR 2.29) is further investigating the efficacy of another PD-L1 inhibitor, atezolizumab (+ non-platinum based chemotherapy + bevacicumab vs placebo) in recurrent ovarian cancer patients. Overall, the combination of nivolumab with bevacizumab showed activity in patients with relapsed ovarian cancer, with greater activity in the platinum-sensitive group. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Phase 1a study of anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin DNIB0600A in patients with non-small cell lung cancer and platinum-resistant ovarian cancer	Gerber DE et al.	Clin Cancer Res.	https://pubmed.ncbi.nlm.nih.gov/31540980/
2	Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FRα)--targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer	O'Malley DM et al.	Gynecol Oncol.	https://pubmed.ncbi.nlm.nih.gov/32081463/
3	Pazopanib and fosbretabulin in recurrent ovarian cancer (PAZOFOS): A multi--centre, phase 1b and open-label, randomised phase 2 trial	Morgan RD et al.	Gynecol Oncol.	https://pubmed.ncbi.nlm.nih.gov/31932108/
4	Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer: A phase 2 clinical trial	Liu JF et al.	JAMA Oncol.	https://pubmed.ncbi.nlm.nih.gov/31600397/

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

Treatment of ovarian sex cord stromal and germ cell tumours

Natalia Rodriguez Gómez-Hidalgo

Peiretti et al. published a retrospective analysis of 170 patients with ovarian granulosa cell tumour with the aim to evaluate the role of laparoscopy in restaging these patients. In all, 145 had an adult ovarian granulosa cell tumour on pathological review. Of the 81 who were incompletely staged upfront, the authors compared 56 patients who underwent laparoscopic restaging with 25 patients who underwent laparotomy. Eighty-four patients (49.5%) received standard primary surgical staging, including hysterectomy. Eighty-six patients (50.5%) underwent conservative surgery for fertility preservation. No statistically significant difference between laparoscopy and open surgery was detected in the proportion of upstaged patients after second surgery (19% and 28%, p = 0.36). In this series, 3.6% of patients had a diagnosis of endometrial cancer or complex atypical hyperplasia, confirming the well-known association with ovarian granulosa cell tumour and endometrial pathology. Adjuvant chemotherapy was given to the upstaged patients who had a final stage of IIB–IIIC. The authors concluded that laparoscopic restaging seems to be a feasible and safe technique to complete surgical staging in patients with ovarian granulosa cell tumours that were not adequately staged. Follow-up data were not presented in the study. Therefore, no conclusions on the role of laparoscopy for other oncological outcomes could be made. [1]

Zhao et al. investigated the treatment patterns in a cohort of 40 patients with recurrent adult-type granulosa cell ovarian tumour. They analysed the impact of clinical and pathological characteristics on progression-free survival. All patients with granulosa cell ovarian tumour had primarily been treated with surgery. At primary diagnosis, 11 patients had not received adjuvant chemotherapy and 29 patients had received adjuvant treatment. The majority (n = 32) had multiple lesions. At relapse, three patients were treated with surgery alone, six with chemotherapy alone, and 31 with surgery combined with adjuvant chemotherapy. Twenty-four patients had a second relapse, and 11 were subsequently diagnosed with a third relapse. Progression-free survival after recurrence was median 25 months (range 0–94 months). Patients with a progression-free survival of ≥ 61 months (p = 0.004) had a 3.5-fold lower risk of a second recurrence than patients with < 61 months (HR 3.537, 95% CI: 1.503–8.327, p = 0.004). Patients with residual disease after secondary cytoreduction had a 6.6-fold higher risk of death than that of patients with complete resection of lesions (HR 6.586, 95% CI: 1.909–22.730, p = 0.003). In conclusion, maximal cytoreductive effort is crucial in patients with recurrent adult-type granulosa cell ovarian tumour. [2]

Wang et al. retrospectively reviewed 75 patients with stage I pure immature teratoma who underwent fertility-sparing surgery at primary treatment. They analysed the associations between clinical parameters and recurrence. Complete staging surgery was performed in 26 patients (34.7%). Lymphadenectomy was performed in 29.3% of patients. Fifty-one patients (68%) received postoperative adjuvant chemotherapy: 37 patients received bleomycin-etoposide-cisplatin, 11 patients were treated with bleomycin-vincristine-cisplatin, and three with other regimens. Recurrence rates in the complete staging surgery group (3.8%) were similar to the incomplete staging group (6.1%) (p = 0.69). There was no significant difference in progression-free survival between patients with complete and incomplete staging (five-year rates: 96.2% vs 93.8%, p = 0.69). In the subgroup of 49 patients with incomplete staging surgery, adjuvant chemotherapy was not associated with reduced recurrence (p = 0.33). In addition, lymphadenectomy was not associated with recurrence rates. The study shows an overall excellent prognosis of early-stage pure immature teratoma after fertility-sparing surgery. The study is limited by its retrospective design, and, as in all studies on rare tumours, it was limited by the number of patients included. Although the European Society for Medical Oncology guidelines recommend complete staging surgery in clinical practice, the therapeutic value of full lymphadenectomy and adjuvant chemotherapy in early-stage immature teratoma remains an issue of debate. Furthermore, in the MITO-9 study, adjuvant chemotherapy did not improve the recurrence rates; therefore, the results suggested advocated surveillance for stage I immature teratoma, regardless of grade. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Comparison between laparoscopy and laparotomy in the surgical re-staging of granulosa cell tumors of the ovary	Peiretti M et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/31954531
2	Characteristics and treatment results of recurrence in adult-type granulosa cell tumor of ovary	Zhao D et al.	J Ovarian Res	https://pubmed.ncbi.nlm.nih.gov/32059683
3	Role of staging surgery and adjuvant chemotherapy in adult patients with apparent stage I pure immature ovarian teratoma after fertility-sparing surgery	Wang D et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32179695

Borderline ovarian tumours

Anton Ilin

There is still uncertainty regarding the risk of developing ovarian cancer after primary borderline ovarian tumour treatment. A Danish group published the treatment results of 4,281 women with serous and mucinous borderline ovarian tumours and described the incidence of the most common types of ovarian cancer after primary treatment. Serous borderline ovarian tumour correlated with the development of serous ovarian cancer (SIR 9.2, 95% CI: 6.8–12.2) and mucinous borderline ovarian tumours with mucinous ovarian cancer (SIR 18.6, 95% CI: 10.8–29.8). The standardised incidence ratio was higher in a group of patients with serous borderline ovarian tumours in comparison with mucinous borderline ovarian tumours and remained elevated more than ten years and five to nine years, respectively [1].

Plett et al. assessed risks for relapse as well as the fertility potential of 352 patients with borderline ovarian tumours at FIGO stages I–IV. The lowest recurrence rate was 1.1% in the group with stage I, compared to 25.5% in advanced stages (HR 27, 95% CI: 7.7–95, $p \leq 0.001$). The authors found that, among 41 patients who underwent fertility-sparing surgery and attempted to conceive, pregnancy occurred in 82.9%. There were no statistically significant factors that influenced pregnancy outcome. [2]

Jia et al. retrospectively assessed the results of conservative treatment in 94 patients (≤40 years old) with bilateral serous borderline ovarian tumours. Patients were categorised by one of three treatment modalities: bilateral ovarian cystectomy (n = 48), unilateral adnexectomy plus contralateral cystectomy (n =31), and radical surgery (n = 15). Fourteen patients (15%) experienced invasive recurrence, and three (3%) died of progressive disease. Forty-nine patients (62%) attempted to conceive after surgery; 23 (47%) obtained 27 pregnancies, resulting in 19 live births. Moreover, there was no difference in disease-free survival ($p = 0.13$) or pregnancy rate (41% vs 50%, $p = 0.56$) between the unilateral and bilateral procedures [3].

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Risk of specific types of ovarian cancer after borderline ovarian tumors in Denmark: A nationwide study	Hannibal CG et al.	Int J Cancer	https://pubmed.ncbi.nlm.nih.gov/31930502/
2	Fertility-sparing surgery and reproductive-outcomes in patients with borderline ovarian tumors	Plett H et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32115229/
3	Oncofertility outcomes after fertility-sparing treatment of bilateral serous borderline ovarian tumors: results of a large retrospective study	Jia SZ et al.	Hum Reprod	https://pubmed.ncbi.nlm.nih.gov/32048711/

Surgical treatment of primary and recurrent endometrial cancer

Piotr Lepka

GOG 244 is the largest prospective multi-institutional study evaluating the incidence and severity of lymphoedema after lymph node dissection among patients with endometrial (n = 734), cervical (n = 138), and vulvar (n = 42) cancers using objective measurements over a two-year interval. Leg volume was calculated preoperatively and postoperatively at four to six weeks and at three, six, nine, 12, 18, and 24 months. Lymphoedema was categorised by a leg volume change from baseline as mild, moderate, severe as follows: at or below 10%, 10–19%, 20–40%, or >40%, respectively. The incidence of leg volume change was observed in 34% of endometrial, 35% of cervical, and 43% of vulvar cases, respectively. The peak incidence of lymphoedema was at the four-to-six week assessment. Logistic regression analysis showed a decreased risk of leg volume change for patients older than 65, while increased risk was shown for patients with a lymph node count greater than eight in the endometrial cohort. Potential limitations of the study included the large number of research associates involved in the assessments, the high proportion of patients (50%) lost to follow-up, and discrepancies in measurements identified in 32% of patients. [1]

In a multicentre retrospective study, Matsuo et al. assessed the association between ovarian conservation and oncological outcome in surgically-treated patients < 50 years old between 2000 and 2014 (n = 1,196 from the US and n = 495 from Japan) with endometrial cancer stage I grade 1–2. During the study period, the ovarian conservation rate significantly increased only in the US group. Ovarian conservation in the US cohort was not associated with disease-free survival, overall survival, or metachronous secondary malignancy. In the Japanese cohort, ovarian conservation was associated with decreased disease-free survival and an increased risk of a metachronous malignancy (ovarian cancer) but not associated with overall survival. Ovarian recurrence or metachronous secondary ovarian cancer occurred after a median time of 5.9 years. Study strengths included the large patient sample, rigorous eligibility criteria, inclusion of 30 covariates, and comprehensive outcome analysis. Weaknesses included the relatively short follow-up time, lack of central pathology review, lack of outcome related to surgical menopause. [2]

In a randomised controlled study, Gezer et al. evaluated two different sites of tracer injection for sentinel lymph node detection in endometrial cancer. 99m-technetium was injected into the cervix at the 3- and 9-o'clock positions of the uterine cervix (n = 40) and into the fundal endometrium using a transcervical catheter (n = 41). The detection rate of at least one sentinel lymph node was 80% for the cervical group and 85% for the endometrial group. Sensitivity was 66.6% for both groups. The negative predictive value was 96.6% and 96.9%, respectively. Transcervical endometrial tracer injection in endometrial cancer revealed similar pelvic but significantly higher para-aortic sentinel node detection ($p < 0.001$). Study strengths included the fact that all patients underwent a complete pelvic and para-aortic lymphadenectomy procedure. Weaknesses included the small cohort from a single institution and the use of only 99mTc as a tracer. [3]

Bollino et al. showed differences in sentinel lymph node mapping according to histology and anatomy, based on data from two previous prospective sentinel lymph node studies in endometrial cancer patients. Cervically injected indocyanine green was used as a tracer, and an ipsilateral re-injection was performed in case of non-display of the upper and/or lower paracervical pathways. The bilateral mapping rates of the upper and lower paracervical pathways were 88.9% and 39.7%, respectively. Seventy-two percent of all sentinel nodes were typically positioned along the upper paracervical pathway (interiliac and/or proximal obturator fossa), and 94.6% of pelvic-node-positive women had at least one metastatic sentinel lymph node at either of these positions. Two women with high-risk histologies (n = 148) had isolated metastases along the lower paracervical pathway compared with no metastases in the upper pathway in women with grade 1–2 endometrial cancer. The author recommended that sentinel lymph nodes along the upper paracervical pathway should be identified in all endometrial cancer histological subtypes with an ipsilateral re-injection of tracer in case of lack of mapping. If mapping along the upper pathway is not achieved following re-injection, the authors propose that nodes at defined typical positions for the sentinel lymph nodes (interiliac and proximal obturator) should be removed instead of a site-specific full lymphadenectomy. Detection of sentinel lymph nodes along the lower paracervical pathway can be restricted to high-risk histologies, and a full pre-sacral lymphadenectomy should be performed in case of non-display. False-negative results could not be estimated because a complementary lymphadenectomy was not performed. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	GOG 244-The lymphedema and gynaecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients	Carlson JW et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31837831
2	Recurrence, death, and secondary malignancy after ovarian conservation for young women with early-stage low-grade endometrial cancer	Matsuo K et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31427143
3	Cervical versus endometrial injection for sentinel lymph node detection in endometrial cancer: a randomized clinical trial	Gazer S et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/32029429
4	Pelvic sentinel lymph node biopsy in endometrial cancer-a simplified algorithm based on histology and lymphatic anatomy	Bollino M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/32075897

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

Zoia Razumova

DNA damage response (DDR) pathways

The efficiency of chemotherapy is often influenced by DNA damage induction in malignant cells. Therefore, externally activated DNA damage response pathways could help to overcome possible resistance to therapy. The most important DNA damage response pathways are the cross-talking ataxia telangiectasia mutated and Rad3 related and checkpoint kinase 1 (ATR-Chk1) and ataxia telangiectasia mutated and Rad3 related and checkpoint kinase 2 (ATM-Chk2) pathways.

Takeuchi et al. studied the role of inhibitors of DNA damage response pathways as potential anti-tumour molecular-targeted therapy. The combined effect of ATM or ATR inhibitors, conventional DNA-damaging chemotherapy agents (doxorubicin and cisplatin), and irradiation were explored in endometrial cancer cells. The described inhibitors significantly increased the sensitivity of the cells to doxorubicin, cisplatin, and irradiation. Cell proliferation was inhibited by both inhibitors synergistically. DNA-damage-response-pathway-targeting molecular therapies may be promising treatment strategies for endometrial cancer. However, the authors did not investigate these effects in vitro. Therefore, further evaluation of effectiveness and adverse effects using endometrial cancer xenografts in vivo is required. [1]

Receptor for advanced glycation end products (RAGE)

Healey et al. investigated the possibility of targeting the Receptor for Advanced Glycation End products (RAGE) using an antibody drug conjugate therapeutic method. The RAGE expression was investigated in endometrial tissues of 161 patients, including 70 patients in the control group, 54 diagnosed with type I endometrial cancer , and 37 with type II endometrial cancer . There was an association between increased expression of RAGE and endometrial cancer ($p < 0.0001$). Also, overexpression and disease-free survival, as well as overall survival, were negatively correlated ($p < 0.05$). The authors explored this finding further by developing novel RAGE-targeting antibody drug conjugates. RAGE-targeting antibody drug conjugates were shown to be up to 100 times more effective in endometrial cancer cells compared to non-cancer cells and up to 200 times more cytotoxic than chemotherapy alone. RAGE-targeting antibody drug conjugates were not toxic in a mouse model in vivo. Moreover, they significantly decreased cancer growth in a xenograft mouse model. The authors concluded that the present findings could be useful for the development novel therapeutic drugs for patients with endometrial cancer. [2]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Anti-tumor effect of inhibition of DNA damage response proteins, ATM and ATR, in endometrial cancer cells	Takeuchi M et al.	Cancers (basel).	https://pubmed.ncbi.nlm.nih.gov/31805725/
2	Antibody drug conjugates against the receptor for advanced glycation end products (RAGE), a novel therapeutic target in endometrial cancer	Healey GD et al.	J Immunother Cancer.	https://pubmed.ncbi.nlm.nih.gov/31665084/

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

Kamil Zalewski

While patients with stage III carcinoma of the endometrium are in many countries treated with chemotherapy and external beam radiation, the optimal order of those modalities is unknown. Latham et al. analysed the data of 6,981 women from The National Cancer Database [5,116 patients (73.3%) received chemotherapy before external beam radiation, 696 (10.0%) received external beam radiation before chemotherapy, and 1,169 (16.7%) received concurrent therapy] to explore patterns of care and differences in outcome outcomes. The use of chemotherapy before external beam radiation is rising (from 39.9% in 2004 to 75.5% in 2015), while the administration of external beam radiation before chemotherapy has decreased (from 34.0% to 4.4%). While there was no clear difference in survival whether chemotherapy or external beam radiation was initiated first, concurrent therapy was related to a 47% increased risk of mortality (HR 1.47, 95% CI: 1.31–1.66). Administering chemotherapy first is associated with improved survival compared to concurrent therapy (25% higher (HR 1.25, 95% CI: 1.13–1.39). The study´s strengths include the large number of patients included and the assessment of treatment patterns over time. However, treatment details on the specifics on chemotherapy and external beam radiation are lacking, cancer-specific survival is unavailable, and multiple unmeasured confounders may have influenced both the allocation of treatment and outcomes. [1]

Yeung et al. published a large-scale multi-institutional phase III clinical trial comparing symptoms reported by patients and clinicians during radiotherapy using both clinician-reported National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scores and patient-reported outcomes version of the CTCAE (PRO-CTCAE). Patients with cervical or endometrial carcinoma that required postoperative external beam radiation were randomised either to standard four-field external beam radiation or intensity-modulated external beam radiation. In this trial, physician-reported adverse events revealed no difference between arms, whereas patient-reported adverse events showed reduced symptoms with intensity-modulated external beam radiation compared to standard external beam radiation. Despite several potential limitations of the study (various periods in which the symptoms were measured by the patient and the doctor, low compliance in completing the PRO-CTCAE questionnaire, difficulties in direct comparisons of patient- and clinician-reported symptomatic adverse events) these findings demonstrate the increased sensitivity of patient-reported symptomatic adverse events, which may be crucial when comparing toxicity between two different regimens. [2]

Lymphovascular space invasion is an independent risk factor for recurrence and poor survival in early-stage endometrioid endometrial carcinoma, but optimal adjuvant treatment is unknown. In their multi-institutional, retrospective cohort study, Beavis et al. analysed prospectively-maintained data of 478 stage I or II endometrioid endometrial carcinoma patients with lymphovascular space invasion who underwent hysterectomy+/–lymphadenectomy and were treated postoperatively with observation (OBS, 30% of patients), radiation (RAD, external beam and/or vaginal brachytherapy, 48.5% of patients), or chemotherapy (CHEMO)+/–RAD (21.5% of patients). Adjuvant treatment improved progression-free survival regardless of the type of adjuvant treatment and identified a subgroup with grade 3 disease and lymphovascular space invasion in whom progression-free survival was significantly improved with CHEMO+/–RAD when compared to either RAD (HR 0.25, 95% CI: 0.12–0.52) or OBS alone (HR 0.10, 95% CI: 0.03–0.32). The study was not powered to detect any difference in overall survival by treatment type. The current study was limited by its retrospective nature and lack of central pathology review; additionally, only patients with "definitive" lymphovascular space invasion were included and the number of those with questionable or possible lymphovascular space invasion was not recorded. However, the study's strengths included one of the largest sample sizes and a rigorous statistical design. [3]

Lorusso et al. published the results of a randomised (1:1) phase II clinical trial of carboplatin-paclitaxel and carboplatin-paclitaxel-bevacizumab in patients (n = 108) with advanced or recurrent endometrial carcinoma. This is the first randomised trial addressing the role of bevacizumab in combination with carboplatin-paclitaxel in comparison to standard chemotherapy in advanced and/or recurrent endometrial carcinoma, but has several limitations: The study failed to meet its primary endpoints, statistical methodology was adapted during the study, patient-reported outcomes were not reported. The results of this study are in detail discussed in the chapter by Stamatios Petousis in this LiFE 11 report. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Sequencing of therapy in women with stage III endometrial carcinoma receiving adjuvant combination chemotherapy and radiation	Latham AH et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31395371
2	Improvement in patient-reported outcomes with intensity-modulated radiotherapy (RT) compared with standard RT: a report from the NRG Oncology RTOG 1203 study	Yeung AR et al.	J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/32073955
3	Adjuvant therapy for early stage, endometrial cancer with lymphovascular space invasion: Is there a role for chemotherapy?	Beavis AL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31948730
4	Carboplatin-paclitaxel compared to carboplatin-paclitaxel-bevacizumab in advanced or recurrent endometrial cancer: MITO END-2 – A randomized phase II trial	Lorusso D et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31677820

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

Stamatios Petousis

Lorusso et al. published the results of MITO END-2, a randomised phase II trial in which carboplatin-paclitaxel was compared to carboplatin-paclitaxel-bevacizumab in patients with advanced or recurrent endometrial cancer. Patients with recurrent disease represented about 60% of the included patients overall. Progression-free survival, overall survival, and overall survival rate were not significantly improved by the addition of bevacizumab. Specifically, progression-free survival was 13.7 months in patients with addition of bevacizumab versus 10.5 months without (HR 0.84, p = 0.43, while the overall survival was 40.0 months vs. 29.7 months (HR 0.71, p = 0.24), respectively. Interestingly, despite the initially non-significant difference, the authors highlighted that progression-free survival became significantly different when performing exploratory analysis with the Breslow test. The authors concluded bevacizumab combined with chemotherapy should be further explored in larger populations because these preliminary data suggested some effectiveness of this antiangiogenic agent. [1] The limitations of the study are higlighted in the chapter by Kamil Zalewski.

In a retrospective study, Legge et al. examined the main parameters associated with post-relapse survival in a large sample of 210 recurrences in 1,503 patients. Only the pattern of recurrence and treatment approach were independent predictors of post-relapse survival in the multivariate analysis. Specifically, radical surgery ± chemotherapy was indicated to have the best survival effect on recurrences compared with radiotherapy ± chemotherapy, chemotherapy, or hormonotherapy/none. Indeed, chemotherapy alone was indicated to have a 2.8-fold increased risk of recurrence compared with surgery ± chemotherapy. Furthermore, the recurrence to the lymph nodes had a 61% lower risk of secondary recurrence compared with the central-pelvic type of recurrence. [2]

Soliman et al. published a phase II, open-label trial to examine the therapeutic impact of everolimus, letrozole, and metformin in 62 women with advanced or recurrent endometrioid endometrial cancer. Women with ≤ 2 prior chemotherapy regimens for recurrence were included. Patients were required to have a baseline biopsy for molecular analysis to determine whether molecular features at the time of recurrence could predict response to therapy. The therapeutic regimen included everolimus 10 mg orally, letrozole 2.5 mg orally, and metformin 500 mg orally twice a day on a four-week cycle. This resulted in a 50% clinical benefit and 28% overall response in these patients. Positive progesterone receptor expression was associated with clinical benefit (89.5% vs 27.3%, p = 0.001). The median duration of response was seven months, with a six-month progression-free survival of 41%. These results compared favourably with currently approved therapies for recurrent endometrial cancer, especially in progesterone receptor-positive tumours, underlying the need for further validation studies. [3]

Finally, in a phase II study, Konstantinopoulos et al. evaluated avelumab 10 mg/kg administered intravenously every two weeks in 33 recurrent/persistent endometrial cancer patients. The authors evaluated this PD-L1 inhibitor in a mismatch-repair-deficient (MMRD)/POLE patient cohort and a mismatch-repair-proficient (MMRP) patient cohort. Avelumab exhibited promising activity in MMRD patients regardless of PL-D1 status, while the activity of avelumab in MMRP/non-POLE mutated patients was low. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Carboplatin-paclitaxel compared to carboplatin-paclitaxel-bevacizumab in advanced or recurrent endometrial cancer: MITO END-2 - A randomized phase II trial	Lorusso D et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/31677820
2	Clinical outcome of recurrent endometrial cancer: analysis of post-relapse survival by pattern of recurrence and secondary treatment	Legge F et al.	International Journal of Gynecological Cancer	https://pubmed.ncbi.nlm.nih.gov/31792085/
3	Everolimus, letrozole, and metformin in women with advanced or recurrent endometrioid endometrial cancer: a multi-center, single arm, phase II study	Soliman PT et al.	Clinical Cancer Research	https://www.ncbi.nlm.nih.gov/pubmed/31628143
4	Phase II study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer	Konstantinopoulos PA et al.	Journal of Clinical Oncology	https://www.ncbi.nlm.nih.gov/pubmed/31461377

Uterine sarcoma

Marcin Bobiński

The French Sarcoma Group published the results of the LMS03 study. The phase II study was designed to assess the efficacy of pazopanib+gemcitabine combination followed by maintenance treatment with pazopanib in patients with relapsed/metastatic leiomyosarcoma (including uterine leiomyosarcoma). Overall, the study failed to prove the efficacy of this combination. One of the study's strengths was the complex study design based on the Simons method, which minimised enrolled cases. Another study advantage was the well-calculated sample size and double-checked histology in each enrolled case. All these characteristics are important in rare diseases such as leiomyosarcoma and are considered examples for future study designs. Study weaknesses included the fact that only 60% of enrolled patients had tumours originating in the uterus, and no analysis of results respecting tumour origin was performed. Additionally, no control arm was included in the study design. The authors underlined the importance of tolerability among patients with relapsed leiomyosarcoma. [1]

Köhler et al. studied a novel risk-scoring system to differentiate benign leimomyosarcomas and leiomyosarcomas. The score, which achieved a high accuracy (AUC = 0.969), included multiple clinical factors such as patient characteristics, clinical symptoms, tumour size, and ultrasonographic features. The scoring system is based on the retrospective analysis of 839 cases (618 leiomyomas and 221 leiomyosarcomas) and was tested on an independent cohort of 281 patients (206 leiomyomas and 73 leiomyosarcomas). The authors recommended additional assessments, such as hysteroscopy and lactate dehydrogenase levels in suspected cases. Even though the results are promising, the results warrant further validation. A study strength was the multicentre study cohort, while the retrospective design may have led to selection bias. Additionally, the tumour ultrasonographic features were defined by local practitioners and were not verified when enrolling patients into the study. An online version of the risk calculator based on the introduced scoring systemhas been made available: http://bioinfsync.med.uni-greifswald.de:3838/LMS [2]

An analysis of clinical and ultrasound characteristics of 195 uterine sarcomas (including 116 leiomyosarcomas, 48 endometrial stromal sarcomas, and 31 undifferentiated endometrial sarcomas) was published by Ludovisi et al. The multicentre, international, retrospective trial consisted of two steps: identification of records and ultrasonographic images of patients suffering from uterine sarcomas, followed by expert review of each case by 16 experienced ultrasonographers and identification of its characteristics. Uterine sarcomas typically appeared as solid masses with inhomogeneous echogenicity, sometimes with irregular cystic areas but only very occasionally with fan-shaped shadowing. Most are moderately or very well vascularised. The patients were diagnosed between 1996 and 2016 in various centres, so there was no central pathological evaluation. Additionally, the ultrasonographers reviewing images were not blinded; and there was no control group with, for example, leiomyoma patients. Trial strengths included the large cohort and collective analysis of images. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	A phase II of gemcitabine combined with pazopanib followed by pazopanib maintenance, as second-line treatment in patients with advanced leiomyosarcomas: A unicancer French Sarcoma Group study (LMS03 study)	Pautier P et al.	Eur J Cancer.	https://pubmed.ncbi.nlm.nih.gov/31835236/
2	Benign uterine mass-discrimination from leiomyosarcoma by a preoperative risk score: a multicenter cohort study	Köhler G et al.	Arch Gynecol Obstet.	https://pubmed.ncbi.nlm.nih.gov/31677088/
3	Imaging in gynecological disease (15): clinical and ultrasound characteristics of uterine sarcoma	Ludovisi M et al.	Ultrasound Obstet Gynecol.	https://pubmed.ncbi.nlm.nih.gov/30908820/

Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Chrysoula Margioula-Siarkou

Li et al. analysed 162 patients who underwent chemoradiotherapy for stage IVB cervical cancer and 54 patients with chemoradiotherapy plus consolidating pelvic surgeryidentified in the SEER (surveillance, Epidemiology and End Results) database. Surgery with chemoradiotherapy tended to prolong the survival (HR 0.36, 95% CI: 0.21–0.61, $p < 0.001$) compared with chemoradiotherapy, especially in patients without visceral metastasis (HR 0.31, 95% CI: 0.14–0.70, $p = 0.005$). However stage IVB cervical cancer is a heterogenous group of patients due to variation in local tumour spread and number and site of distant metastasis. Moreover, there was no detailed information about chemoradiotherapy protocols or postoperative morbidity available in the study. Only patients with radical or extended hysterectomy and pelvic exenteration were included, but no subgroup analysis was performed. [1]

In their prospective proof-of-principle study, Klapdor et al. showed that peritoneal contamination with cervical secretion is a frequent event occurring during intracorporal colpotomy for laparoscopic hysterectomy. Twelve patients undergoing laparoscopic or robotic hysterectomy indicated for benign pathology underwent injection of indocyanine green to the external cervical ostium. During intracorporal colpotomy, a picture under white and fluorescent light was taken. Contamination was observed at the vaginal edge, peritoneum, and on laparoscopic instruments in 9/12 (75%) patients. In 60% of surgeries, laparoscopic instruments were contaminated with indocyanine green. The prognostic role of the observed contamination is still uncertain but the authors suggest this could be used as a quality assessment tool of surgical technique. [2]

Tesfai et al. retrospectively studied 19 patients with cervical cancer > 2 cm, who were treated with neoadjuvant chemotherapy prior to abdominal radical trachelectomy, in an effort to preserve fertility. Oncological and obstetric outcomes were analysed: 37% of patients were diagnosed with cervical cancer stage IB1, 53% with stage IB2, and 10% with stage IIA (FIGO 2009 classification). The majority (74%) had squamous cell histology. Chemotherapy involved six cycles of weekly paclitaxel 70 mg/m^2 and cisplatin 70 mg/m^2. Successful fertility-sparing surgery was achieved in 74% of the patients. Three out of 19 women (15.7%) were diagnosed with a relapse; two of them had undergone successful radical trachelectomy. There was no statistically significant difference in recurrence-free survival between the successful and unsuccessful abdominal radical trachelectomy groups. Post-chemotherapy tumour volume reduction was correlated with the success of fertility-sparing surgery ($p = 0.036$). Non-squamous histology and non-response/stable dissease only during neoadjuvant chemotherapy were unfavourable prognostic factors. Three women that were successfully treated with abdominal radical trachelectomy had eight pregnancies, six of which ended in caesarean deliveries at term. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Surgery of primary sites for stage IVB cervical cancer patients receiving chemoradiotherapy: a population- based study	Li H et al.	J Gynecol Oncol.	https://doi.org/10.3802/jgo.2020.31.e8
2	Peritoneal contamination with ICG-stained cervical secretion as surrogate for potential cervical cancer tumor cell dissemination: A proof-of-principle study for laparoscopic hysterectomy	Klapdor R et al.	Acta Obstet Gynecol Scand.	https://pubmed.ncbi.nlm.nih.gov/31242322/
3	Fertility-sparing surgery of cervical cancer >2 cm (International Federation of Gynecology and Obstetrics 2009 stage IB1–IIA) after neoadjuvant chemotherapy	Tesfai FM et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/31744889/

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

Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

The phase II study published by Santin et al. included 25 patients with persistent recurrent or metastatic cervical cancer who were treated with nivolumab until progression or unacceptable toxicity. Over 90% of the patients had been treated with radiotherapy before. The median follow-up for survival was 42 weeks. One patient had a partial response (4%) with a duration of response of 3.8 months. An additional eight patients (36.4%) showed stable disease. There were no significant associations between PD-L1 status measured by immunohistochemistry on tumour cells, immune cells, or by combined positive score. Eighty-four percent of patients experienced treatment-related adverse events; the majority of those were grade 1 or 2. The response rates were notably much lower than what has been reported from Checkmate, with 26% responding, and the Keynote studies (13.3% and 17% OR). The authors highlight three patients with partial response in the target lesions but with new lymph nodes which qualified for progressive disease according to RECIST. Also, in these patients, prolonged overall survival was observed. The study is limited by the small sample size, the lack of a comparator regime, and the lack of assessing tumour status with irRECIST. [1]

Hong et al. published a phase II expansion cohort of patients with cervical cancer treated with tisotumab vedotin. Tisotumab vedotin is an antibody-drug conjugate comprising a tissue-factor-specific, fully human monoclonal antibody conjugated to the clinically validated microtubule-disrupting agent monomethyl auristatin E. Tisotumab vedotin delivers monomethyl auristatin E to tissue-factor-expressing cells to induce direct cytotoxicity and bystander killing of neighbouring cells. Fifty-five patients with locally advanced and/or metastatic cervical cancer were treated with 2.0 mg/kg intravenous infusion every three weeks. The majority had squamous histology, and 51% had received ≥2 prior lines of treatment. The median follow-up was 3.8 months. Ten patients (18%) discontinued treatment due to an adverse event, with peripheral neuropathy being the most common (9%). Seven patients (13%) had an adverse event leading to dose reduction. More than half of the patients (56%) experienced adverse events of grade ≥3. The most common adverse events of all grades were epistaxis (51%), fatigue (51%), nausea (49%), conjunctivitis (42%), and alopecia (40%). Ocular events were reduced after the implementation of mitigation measures. The investigator-assessed confirmed objective response rate was 24% (95% CI: 13%–37%) with a median duration of response of 4.2 months. The median progression-free survival was 4.2 months (95% CI: 2.1–5.3), and the six-month progression-free survival rate was 29% (95% CI: 17%–43%). There was no association between expression of tissue factor and response. Tisotuman vedotin is currently explored in combination with bevacizumab, pembrolizumab, and carboplatin. A randomised study comparting tisotumab with non-platinum single-agent chemotherapy is also planned. [2]

Mayadev et al. published a phase I trial of sequential treatment ipilimumab (anti CTLA 4) after curative radio-chemotherapy in 34 patients with node-positive stage IB1-IV CC. IMRT was not permitted in the study, which is now considered the standard of care. The median follow-up was 14.8 months. Two patients were not eligible, and the efficacy analysis included 32 patients. Nine (29%) had positive para-aortic nodes. Thirteen patients did not receive any ipilimumab; reasons included cisplatin allergy or unresolved toxicity after radiation. Twenty-one patients completed at least two cycles. Twelve-month-progression-free-survival was 81%; 12 months was 90%. The translational part of the study showed sustained upregulated PD-1 on CD4 and CD8 cells during sequential immunotherapy. The follow-up was too short to detect durable responses. There was no significant association between HPV status and HLA-A*0201 status, but the study was too small to draw definite conclusions. The study establishes early evidence for the combination of radio-chemotherapy with immunotherapy which is currently explored in several phase III studies. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Phase II evaluation of nivolumab in the treatment of persistent or recurrent cervical cancer (NCT02257528/NRG-GY002)	Santin AD et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/31924334/
2	Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer	Hong DS et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/31796521/
3	Sequential ipilimumab after chemoradiotherapy in curative-Intent treatment of patients with node-positive cervical cancer	Mayadev JS et al.	JAMA Oncol	https://pubmed.ncbi.nlm.nih.gov/31774464/

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

Khayal Gasimli

Guo et al. explored the clinical efficacy and safety of apatinib in patients with advanced-stage or recurrent cervical cancer. This controlled, multicentre, phase II study divided 52 patients into two groups (1:1 ratio): the apatinib-treated and the control group. In the apatinib-treated group, patients with recurrent cervical cancer received apatinib in combination with carboplatin and paclitaxel as first-line chemotherapy. Patients with advanced cervical cancer were treated with apatinib with concurrent chemo-brachytherapy. In the control group, treatment was either chemotherapy or concurrent chemo-brachytherapy alone. The median follow-up time was 14 months. Proteinuria, hypertension, hand-foot syndrome, and mucositis as typical side effects of vascular endothelial growth factor receptor 2 inhibition were observed, with the highest incidence rates in patients treated with apatinib. Studies with larger cohorts and long-term follow-up are required to further assess the efficacy of apatinib in cervical cancer. [1]

Xiao et al. examined the clinical response and safety of apatinib as a monotherapy in recurrent and metastatic cervical cancer after radiotherapy or surgical treatment. The retrospective study included 48 patients with more than two previous cancer treatments. Apatinib was administered until disease progression, unmanageable toxicity, or death. Response rates to apatinib were evaluated by gynaecological examination and using MRI or PET-CT after each cycle of treatment. After a median treatment time of 8.2 months and follow-up of 14.5 months, progression-free survival and overall survival were 4.6 months (95% CI: 3.31–5.26) and 13.9 months (95% CI: 8.37–17.96), respectively. The most common grade 3 side effects were hypertension, fatigue, and haemorrhage. Leukopenia or neutropenia of grade 4 were diagnosed in four patients. [2]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Apatinib combined with chemotherapy or concurrent chemo-brachytherapy in patients with recurrent or advanced cervical cancer: A phase 2, randomized controlled, prospective study	Guo Q et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/32176061
2	Clinical response and safety of apatinib monotherapy in recurrent, metastatic cervical cancer after failure of chemotherapy: a retrospective study	Xiao Y et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31788992

Radiotherapy of primary and recurrent cervical cancer

Erbil Karaman and Paweł Bartnik

Perkins et al. conducted a multi-institutional study to evaluate overall survival and therapy outcomes between patients who had undergone both whole pelvic radiation and chemotherapy versus chemotherapy alone in the treatment of stage IVB cervical cancer. The median age in their study was 53 years. Ninety-five patients were included in the study analysis. The authors reported that the whole pelvic radiation with chemotherapy group showed significantly higher overall survival (41.6 vs 17.6 months, $p < 0.01$). The rates of ureteral obstruction, genital haemorrhage, pelvic infectious status, abdominal pelvic pain, and formation of fistula were not statistically different between the groups (all $p > 0.05$). The authors stated that whole pelvic radiation, in addition to chemotherapy, has a significant overall survival benefit. However, future studies are needed to reach more comprehensive data regarding the subgroup analysis for this new therapy optionin this heterogenous patient group. [1]

A cohort study by Simmonds et al. analysed the association between HIV status and the PET-CT among consecutive cervical cancer patients initially staged as FIGO IIB–IIB. The authors aimed to determine whether HIV-positive patients more often presented false-positive nodal involvement in PET- chemotherapy, resulting in unnecessary radiotherapy fields modification or different treatment intent. The observational study of 192 HIV-negative and 86 HIV-positive patients showed that nodal involvement was detected in over 80% of women—87.2% in the HIV-positive and 82.8% in the HIV-negative group. Similarly, differences in identified distant metastases were not statistically significant; altogether, 54 women had metastatic lesions. Upstaging was not associated with HIV status with 87.2% of HIV-positive and 83.9% of HIV-negative patients who were upstaged. Hyperfractionated external beam radiotherapy was introduced in 14.3% of HIV-positive and 8.2% of HIV-negative women. Palliative external beam radiotherapy was initiated in 10.7% of HIV-positive and 12.5% HIV-negative patients. HIV status was not associated with PET-CT findings nor with the treatment intent after PET-CT. [2]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Incorporation of whole pelvic radiation into treatment of stage IVB cervical cancer: A novel treatment strategy	Perkins V et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31810653
2	HIV status does not have an impact on positron emission tomography-computed tomography (PET-CT) findings or radiotherapy treatment recommendations in patients with locally advanced cervical cancer	Simonds H et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31413068

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

Primary and recurrent vulvar cancer treatment

María de los Reyes Oliver and Rubén M. Betoret

Sentinel lymph node detection is considered standard treatment for early-stage vulvar squamous cell cancer, along with radical excision of the tumour. Froeding et al. presented a nationwide prospective assessment of the procedures registered prospectively in the Danish Gynaecologic Cancer Database from 2011 to 2017 and performed on 286 stage IB–II vulvar squamous cell cancer patients, treated according to the GROINSS-V protocols. A majority (66.4%) were sentinel-lymph-node-negative; among these, 12.1% experienced recurrence in the 30-month follow-up. Early isolated groin recurrence five to 17 months after primary surgery was experienced by 2.1%: 7.4% had vulvar recurrence, 0.5% vulvar and groin relapse, and 2.1% were diagnosed with distant metastases. The three-year overall survival was 84% and disease-specific survival of 93% in the negative sentinel lymph node group with 58% overall survival after recurrence. [1]

Utilising sentinel node technique after prior vulvar excision is still debated because the local or radical resection may disrupt lymphatic channels and alter the accuracy of the procedure. Nica et al. retrospectively reported on the outcome of 24 patients with clinically negative nodes treated with scar re-excision and sentinel-lymph-node-negative procedure in two university referral centres for staging surgery after prior vulvar excision of vulvar tumours < 4 cm. Patients who had previous tumour excision were more likely to be younger ($p = 0.0001$), have a smaller tumour ($p = 0.002$), and less depth of invasion ($p = 0.02$). In the wide local excision of the scar specimen, 11 patients (46%) had no residual disease; eight patients (33%) had only vulvar intraepithelial neoplasia (VIN III); four patients (17%) had carcinoma in situ with focal invasion; and one patient (4%) had invasive carcinoma within the second specimen, resected with clear margins. The authors confirmed no difference in location and time of recurrence when compared to 106 patients with concomitant wide local excision and sentinel lymph nodes. Injecting radiotracers on the remaining vulvar scars showed the non-negative impact on oncologic outcomes. [2]

Intensity-modulated radiotherapy (IMRT) is suited for locally advanced vulvar squamous cell cancer and not amenable to upfront surgery. Rishi et al. described outcomes and toxicity in a retrospective series of 26 patients treated uniformly with curative high-dose intensity-modulated radiotherapy without planned follow-up surgery. The complete response at three months after RT completion and persistent lymph node disease were the strongest predictors of outcome. Actuarial one- and two-year overall survival were 91% and 62%, respectively. Tumour doses > 66Gy significantly increased the risk of high-grade soft tissue toxicity. [3]

Garganese et al. described molecular profiles of vulvar Paget´s disease in a retrospective study on 41 patients, being first to describe PD-L1 expression in 10% non-invasive and 27% invasive vulvar Paget´s disease cells. They show that at least 70% of vulvar Paget´s disease tumours are ER-positive and report ER expression in metastatic lymph node sites, which has never been reported before. The authors concluded that, despite the limits of the study, such as the retrospective design, small sample size, heterogeneity of clinical characteristics and treatments delivered, and the short median follow up, some relevant conclusions can be derived to explore new treatment options in these patients. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Recurrence and survival rates in node negative patients after sentinel node biopsy for early-stage vulva cáncer- A nationwide study	Froeding LP et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31711658
2	Long term outcomes in patients with sentinel lymph nodes (SLNs) identified by injecting remaining scar after previously excised vulvar cancer	Nica A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31451293
3	High-dose intensity-modulated chemoradiotherapy in vulvar squamous cell carcinoma: Outcome and toxicity	Rishi A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31771865
4	The vulvar inmunohistochemical panel (VIP) project: molecular profiles of vulvar Paget´s disease	Garganese G et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31297606

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

Hereditary gynaecological cancer

Sara Giovannoni and Ariel Glickman

The new ASCO Guidelines on germline and somatic tumour testing in ovarian cancer emphasised the importance for all epithelial ovarian cancer patients to undergo a germline genetic test for BRCA1/2 at the time of diagnosis, irrespective of their clinical features or family cancer history. Additionally, somatic tumour testing should be performed in patients who do not carry a germline pathogenic BRCA1/2 variant. First- or second-degree blood relatives of women with germline pathogenic gene mutations or variants should be offered individualised genetic risk evaluation. Routine tumour testing using homologous recombination deficiency assays was not recommended. Current homologous recombination deficiency assays do not provide sufficient differentiation of patient response to PARP inhibitors to routinely recommend their use. Women with clear cell, endometrioid, or mucinous ovarian cancer should be tested for mismatch repair deficiency. However, no assay has been prospectively validated to detect mismatch repair deficiency in ovarian cancer or to predict response to immune checkpoint inhibitors. [1]

Vos et al. published the results of a feasibility study detecting somatic BRCA1/2 gene mutations in ovarian cancer patients (including epithelial, endometrioid, clear cell, mucinous carcinoma, and excluding borderline histology) as a pre-screening analysis for PARP inhibitors treatment. In all, 315 formalin-fixed paraffin-embedded tissues were tested using a single-molecule molecular inversion probe enrichment followed by next-generation sequencing and multiplex ligation-dependent probe amplification. Pathogenic variants were detected in 16.7% of these patients. The variants included 56.8% of hereditary pathogenic variants and somatic variants in 43.2%. According to the authors, universal tumour BRCA1/2 testing in ovarian cancer patients is feasible and effective and can improve the rate of patients eligible for PARP inhibitors, allowing the identification of more variants compared with conventional genetic predisposition testing of DNA from blood. They finally suggested replacing BRCA1/2 genetic testing with BRCA1/2 tumour DNA testing as a pre-screen for genetic predisposition. [2]

Yang et al. performed an observational study to estimate tubo-ovarian carcinoma and breast cancer risks for RAD51C and RAD51D pathogenic variant carriers. Data from 6,178 families (125 with pathogenic variants in RAD51C) and 6,690 families (60 with pathogenic variants in RAD51D) were analysed.

The estimated tubo-ovarian carcinoma relative risks were 7.55 for RAD51C and 7.60 for RAD51D pathogenic variant carriers. Relative risks increased with age until 60–69 and then decreased for RAD51C and peaked in the 50–59 age group for RAD51D. The estimated cumulative risks of developing tubo-ovarian carcinoma for a woman with a RAD51C or RAD51D pathogenic variant was 1% or 0.8% to age 50 and 11% or 13% to age 80. The authors emphasised that cancer risk differs based on cancer family history. For RAD51C/D pathogenic variant carriers whose mother and sister developed tubo-ovarian carcinoma at 50 years, the risk of developing tubo-ovarian carcinoma by age 80 is 32–36%. Even though this is the largest study to date, the age-specific results were based on relatively small numbers in each age group. Variations in risks by variant type were not analysed, and no cancer subtype analysis was performed. Nevertheless, the study suggests RAD51C and RAD51D pathogenic variant carriers as candidates for risk-reducing salpingo-oophorectomy. The authors concluded that this might in particular apply to women older than 50. Furthermore, RAD51C/RAD51D pathogenic variant carriers with a family history of breast cancer may also be candidates for risk-reducing mastectomies. [3]

Mavaddat et al. assessed the effect of risk-reducing salpingo-oopforectomy on breast cancer risk in a prospective cohort study of 2,272 BRCA1 and 1,605 BRCA2 mutation carriers. In this cohort, 426 women developed breast cancer. The observational period included a mean of 5.4 and 4.9 years for BRCA1 and BRCA2, respectively.

No association between risk-reducing salpingo-oophorectomy and breast cancer risk for BRCA1 (HR 1.23, 95% CI: 0.94–1.61) or BRCA2 (HR 0.88, 95% CI: 0.62–1.24) mutation carriers was detected. For BRCA2 mutation carriers, hazard ratios were 0.68 (CI: 0.40–1.15) and 1.07 (CI: 0.69–1.64) for risk-reducing salpingo-oophorectomy carried out before or after age 45 years, respectively. The hazard ratio for BRCA2 mutation carriers decreased with increasing time since risk-reducing salpingo-oophorectomy (HR 0.51, 95% CI 0.26–0.99 for five years or longer after risk-reducing salpingo-oophorectomy).

According to the authors, risk-reducing salpingo-oophorectomy does not reduce breast cancer risk for BRCA1 mutation carriers. However, a potentially beneficial effect for BRCA2 mutation carriers was observed, particularly after five years following risk-reducing salpingo-oophorectomy.

While this is the largest prospective cohort of mutation carriers to date, the number of breast cancer cases was still limited, and so the confidence limits for the hazard ratio estimates were wide. Additional data would be needed to determine if there is a modest protective effect of risk-reducing salpingo-oophorectomy for BRCA mutation carriers. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline	Konstantinopoulos PA et al.	J Clin Oncol.	doi.org/10.1200/JCO.19.02960
2	Universal tumor dna BRCA1/2 testing of ovarian cancer: prescreening PARPi treatment and genetic predisposition	Vos JR et al.	J Natl Cancer Inst.	doi.org/10.1093/jnci/djz080
3	Ovarian and breast cancer risks associated with pathogenic variants in RAD51C and RAD51D	Yang X et al.	J Natl Cancer Inst.	doi.org/10.1093/jnci/djaa030
4	Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of BRCA1 and BRCA2 mutation carriers	Mavaddat N et al.	Breast Cancer Res.	doi.org/10.1186/s13058-020-1247-4

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

Screening of gynaecological cancer

Geanina Dragnea

Cervical cancer

The World Health Organisation is developing a global strategy for eliminating cervical cancer by 2120 at a threshold incidence of four cases per 100,000 women-years in 78 low-income and lower-middle-income countries. This is known as the 90–70–90 WHO triple-intervention strategy because the targets by 2030 are 90% coverage with a nine-valent HPV vaccination, 70% coverage of twice lifetime screening with HPV testing, and 90% of women having access to cervical precancer and cancer treatment. Three models were evaluated: girls-only vaccination (first model), girls-only vaccination and once-lifetime screening (second model), and girls-only vaccination and twice-lifetime screening (third model). By 2030, the first model would have minimal impact on cervical cancer mortality, leading to a 0.1% reduction, but the third model would reduce mortality by 34.2% (with similar results for the second model). By 2070, the first model would reduce mortality by 61.7%, the second model by 88.9%, and the third model by 92.3%. By 2120, the first model would reduce mortality by 89.5%, the second model by 97.9%, and the second model by 98.6%. With the first model, the elimination of cervical cancer could occur between 2059 and 2102, but introducing twice-lifetime screening accelerates elimination by 11–31 years. These findings emphasise the importance of acting immediately on three fronts: to scale up vaccination, screening, and treatment for pre-invasive and invasive cervical cancer. [1, 2]

The ARTISTIC trial cohort of 24,496 women estimated the long-term CIN3 risks associated with different triage strategies for HPV+ with normal cytology or low-grade dysplasia to reduce unnecessary referrals to colposcopy. After three rounds of screening (3 years apart), the ten-year cumulative risk of CIN3+ was much higher for women with HPV16/18 infection (19.4% with borderline/low-grade cytology and 10.7%, with normal cytology), compared to those with other HPV types (7.3% borderline/low-grade cytology and 3.2% with normal cytology). Comparing these protocols with current NHSCSP (NHS Cervical Screening Program) policy, the authors concluded that recall intervals of one year for HPV16/18+ and two years for other high-risk HPV+ are justified for women with normal cytology and might also be considered for women with borderline/low-grade cytology to reduce recalls on colposcopy referrals. [3]

A national cohort study from Australia included 250,648 women and assessed the effectiveness of quadrivalent HPV vaccines by the number of doses against CIN2+/AIS/cancer in up to seven years post-vaccination. With adjustment for age at vaccination amongst the vaccinated group, the adjusted hazard ratios for one-dose and two-dose recipients were comparable to three-dose recipients (one dose 1.01 (95% CI: 0.81–1.26), two doses 1.00 (95% CI: 0.85–1.17). These findings support the hypothesis that one-dose vaccination may be a viable strategy when working towards the global elimination of cervical cancer. [4]

A cross-sectional study of 1,620 women aged 18–26 investigated HPV infection prevalence among women by the number of quadrivalent vaccine doses received. Compared with unvaccinated women (a prevalence of 12.5%), infection with HPV type 6, 11, 16, or 18 was significantly less prevalent among women who received one dose (2.4%), two doses (5.1%), or three doses (3.1%) of HPV vaccine, with no significant difference in prevalence for one dose versus two doses or one dose versus three doses. This study suggests that women who received one dose of the HPV vaccine may have gained similar protection against vaccine-type infections compared with those who received additional doses. [5]

Endometrial cancer

A prospective multicentre cohort study on 59 endometrial carcinoma patients and 31 control patients (with benign gynaecological conditions) assessed whether mutational analysis of cervical cytology or pipelle endometrial biopsies improved the diagnostic accuracy of traditional histopathological diagnosis of endometrial carcinoma. The single-molecule molecular inversion probes were designed to amplify segments for hotspots in oncogenes (CTNNB1, KRAS, MTOR, PIK3CA, and POLE) and all coding and splice-site sequences of tumour suppressor genes (ARID1A, PTEN, TP53). Traditional histopathological assessment by preoperative pipelle yielded a sensitivity and specificity of 79% and 100%. A mutational analysis of Pap brush samples, cervico-vaginal self-samples, and pipelle endometrial biopsies yielded a sensitivity of 78%, 67%, and 96% with a specificity of 97%, 97%, and 94%, respectively. Combining one of these three methods with histopathological pipelle endometrial biopsy yielded a sensitivity of 96%, 93%, and 96%, respectively. Mutational analysis of either cervical cytology or pipelle endometrial biopsies may improve the diagnosis of endometrial carcinoma. Limitations include a relatively high rate (21%) of pipelle biopsies assessed as benign or inconclusive. Further, the control group did not consist of patients presenting with postmenopausal bleeding (and no cancer) but of patients treated for other benign gynaecological conditions. [6]

Ovarian cancer

The value of a new potential biomarker, HE4 Ag-AAb complexes, in the early detection of ovarian cancer was evaluated using sera from patients enrolled in the Normal Risk Ovarian Cancer Screening Study with early- (n = 73) and late-stage ovarian cancers (n = 49) and without ovarian cancer (n = 212). CA 125, human epididymis protein 4 (HE4), anti-HE4 autoantibody, and HE4 Ag-AAb complexes were measured. The sensitivities of these markers to detect early-stage (I/II) disease were 7% for HE4 autoantibody, 18% for HE4 antigen levels, 38% for HE4 Ag-AAb complexes, and 63% for CA 125, at 98% specificity for healthy women. The sensitivities in detection of late-stage (III/IV) disease was 4% for HE4 autoantibody, 43% for HE4 antigen levels, 31% for HE4 Ag-AAb complexes, and 90% using CA 125. The most impressive impact of HE4 Ag-AAb complexes was seen in improving detection by CA 125 in early-stage (I/II) disease. The combination CA 125 + HE4 Ag-AAb complexes identified 81% of such cases, whilst the combination CA 125 + HE4 Ag identified only 63% of cases with early disease. In the validation set of 69 preoperative sera from patients with stage I/II invasive epithelial ovarian/tubal/peritoneal cancer and 200 sera from healthy controls, the combination CA 125 + HE4 Ag-AAb complexes had an even greater sensitivity of 86% to detect early cancer, with 95% specificity. [7]

Screening of gynaecological cancer

Geanina Dragnea

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries	Canfell K et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/32007142
2	Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries.	Brisson M et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/32007141
3	Triaging women with human papillomavirus infection and normal cytology or low-grade dyskaryosis: evidence from 10-year follow up of the ARTISTIC trial cohort	Gilham C et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/31541495
4	Is one dose of human papillomavirus vaccine as effective as three? A national cohort analysis	Brotherton JM et al.	Papillomavirus Res.	https://www.ncbi.nlm.nih.gov/pubmed/31319173
5	Prevalence of human papillomavirus infection by number of vaccine doses among US women	Sonawane K et al.	JAMA Netw Open	https://www.ncbi.nlm.nih.gov/pubmed/31880792
6	Mutational analysis of cervical cytology improves diagnosis of endometrial cancer: A prospective multicentre cohort study	Reijnen C et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31523803
7	Human epididymis protein 4 antigen-autoantibody complexes complement cancer antigen 125 for detecting early-stage ovarian cancer	Yang WL et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31714597

Prevention and management of surgical complications

Martina Borghese

Komatsu et al. assessed the incidence of deep vein thrombosis in 205 patients, which was found significantly higher in ovarian cancer patients compared to other gynaecological cancers. The postoperative D-dimer value was found to be significantly higher than preoperative, especially in patients who received adjuvant chemotherapy. The cut-off value of D-dimer was 1.55 µg/mL preoperatively and 1.95 µg/mL postoperatively. [1]

Carlson et al. investigated the association between lymphoedema and gynaecologic oncologic surgery from GOG study 244, finding that, among 914 analysed patients, the incidence of lymphoedema was 34%, 35%, and 43% for endometrial, cervical, and vulvar cancer patients, respectively. The study is discussed in detail in the chapter on Surgical treatment of primary and recurrent endometrial cancer by Piotr Lepka. [2]

Kumar et al. described a quality improvement study to improve the rate of normothermia in gynaecologic surgery patients and decrease surgical morbidity: the authors were able to achieve higher rates of normothermia through an algorithm-driven intraoperative temperature control via digital thermostats and by prewarming with Bair Paws Flex gowns, at a relatively low cost. [3]

Obermaier et al. compared the incidence of intra- and postoperative adverse events after minimally invasive surgery versus open surgery in 631 cervical cancer patients enrolled in The Laparoscopic Approach to Carcinoma of the Cervix trial. A similar overall incidence of adverse events was observed between the two groups (54% in the minimally invasive group vs 48% in the open group, 95% CI: -2.2–14.7%, p = 0.14). [4]

Mullen et al. reported that frailty, calculated using 11 comorbidities previously validated, is significantly associated with wound complications in obese gynaecologic oncologic patients: in their study of 163 patients, wound complications occurred in 28 (50%) of frail and 24 (22.4%) of non-frail patients. The authors concluded that frailty is a useful tool in identifying patients at highest risk and should be incorporated into preoperative counselling. [5]

Same-day discharge of gynaecologic oncologic patients following ileostomy closure seems to be feasible and safe, according to the study from Nguyen et al. Early discharge was not associated with an increased rate of adverse events or readmissions (13% vs 24.5%, p = 0.24) and might be a safe alternative to routine hospitalisation in carefully selected patients. [6]

Data influencing the choice of the use of bowel preparation before gynaecologic surgery mainly come from the colorectal literature, and the evidence is still controversial: Kalogera et al. recently analysed 38,539 gynaecologic oncologic patients undergoing both minimally invasive and open surgery, and reported that bowel preparation does not protect against major surgical complications. The rate of surgical site infections, anastomotic leaks, and overall major morbidity was similar between the two groups. The authors concluded that bowel preparation may be safely omitted. [7]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Deep vein thrombosis and serum D-dimer after pelvic lymphadenectomy in gynecological cancer	Komatsu H et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/32276932
2	GOG 244-The lymphedema and gynecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients	Carlson JW et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31837831
3	Improving the rate of surgical normothermia in gynecologic surgery	Kumar A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31285083
4	Incidence of adverse events in minimally invasive vs open radical hysterectomy in early cervical cancer: results of a randomized controlled trial	Obermair A et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/31586602
5	Modified frailty index is predictive of wound complications in obese patients undergoing gynecologic surgery via a midline vertical incision	Mullen MM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/32001077
6	Same-day discharge of gynecologic oncology patients following ileostomy closure is feasible and safe	Nguyen JMV et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31776039
7	Use of bowel preparation does not reduce postoperative infectious morbidity following minimally invasive or open hysterectomies	Kalogera E et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/32112733

Cancer in pregnancy

Michael J. Halaska

Shiomi et al. reported on a rare case of endometrial cancer associated with a pregnant patient who underwent an urgent caesarean delivery in the 35th gestational week due to antepartum bleeding caused by placenta previa. A hysterectomy was performed, finding a pattern similar to that of endometrial cancer not related to pregnancy. Immunohistochemistry revealed an overexpression of the oestrogen and progesterone receptors with negative p53 expression. A staging reoperation confirmed IA stage endometrial cancer with no evidence of disease at four years. A literature review found another 25 cases, generally with an excellent prognosis. [1]

Maggen et al. collected a data set of 13 patients with gastric cancer found during pregnancy using the database of the International Network on Cancer, Infertility, and Pregnancy. The median age of diagnosis was 22 weeks of gestation. Ninety-two percent of patients died, most of them within six months after diagnosis. Chemotherapy could be administered during pregnancy, but the deterioration of the patients should be considered. [2]

An analysis of breastfeeding in 39 patients diagnosed with breast cancer during pregnancy was performed by Lee et al. Only three women breastfed even though 61% underwent lumpectomy and 35% unilateral mastectomy. Currently, breastfeeding is not contraindicated if last chemotherapy was given three weeks before delivery. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Endometrial carcinoma in a gravid uterus: a case report and literature review	Shiomi M et al.	BMC Pregnancy Childbirth	https://pubmed.ncbi.nlm.nih.gov/31747899/
2	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://pubmed.ncbi.nlm.nih.gov/31529466/
3	Contemporary management of breast cancer during pregnancy and subsequent lactation in a multicenter cohort of young women with breast cancer	Lee GE et al.	Breast J	https://pubmed.ncbi.nlm.nih.gov/31318125/

Treatment of elderly patients with gynaecological cancers

Alex Mutombo

In a retrospective study of 1,799 patients with endometrial cancer managed at a Spanish university hospital in the Canary Islands, Benito et al. found that elderly patients were less likely to receive surgery (68.2% vs 92.4%), lymphadenectomy (10.3% vs 26.2%), and adjuvant treatment (37.1% vs 51.2%) than younger patients, with high rates of treatment given with palliative intention (27.6% vs 4%). Elderly patients showed poor cancer-specific survival rates [61.4 months (95% CI: 51.7–71.1) vs 226 months (95% CI: 218.9–233.1), respectively]. [1]

In a case-control study, Amadio et al. reviewed and analysed data on patients with primary or recurrent epithelial ovarian cancer who received platinum-based chemotherapy plus bevacizumab. The occurrence of serious (grade ≥ 3) adverse events did not increase among the older group (≥ 65 years). Creatinine serum levels > 1.1 g/dL, estimated glomerular filtration rate ≤ 60 mL/min, ≥ 3 comorbidities were independently associated with higher rates of severe toxicity. Study limitations include the retrospective observational design, risk of selection bias, and inability to control for factors influencing treatment decision-making. [2]

Kato et al. also retrospectively assessed chemotherapy use in 253 ovarian cancer patients categorised into a platinum-sensitive group (n = 135) and a platinum-resistant group (n = 118). In the resistant group, the percentage of patients aged 70–74 or 75–79 who received chemotherapy was significantly lower than the percentage among patients aged ≤ 64 years, respectively (p = 0.01, p = 0.01). [3]

In a retrospective cohort study of 50 patients with high-grade serous ovarian cancer, Nadaraja et al. found that the expression of 81 genes was significantly altered in older patients experiencing progression after first-line platinum-based treatment within six months versus those who progressed later than 12 months. They suggested low expression of ARAP1 to be a potential marker of poor prognosis in the elderly. [4]

In a study on the association of comprehensive geriatric assessment and overall survival among 120 older gynaecologic oncology patients > 70 years, Michaan et al. found no association between age, body mass index (BMI), and cancer type to overall survival. This study was conducted with an oncology referral centre and may not be representative of the general oncologic population. Patients with ovarian cancer and higher disease stage were over-represented. [5]

A study by Klapheke et al. aimed to assess factors associated with depressive symptoms in women aged 65 and older previously diagnosed with cervical, ovarian, or uterine cancer (n = 1,977) in the Surveillance, Epidemiology, and End Results - Medicare Health Outcomes Survey database. The prevalence of depressive symptoms was higher among older women with gynaecologic cancer (31.9%, 32.2%, and 25.3% for cervical, ovarian, and uterine cancer, respectively) compared to cancer-free older women (24.9%) (p = 0.05). [6]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Management of endometrial cancer in patients aged 80 years and older: Identifying patients who may benefit from a curative treatment	Benito V et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/31550627
2	ToleRability of BevacizUmab in elderly Ovarian cancer patients (TURBO study): a case--control study of a real-life experience	Amadio G et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31788996
3	Treatment strategies for recurrent ovarian cancer in older adult patients in Japan: a study based on real-world data	Kato MK et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/32144536
4	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
5	Comprehensive geriatric assessment is correlated to overall survival among gynaecologic oncology patients	Michaan N et al.	Jpn J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31822898
6	Depressive symptoms and health-related quality of life in older women with gynecologic cancers	Klapheke AK et al.	J Geriatr Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31668948

Epidemiology of gynaecological cancers

Kemal Güngördük

Endometrial cancer

A population-based case-control study of 522 incident endometrial cancer cases and 976 population controls demonstrated that higher levels of androstenedione were associated with increased endometrial cancer risk (OR 1.44, 95% CI: 1.04–2.02). In contrast, higher levels of sex-hormone-binding globulin correlated to a 61% reduced risk of endometrial cancer (OR 0.39, 95% CI: 0.19–0.84). [1]

In another systematic review and meta-analysis, weight loss was associated with lower endometrial cancer risk (RR range 0.61–0.96), whereas weight cycling was associated with higher endometrial cancer risk (OR range 1.07–2.33). Furthermore, bariatric surgery is associated with a decreased risk of endometrial cancer (OR 0.41, 95% CI: 0.22–0.74). [3]

Ovarian cancer

A population-based cohort study of 1,340,097 women with a first live birth in Sweden 1982–2012 demonstrated that women with an infertility diagnosis who used assisted reproductive technology had a higher risk of ovarian cancer (aHR 1.79, 95% CI: 1.18–2.71) and borderline tumour (aHR 1.48, 95% CI: 0.90–2.44) compared to women with non-assisted-reproductive-technology births. [4]

Steward et al. reported in an Australian population-based cohort study that pelvic inflammatory disease was associated with an increased risk of serous borderline tumour (HR 1.95, 95% CI: 1.22–3.10) and low-grade serous ovarian carcinoma (HR 2.90, 95% CI: 1.21–6.94). In addition, infertility related to a pelvic-inflammatory-disease (HR 1.98, 95% CI: 1.20–3.26) and ectopic pregnancy (HR 2.44, 95% CI: 1.20–4.96) were associated with an increased risk of serous borderline tumour. [5]

A Swedish prospective population-based matched-cohort study showed that current combined menopausal hormonal therapy use was associated with a modestly increased risk of ovarian cancer (OR 1.38, 95% CI: 1.18–1.62), while no consistent risk was found among past users (OR 1.00, 95% CI: 0.84–1.18). Non-significant positive associations were observed for sequential menopausal hormonal therapy regimens (OR 1.87, 95% CI: 0.70–5.08; OR 1.54, 95% CI: 0.96–2.47, respectively). [6]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Case-control study of endogenous sex steroid hormones and risk of endometrial cancer	Friedenreich CM et al.	Cancer Causes Control.	https://www.ncbi.nlm.nih.gov/pubmed/31865473
2	Tubal ligation and endometrial Cancer risk: a global systematic review and meta-analysis	Loghmani L et al.	BMC Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31604465
3	Intentional weight loss, weight cycling, and endometrial cancer risk: a systematic review and meta-analysis	Zhang X et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/31451560
4	Assisted reproductive technology and risk of ovarian cancer and borderline tumors in parous women: a population-based cohort study	Lundberg FE et al.	Eur J Epidemiol.	https://www.ncbi.nlm.nih.gov/pubmed/31377935
5	Association between pelvic inflammatory disease, infertility, ectopic pregnancy and the development of ovarian serous borderline tumor, mucinous borderline tumor and low-grade serous carcinoma	Stewart LM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/31983516
6	Menopausal hormone therapy treatment options and ovarian cancer risk: A Swedish prospective population-based matched-cohort study	Simin J et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/31584190

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

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

Joanna Kacperczyk-Bartnik

Molecular background

King et al. compared molecular characteristics of complete hydatidiform moles (n = 4) and first-trimester placentas (n = 40). In complete hydatidiform moles, the overall gene expression levels and activity of immune pathways were increased. The expression of placenta-specific transcripts in complete hydatidiform moles was decreased when compared to normal first-trimester placentas. What is more, in complete hydatidiform moles, up-regulation was detected in most of the differentially expressed genes (72%). Epigenetic reprogramming and parental imprinting were dysregulated in the pathological tissues. [1]

Lung metastases and response to treatment

In a historical cohort study, Frijstein et al. analysed whether the presence of lung metastases in 65 low-risk gestational trophoblastic neoplasia patients (n = 65) could result in a different outcome compared to women with no metastatic disease (n = 975). Lung metastases were associated with more frequent methotrexate resistance (60% vs 38.9%; $p < 0.001$), a higher median number of methotrexate courses until remission (9 vs 6; $p < 0.001$) and higher recurrence rate (9.2% vs 2.7%; $p = 0.012$). [2]

Treatment protocols

In a retrospective cohort study, Braga et al. evaluated the outcome of low-risk gestational trophoblastic neoplasia patients managed between 1990 and 2017. The first group was treated with a standard eight-day methotrexate and folic acid regimen (n = 538). The second group included patients with a 16-hour delay in the administration of the last methotrexate dose in cases in which scheduling standard eight-day treatment was not possible over weekends (n = 98). Women treated with the modified regimen presented a higher incidence of metastatic lung disease (22.5% vs 10.6%, $p = 0.002$). There were no differences regarding remission rate in first- and second-line treatment, the number of cycles in first-line treatment, the time to switch to second-line therapy, chemoresistance, relapse, or mortality between the groups. [3]

Maestá et al. examined in a retrospective cohort study the outcome and toxicity of actinomycin D as second-line treatment in methotrexate-resistant low-risk gestational trophoblastic neoplasia patients, administered either in a five-day regimen (10–12 μg/kg per day, n = 53) or pulsed (1.25 mg/m^2, n = 15) every 14 days. Sustained remission rates in both second-line regimens were comparable—71.7% in five-day and 73.3% in the pulsed regimen. HCG remission was obtained faster and with fewer cycles in the five-day regimen group with a median 21 versus 47 days ($p = 0.04$) and median one cycle versus two cycles ($p < 0.001$). Lower toxicity was observed in the pulsed actinomycin D regimen: thrombocytopenia (0% vs 64.6%, $p < 0.001$), oral mucositis (16.7% vs 60.4%, $p = 0.009$), grade 3 oral mucositis (0% vs 37.9%, $p = 0.045$), grade 2 alopecia (16.7% vs 70.6%, $p = 0.02$). [4]

Sato et al. investigated the outcome of choriocarcinoma and high-risk gestational trophoblastic neoplasia patients treated with four-day methotrexate, etoposide, and actinomycin D regimen. The retrospective cohort analysis included 29 women managed between 1999 and 2015. During the average follow-up lasting 53.9 months, 23 (73.9%) patients achieved complete remission, and six (20.7%) patients developed resistance to the four-day methotrexate, etoposide, and actinomycin D regimen. Adverse effects included leukocytopenia (82.5%), anaemia (77.6%), nausea (63.4%), stomatitis (60.7%), hepatotoxicity (53.6%), constipation (49.7%), thrombocytopenia (48.6%), vomiting (23%), and diarrhoea (5.5%). [5]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Dysregulation of placental functions and immune pathways in complete hydatidiform moles	King JR et al.	Int J Mol Sci.	https://pubmed.ncbi.nlm.nih.gov/31658584
2	Lung metastases in low-risk gestational trophoblastic neoplasia: a retrospective cohort study	Frijstein MM et al.	BJOG.	https://pubmed.ncbi.nlm.nih.gov/31794098/
3	Comparison of treatment for low-risk GTN with standard 8-day MTX/FA regimen versus modified MTX/FA regimen without chemotherapy on the weekend	Braga A et al.	Gynecol Oncol.	https://pubmed.ncbi.nlm.nih.gov/31928806
4	Effectiveness and toxicity of second-line actinomycin D in patients with methotrexate-resistant postmolar low-risk gestational trophoblastic neoplasia	Maestá I et al.	Gynecol Oncol.	https://pubmed.ncbi.nlm.nih.gov/32037196
5	The efficacy and toxicity of 4-day chemotherapy with methotrexate, etoposide and actinomycin D in patients with choriocarcinoma and high-risk gestational trophoblastic neoplasia	Sato S et al.	Int J Clin Oncol.	https://pubmed.ncbi.nlm.nih.gov/31520175

Follow-up after gynaecological malignancies

Jenneke Kasius

Beaver et al. assessed the acceptability and feasibility of patient-initiated follow-up amongst stage I endometrial cancer survivors in the United Kingdom. Clinicians were asked to identify eligible patients. Participants had to agree to replace 1–2 hospital appointments with a supported self-management approach. As few as 17 out of 64 eligible patients were recruited. Participants filled out a questionnaire about the service and follow-up regime, their sociodemographic characteristics, and psychological and physical wellbeing. Qualitative interviews were also carried out. The average participant was 59 years old, married, and retired. This selected group of cancer survivors questioned the value of hospital-based follow-up and were very satisfied with patient-initiated follow-up, given they had received sufficient information on signs of recurrence and whom to contact in case they occurred. Patient-initiated follow-up did not result in disadvantages on a physical nor psychological level in any of the participants. The major limitation of the study is selection bias, which affects the generalisability of the study findings. [1]

To evaluate the current follow-up regime in the United Kingdom, Coleman and Newton performed an online survey of members from the British Gynaecological Cancer Society and the National Forum of Gynaecological Oncology Nurses. Respondents originated from 44 out of the 49 cancer centres in the UK. Consultant-based follow-up for five years was the most common follow-up regime. Nurse-led telephone follow-up, and nurse-led follow-up clinics were available in 16 and 20 centres, respectively. Patient initiated follow-up was part of the routine follow-up in 42% of all centres. Patient-initiated follow-up was mostly used for patients after treatment for endometrial cancer (100%) but also after treatment for cervical cancer (32%) or vulvar and ovarian cancer (26%). [2]

Vistad et al. surveyed 546 recurrence-free Norwegian cervical cancer survivors, with a response rate of 57%. The questionnaire was developed by the research group with the aim of exploring the patients' preferences for long-term (longer than five years) follow-up. Cancer (treatment) information was obtained from medical records. At a median of 11 years after diagnosis, 55% of the women preferred follow-up for longer than five years. The questionnaire did not assess the details of the preferred follow-up, such as frequency and exact duration. Determinants associated with preference for long-term follow-up were young age or treatment with chemoradiation instead of surgery. No associations were found between preference for long-term follow-up and self-reported late effects, depression, anxiety, or personality traits. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Exploring the acceptability and feasibility of patient-initiated follow-up for women treated for stage I endometrial cancer	Beaver K et al.	Eur J Cancer Care.	https://pubmed.ncbi.nlm.nih.gov/31812918/
2	Patient initiated follow up after gynaecological malignancy: National survey of current UK practice	Coleman L and Newton C	J Occup Rehabil.	https://pubmed.ncbi.nlm.nih.gov/32240892/
3	Preferences for follow up in long-term survivors after cervical cancer	Vistad I et al.	Acta Obstet Gynecol Scand.	https://pubmed.ncbi.nlm.nih.gov/32232835/

Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

Yang et al. conducted a randomised controlled trial regarding the combined use of megestrol acetate and metformin in 150 patients with endometrial hyperplasia or cancer with cumulative complete response rate (CR) at 16 weeks as primary endpoint. The response rates in all patients were not statistically different (34.3% in the combination group vs 20.7% in the megestrol acetate only group; OR 2.00, 95% CI: 0.89–4.51, p = 0.09). In a stratified analysis, 16-week-complete-response rates in patients with atypical hyperplasia were doubled in the combination group compared to megestrol acetate alone (39.6% vs 20.4%, OR 2.56, 95% CI: 1.06–6.21, p = 0.032). Of the women achieving CR, the vast majority received assisted reproductive treatment with pregnancy rates of 51.8% in the megestrol acetate and metformin group and 48.4% in the MA-only group (p = 0.8). [1]

Ovarian cancer

Wang et al. studied the role of complete staging and neoadjuvant chemotherapy in 75 young patients with pure immature teratoma. This study is discussed in the chapter on "Treatment of ovarian sex cord stromal and germ cell tumours" by Natalia Rodriguez Gómez-Hidalgo. [2]

Cervical cancer

A retrospective analysis of 19 women who received neoadjuvant chemotherapy prior to radical abdominal trachelectomy for tumours > 2 cm was conducted by Tesfai et al. Patients received weekly cycles of cisplatin and paclitaxel, and 58% completed the planned six cycles of treatment. One patient had stable disease only and was treated with radical hysterectomy. Fifteeen of the 18 patients underwent successful fertility-sparing surgery. After median follow-up of 50 months (range 3–144), three patients had relapsed (two of them after successful abdominal trachelectomy), of whom two died. The relapse rate among patients with successful abdominal trachelectomy was 13.3% (2/15 patients). Potential unfavorable prognostic factors included stable or progressive disease on chemotherapy and non-squamous histology, but confirmation in larger prospective studies such as the planned NEOCON-F/CONTESSA study (NCT 04016389) is necessary. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial	Yang BY et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/31961463
2	Role of staging surgery and adjuvant chemotherapy in adult patients with apparent stage I pure immature ovarian teratoma after fertility-sparing surgery	Wang D et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/32179695
3	Fertility-sparing surgery of cervical cancer > 2 cm (International Federation of Gynecology and Obstetrics 2009 Stage IB1-IIA) after neoadjuvant chemotherapy	Tesfai FM et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/31744889

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

Palliative care and quality of life in gynaecological cancers

Nadja Taumberger and Engin Çelik

Graul et al. investigated the effect of interventional video on the quality of palliative care in gynaecologic oncology patients at the University of Pennsylvania's Gynaecologic Oncology Department between February and December 2018. A total of 111 patients were included in the study who had histologically confirmed metastatic gynaecologic disease as defined by persistent or progressive disease despite primary treatment with surgery, chemotherapy, or radiation. Patients were randomised to a palliative care educational video or a non-directive cancer centre video. Primary endpoints were acceptance of palliative care consultation as well as attendance of a palliative care consultation appointment within six months after completing the survey. The majority of patients were diagnosed with tubal-ovarian-peritoneal cancer (74 patients, 66.7%). There was no statistical difference between groups in acceptance of a palliative care referral (interventional group:16 patients, 29%, control group: 15 patients, 27%). Further analysis showed that patients that attended palliative care appointments were more likely to have diabetes, currently smoke, and have a worse performance status. [1]

Spencer et al. assessed humorous digital media attention diversion to improve symptoms during chemotherapy for patients with recurrent gynaecologic cancers. A total of 66 patients who were scheduled to receive chemotherapy for recurrent gynaecologic cancer at the University of Wisconsin Carbone Cancer Centre were included over two years. The primary outcome of negative mood as measured by the PANAS-X instrument was significantly improved after watching humorous films when compared with baseline (mean change −1.68, $p = 0.017$) but also significantly improved after watching non-humorous films when compared with baseline (mean change −1.98, $p = 0.001$). This study showed that digital media attention diversion to patients undergoing chemotherapy for recurrent cancer could significantly improve feelings of negative mood and fear. [2]

A cross-sectional one-time survey from Hubbs et al. addressed the issue of sexual dysfunction in women who have had gynaecological cancer and were either still under treatment or already in follow-up. Eighty-five women from a single centre answered a validated but modified Sexual Function Questionnaire at one of their follow-up appointments. The results showed that, even though sexual enjoyment dropped significantly after cancer treatment, only 25.3% of the women felt that their health care provider should bring up the topic actively. The study supported the fact that gynaecological cancer patients often suffer from sexual dysfunction and that there was need for more studies to evaluate what and especially how patients want this issue to be addressed. [3]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Effect of patient education on palliative care knowledge and acceptability of outpatient palliative care services among gynecologic oncology patients: A randomized controlled trial	Graul A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31831167
2	A digital media attention diversion improves mood and fear in patients receiving chemotherapy for recurrent gynecologic malignancies: results of a randomized trial	Spencer R et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/32122951
3	Sexual quality of life after the treatment of gynecologic cancer: what women want	Hubbs JL et al.	Supportive Care in Cancer	https://link.springer.com/article/10.1007/s00520-019-04756-7

Nutrition and perioperative care

Begoña Díaz de la Noval

Li et al. published a retrospective cohort study applying the Controlling Nutritional Status (CONUT) score to 206 patients with epithelial ovarian cancer before treatment. The CONUT score was calculated using serum albumin levels, total lymphocyte count, and cholesterol levels. The data showed that the prognostic significance of the CONUT score is predictive for overall survival, but not for progression-free survival. The study has the limitations of being retrospective, single-centre, and applying non-verified scales. [1]

Özdemir et al. published a randomised clinical trial on preoperative walking and postoperative gastrointestinal function in 85 endometrial and ovarian cancer patients who were scheduled for staging surgery. The study determined that walking the last night before surgery leads to a faster recovery of bowel function and less paralytic ileus. Additionally, walking before surgery and laparoscopic surgery independently protected against postoperative paralytic ileus. Study limitations included not being blinded and a control group, where patients were not completely sedentary. Also, given the extensive exclusion criteria, the generalisability of results is limited. [2]

A retrospective study by Kohut et al. evaluated perioperative outcome in 10,840 patients after minimally invasive surgery for endometrial cancer. The analysis found an overall low 30-day readmission rate of 3.0%. Risk factors related to readmission included dialysis, increased length of stay, and preoperative weight loss (> 10% loss of body weight in the six months before surgery). Infection was the most common aetiology for readmission, followed by venous thromboembolism. Risk factors related to an increased length of stay were ascites, surgery longer than five hours, and preoperative blood transfusion. Compared to pelvic and/or para-aortic lymphadenectomy, sentinel lymph node dissection was not found to be associated with either increased length of stay or readmission. [3]

Wijk et al. published an international cohort study ($n = 2,101$) that prospectively validated an association between compliance with Enhanced Recovery After Surgery (ERAS) Gynecologic/Oncology guideline elements and a decrease in primary hospital length of stay across all patients ($p < 0.001$) or total complications among low-complexity patients ($p < 0.05$). The study limitations included being an observational study with a mixed population. [4]

The volume-outcome relationship of gynae-oncological centres may help to identify procedures in which centralisation of surgical services may improve outcomes. In a multicentre retrospective study on 1,912 patients by Matsuo et al., the number of high-risk perioperative complications decreased linearly as every additional exenteration (above two procedures a year) a hospital performed per year. [5]

Frequently, a readmission for complications to a hospital different than the original institution at which the surgery was performed is caused by a fragmentation of postoperative care. Cham et al. analysed readmissions after ovarian cancer surgery for 24,569 readmitted patients. They concluded that fragmentation of care is frequent and associated with an increased risk of death. The impact of geographic disparities and limited access to high-quality care may have influenced the results, so an improved discharge planning and coordination of care are suggested. [6]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Prognostic significance of the controlling nutritional status (CONUT) score in epithelial ovarian cancer	Li Y et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/31822507/
2	Impact of pre-operative walking on post- operative bowel function in patients with gynecologic cancer	Özdemir IA et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/31326951/
3	Evaluating unplanned readmission and prolonged length of stay following minimally invasive surgery for endometrial cancer	Kohut A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/31839339/
4	International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery	Wijk L et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/31051119/
5	Hospital surgical volume and perioperative mortality of pelvic exenteration for gynecologic malignancies	Matsuo K et al.	J Surg Oncol	https://pubmed.ncbi.nlm.nih.gov/31746006/
6	Fragmentation of postoperative care after surgical management of ovarian cancer at 30 days and 90 days	Cham S et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/31520627/

Treatment of pre-invasive gynaecological malignancies

Elko Gliozheni

In their single-centre, unmasked randomised (1:1) clinical trial, Greene et al. evaluated whether cryotherapy (n = 200) or loop electrosurgical excision procedure (LEEP) (n = 200) was a more effective treatment for cervical intraepithelial neoplasia (CIN) grade 2 or 3 among women with HIV. The patients were all receiving HIV treatment and were followed up every six months for 24 months with a Papanicolaou test and confirmatory biopsy. Their primary outcome was disease recurrence, defined as CIN grade 2 or higher on cervical biopsy, during the 24-month follow-up period. Over a period of two years, 30% of the patients randomised to cryotherapy experienced recurrence, compared to 19% in the LEEP group (relative risk, 1.71 [95% CI: 1.12–2.65]; risk difference, 7.9% [95% CI: 1.9%–14.0%]; p = 0.01). In this study, women who were taking antiretroviral therapy (ART) for less than two years were immunocompromised or had detectable HIV viral load higher than CIN grade 2 or higher recurrence and were more likely to benefit from LEEP than from cryotherapy. However, there was no significant difference in high-grade cervical disease between cryotherapy and LEEP during follow-up for women with an undetectable viral load, high CD4 cell count (>250/μL), or ART duration of longer than two years. Nevertheless, this study has limitations, such as the small subgroups, a single centre in an urban HIV care facility with one clinician administering all treatment procedures (so the generalisability of these results may be limited), human papillomavirus (HPV) type-specific results are missing, and HIV factors vary with time. [1]

Petrillo et al. aimed to retrospectively assess the role of an HPV vaccine after LEEP in reducing recurrent cervical dysplasia in women with ≥ 2 years of follow-up. Disease recurrence occurred in 16.5% and 7.1% of nonvaccinated and vaccinated women, respectively, and a statistically significant lower incidence of CIN2/CIN3/carcinoma in situ recurrence was found in the vaccinated group (13.6% vs 3.3%). The protective role of HPV vaccination after LEEP was found to be more relevant to protection against severe (CIN3/carcinoma in situ) cervical lesions. HPV testing, with virotype characterisation, was not routinely performed over the whole study period; therefore, in several cases, the results of HPV testing were reported only as the presence of high-risk genotype. The majority of the patients included in the study were administered the quadrivalent HPV vaccine, but there were a few patients who received a bivalent vaccine. HPV genotype at the time of relapse was assessed only in the group of vaccinated women on histological specimens obtained at the time of recurrence. It should also be noted that women administered an HPV vaccine after LEEP were four years younger than nonvaccinated patients. The small sample size, the high drop-out rate, the lack of HPV testing with genotype characterisation could limit the reliability of these findings. [2]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Effect of cryotherapy vs loop electrosurgical excision procedure on cervical disease recurrence among women with HIV and high-grade cervical lesions in Kenya	Greene SH et al.	JAMA network	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6806442/
2	Efficacy of HPV vaccination in women receiving LEEP for cervical dysplasia: A single institution's experience	Petrillo M et al.	Vaccines (Basel)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7157656/

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

Pathology of gynaecological cancers

Nicolas Samartzis and Dimitrios Rafail Kalaitzopoulos

Ovarian cancer

Bodelon et al. conducted a DNA methylation analysis of 162 ovarian epithelial tumours tissues, including high- and low-grade serous, endometrioid, mucinous, clear cell, and ovarian tumours of low-grade malignant potential and classified the epithelial ovarian cancers according to DNA methylation pattern into four new subgroups. The above subgroups are associated with distinct histopathology, genome stability, transcriptomes, and—the most important from a clinical point of view—survival outcomes. Within high-grade serous ovarian cancer tissues, methylation subgroups added significant survival information to expression-derived molecular subgroups. Despite the study's small sample size and lack of treatment information, the authors highlighted the study's strengths: it is the most comprehensive study of methylation of ovarian cancer to date, the same laboratory and analytical methods were used for all samples, and methylation-based subgroups were referred to other genomic features. They concluded that DNA methylation-based epithelial ovarian cancer classification harbours the potential to impact diagnoses and clinical decisions. [1]

Färkkilä et al. previously conducted the TOPACIO trial, a phase I/II clinical trial which examined the combination of PARP inhibitor niraparib and the anti-PD-1 antibody pembrolizumab in 62 patients with recurrent platinum-resistant ovarian cancer. The response of the patients was heterogeneous, with 5% complete response, 13% partial response, and a clinical benefit rate of 65%. The objective of the present study of the same group was to identify predictive markers of the response on this combination therapy. The authors suggested two previously unrecognised predictive factors of response in platinum-resistant ovarian cancer; the mutational signature 3 (Sig3) that reflects the defective homologous recombination DNA repair, and the positive immune score as a marker of interferon-primed exhausted CD8 + T-cells. An improved outcome was associated with the presence of one or both of the above predictive factors (HR = 0.32), while no response was observed in connection with the absence of both markers (ORR 0%). Study limitations included the absence of independent validation of the used biomarkers and technical discrepancies between the different study centres. [2]

Endometrial cancer

de Jonge et al. described the clinicopathological and molecular characteristics of endometrial cancer among germline-mutated BRCA carriers found in a nationwide Dutch cancer registry. The 38 selected endometrial cancers were divided into two groups in accordance to loss of heterozygosity (LOH) and classified as gBRCA associated (LOH pos.) and sporadic (LOH neg.) cancers. gBRCA-associated endometrial cancers represented 60% of the study population and differed from sporadic endometrial cancer by histology (high-grade) and molecular subtype (TP53 mutant). These findings provided novel evidence in favour of EC being part of the gBRCA-associated HBOC syndrome and should be taken into consideration for genetic counselling, surveillance in germline BRCA mutation carriers, and possible treatment strategies with PARP inhibitors in gBRCA-associated endometrial cancer. [3]

Uterine leiomyosarcoma

Croce et al. analysed 60 uterine leiomyosarcomas with NanoCind®, a panel of 75 targeting genes, which divided the heterogenous population of any FIGO stages into two groups differing in relapse-free survival and overall survival. The gene panel had a prognostic factor with better values in comparison to FIGO classification and the genomic index. These results were validated by in an external series (TCGA data) and were potentially clinically relevant stratification factor in clinical trials. [4]

Relevant articles retrieved September 30, 2019 – March 31, 2020

No	Title	Authors	Journal	Link to abstract
1	Molecular classification of epithelial ovarian cancer based on methylation profiling: Evidence for survival heterogeneity	Bodelon C et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/31142506/
2	Immunogenomic profiling determines responses to combined PARP and PD-1 inhibitionin ovarian cancer	Färkkilä A et al.	Nat Commun	https://pubmed.ncbi.nlm.nih.gov/32193378/
3	Germline BRCA-associated endometrial carcinoma is a distinct clinicopathologic entity	de Jonge MM et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/31492746/
4	The Nanocind signature is an independent prognosticator of recurrence and death in uterine leiomyosarcomas	Croce S et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/31796515/

List of contributors, acknowledgements

We acknowledge the support and great individual efforts of the following ENYGO members:

Achimas-Cadariu, Patrick	The Oncology Institute Ion Chiricuță, Cluj-Napoca, Romania
Bartnik, Paweł	2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw, Poland
Betoret, Rubén	Hospital Universitario del Vinalopó, Elche, Spain
Bobiński, Marcin	1st Chair and Department of Gynaecolgical Oncology and Gynaecology, Medical University in Lublin, Poland
Borghese, Martina	Ospedale Mauriziano Umberto I, Turin, Italy
Çelik, Engin	Istanbul University, Faculty of Medicine, Turkey
Díaz de la Noval, Begoña	Gynaecology and Obstetrics Department Hospital Universitario Central de Asturias, Oviedo, Spain
Dragnea, Geanina	CMI Dr. Dragnea Geanina - Pitesti, Romania
Gasimli, Khayal	Goethe University Frankfurt, Department of Gynaecology, Germany/Azerbaijan
Ghosh, Anik	Consultant, Gynaecologic Oncology,Tata Medical Centre, Kolkata, India
Giovannoni, Sara	Policlinico Sant'Orsola Malpighi- Bologna, Italy
Glickman, Ariel	Hospital Clínic Barcelona, Spain
Gliozheni, Elko	Materniteti Koco Gliozheni, Tirana, Albania
Gungorduk, Kemal	Zekai Tahir Burak Women's Health, Education and Research Hospital, Hacettepe University Department of Anatomy, Istanbul, Turkey
Gutic, Bojana	Oncology Institut of Vojvodina, Serbia
Halaska, Michael	3rd Medical Faculty, Charles University in Prague and Faculty Hospital Kralovske Vinohrady, Czech Republic
Ilin, Anton	State Institution of Health "Saint Petersburg Research Center specialized types of medical care (Oncology)", Saint Petersburg, Russia
Kacperczyk-Bartnik, Joanna	2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw, Poland
Kahramanoglu, Ilker	Istanbul University Cerrahpasa School of Medicine, Division of Gynaecologic Oncology, Turkey
Kalaitzopoulos, Dimitrios Rafail	Kantonsspital Schaffhausen, Department of Gynaecological Oncology, Schaffhausen, Switzerland
Karaman, Erbil	Yuzuncu yil University, Medical faculty, Department of Obstetrics and Gynaecology, Division of Gynaecologic Oncology, Van, Turkey
Kasius, Jenneke	Amsterdam University Medical Centers, Gynaecological Oncology, Amsterdam, Netherlands
Lepka, Piotr	Wroclaw Medical University, 2nd Department and Clinic of Gynaecology, Obstetrics and Neonatology, Poland
Lindemann, Kristina	Department of Gynaecological Cancer, Division of Cancer Medicine, Oslo University Hospital, Norway and Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway
Mantiero, Mara	Instituto Nazionale Tumori, Milano, Italy
Margioula-Siarkou, Chrysoula	2nd Department of Obstetrics and Gynaecology, Ippokrateion General Hospital of Thessaloniki, Greece

List of contributors, acknowledgements

Mutombo, Alex	Kinshasa University Hospital, Department of Obstetrics and Gynaecology, Kinshasa, Democratic Republic of Congo
Oliver, Maria de los Reyes	Hospital Universitario 12 de Octubre, Madrid, Spain
Petousis, Stamatios	2nd Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Greece
Razumova, Zoia	Department of Women´s and Children´s Health, Karolinska Institutet at Karolinska University Hospital, Stockholm, Sweden
Rodriguez Gómez-Hidalgo, Natalia	Vall D´Hebron University Hospital, Barcelona, Spain
Şahin Aker, Seda	Ankara University Department of Gynaecologic Oncology, Turkey
Samartzis, Nicolas	Kantonsspital Schaffhausen, Dept GO, Switzerland
Selcuk, Ilker	Zekai Tahir Burak Women's Health Education and Research Hospital, Gynaecological Oncology Clinic, Hacettepe University Department of Anatomy, Ankara, Turkey
Schütz, Anna-Maria	Medical University Graz, Austria
Taumberger, Nadja	Hospital Spittal/Drau Carinthia, Austria / Medical University of Graz, Austria
Theofanakis, Charalampos	Alexandra University Hospital, Athens, Greece
Yaznil, Muhammad Rizki	Universitas Sumatera Utara, Airlangga University, Indonesia
Zalewski, Kamil	Warsaw Medical University, Poland; Department of Gynaecologic Oncology, Holycross Cancer Center, Kielce, Poland

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